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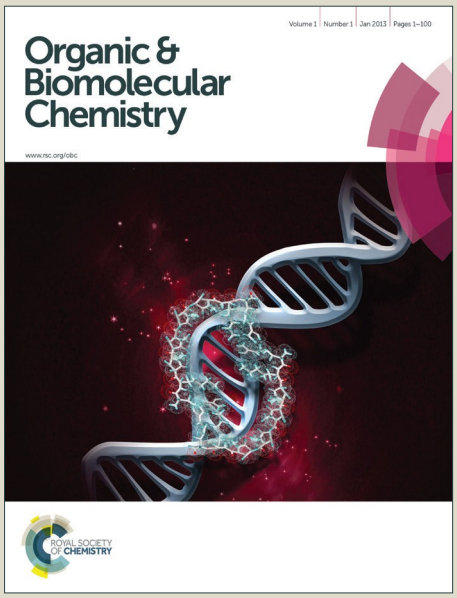




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# Synthesis of crinane utilizing an allylic sulfoxide for the construction of hydroindole ring via vinylogous C-N bond formation

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**Abstract:** The synthesis of crinane is disclosed via intramolecular C-N bond formation by displacement of an allylic sulfoxonium salt. The allylic sulfide precursor was synthesized by a ring-closing metathesis reaction. The quaternary carbon stereocenter was created by alkylation of a benzylic cyanide. The allyl sulfide **14** was prepared by vinylmagnesium bromide addition to an α-chlorosulfide.

## INTRODUCTION

Crinine and related alkaloids, Figure 1, isolated from Amaryllidaceae,[1] possess the *cis*-arylhydroindole core bearing an all-carbon quaternary center. Crinine alkaloids are closely related to the lycorane- and galanthamine type alkaloids that possess a wide range of biological activities.[2] The efficient and stereoselective introduction of the quaternary center vicinal to the tertiary stereocenter and a fused pyrrolidine ring is the central challenge in the efficient synthesis of *cis*-arylhydroindole alkaloids.

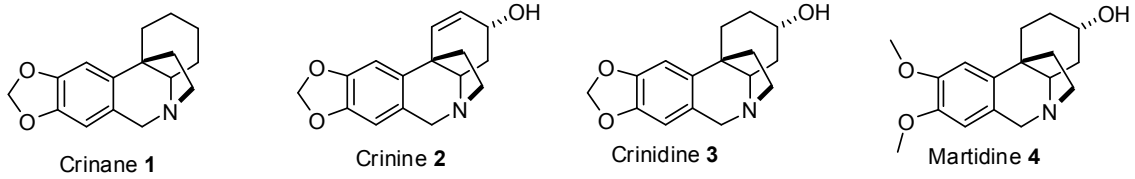


**Figure 1.** Representative crinine type Amaryllidaceae alkaloids.

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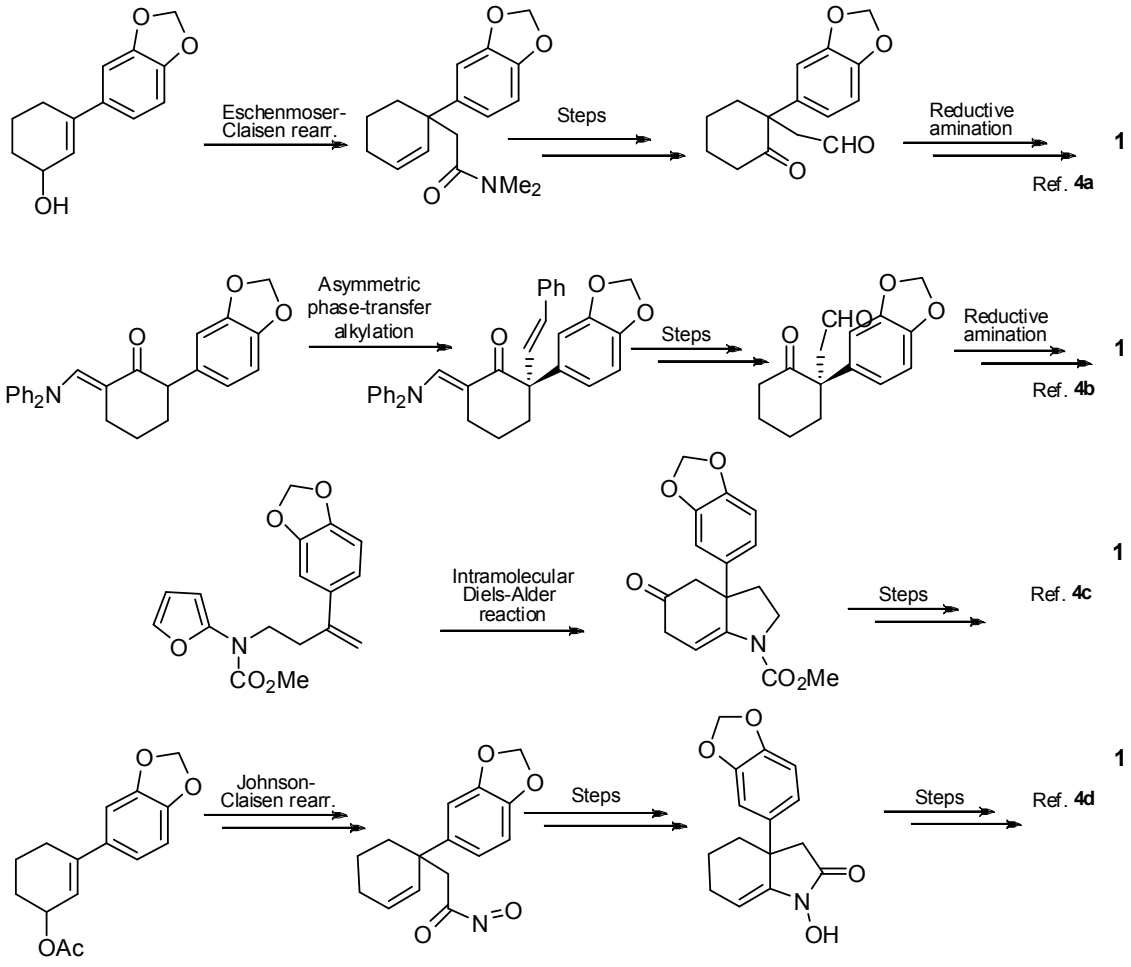
To date, different approaches to the quaternary carbon center have been reported.[3] With reference to crinane, Bisai and coworkers[4a] have employed Eschenmoser-Claisen rearrangement to introduce the quaternary center in the same way as Keck[4d] used Johnson-Claisen rearrangement. Maruoka and coworkers[4b] employed asymmetric phase-transfer alkylation while Padwa[4c] took advantage of the intramolecular Diels-Alder reaction to create the quaternary center and the pyrrolidine ring. A reductive amination was employed to form the C-N bond by Bisai and Maruoka while Keck used the intramolecular nitroso ene reaction, Scheme 1.




**Scheme 1.** Approaches to crinane.

Herein, we report the synthesis of crinane taking advantage of a vinylogous Pummerer type reaction to construct the octahydroindole core. The strategy disclosed herein would provide

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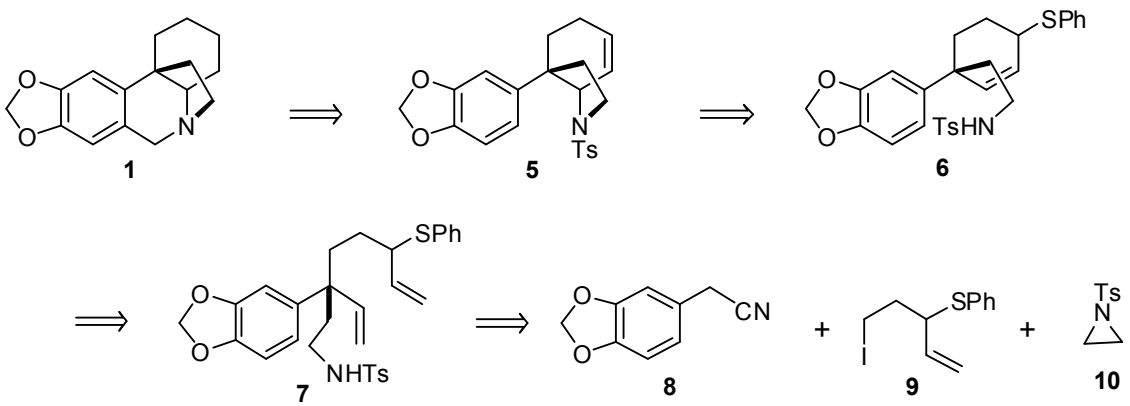
access to several other members of the crinane family by suitable functional group modification of the product resulting from vinylogous Pummerer reaction.

## RESULTS AND DISCUSSION

The retrosynthetic disconnection is depicted in Scheme 2. Crinane was envisaged to be obtained from sulfonamide **5** by a reductive detosylation, reduction followed by a Pictet-Spengler reaction. Compound **5** was imagined to be obtained from the allylic sulfide **6** by a vinylogous Pummerer type reaction. Allylic sulfide **6** can be obtained by a ring-closing metathesis reaction from the diene **7**, which can be assembled by alkylation of cyano compound **8** with iodide **9** and aziridine **10**.




**Scheme 2.** Retrosynthetic disconnection of crinane **1**.

The synthesis began with the silyl ether **11**, obtained by selective monoprotection of 1,3-propane diol, which on treatment with diphenyl disulfide following Hata's protocol[5] yielded the sulfide **12**. Treatment of **12** with *N*-chlorosuccinimide afforded α-chlorosulfide **13** that on reaction with vinylmagnesium bromide[6] furnished the allylic sulfide **14**.

Deprotection of the silyl ether under acid catalyzed conditions followed by iodination[7] of the ensuing alcohol **15** afforded iodide **9**, Scheme 3.[8]

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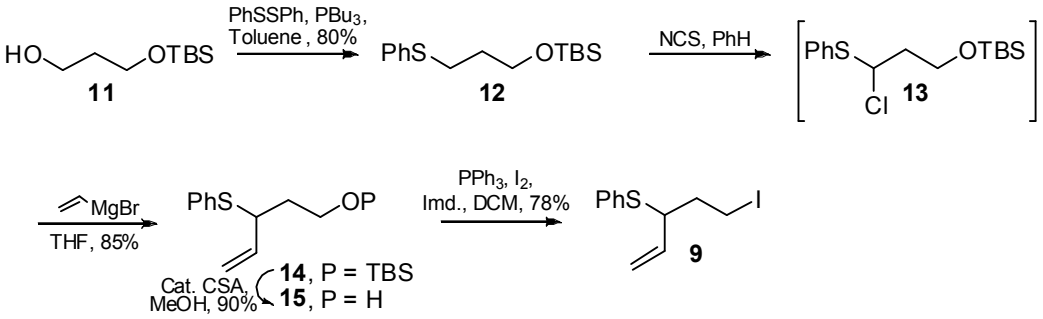


**Scheme 3.** Synthesis of iodide **9**.

Monoalkylation of the commercially available benzylic cyanide **8** with iodide **9** furnished sulfide **16**.[9] The quaternary carbon was created by a second alkylation of the anion[7] generated from **16**, with aziridine **10**.[10] The resulting sulfonamide anion was reacted with di-*tert*-butyl di carbonate to yield compound **17**.[11] Reduction of the cyano group in **17** using DIBAL-H afforded the aldehyde **18** which was subjected to a one-carbon homologation with the ylid generated from the phosphonium salt to furnish the diene **7**. Ring-closing metathesis using Grubbs' II generation catalyst **19** afforded the allylic sulfide **6** with concomitant deprotection of the carbamate group. The sulfide was oxidized to an epimeric mixture of sulfoxides **20** using *m*-CPBA. Activation of the sulfoxide with trifluoroacetic anhydride in the presence of the triethylamine resulted in the formation of the vinyl sulfide **23**. The initially formed sulfonium salt **21** probably gives rise to the sulfenium ion **22** which undergoes vinylogous Pummerer type reaction[12] to yield compound **23**. Compound **23** would be a valuable intermediate for the synthesis of other members of the crinine family by hydrolysis of the alkenyl sulfide to a ketone and further functional group modifications. Alternately, treatment of sulfoxides **20** with trifluoromethanesulfonic anhydride at -78 $^{o}$C resulted in pyrrolidine derivative **5**. The reaction probably proceeds via the initial activation of the sulfoxide to the sulfonium salt **24** which then suffers the loss of sulfenyl triflate by intramolecular displacement to afford compound **5**.[13] The synthesis of crinane was completed

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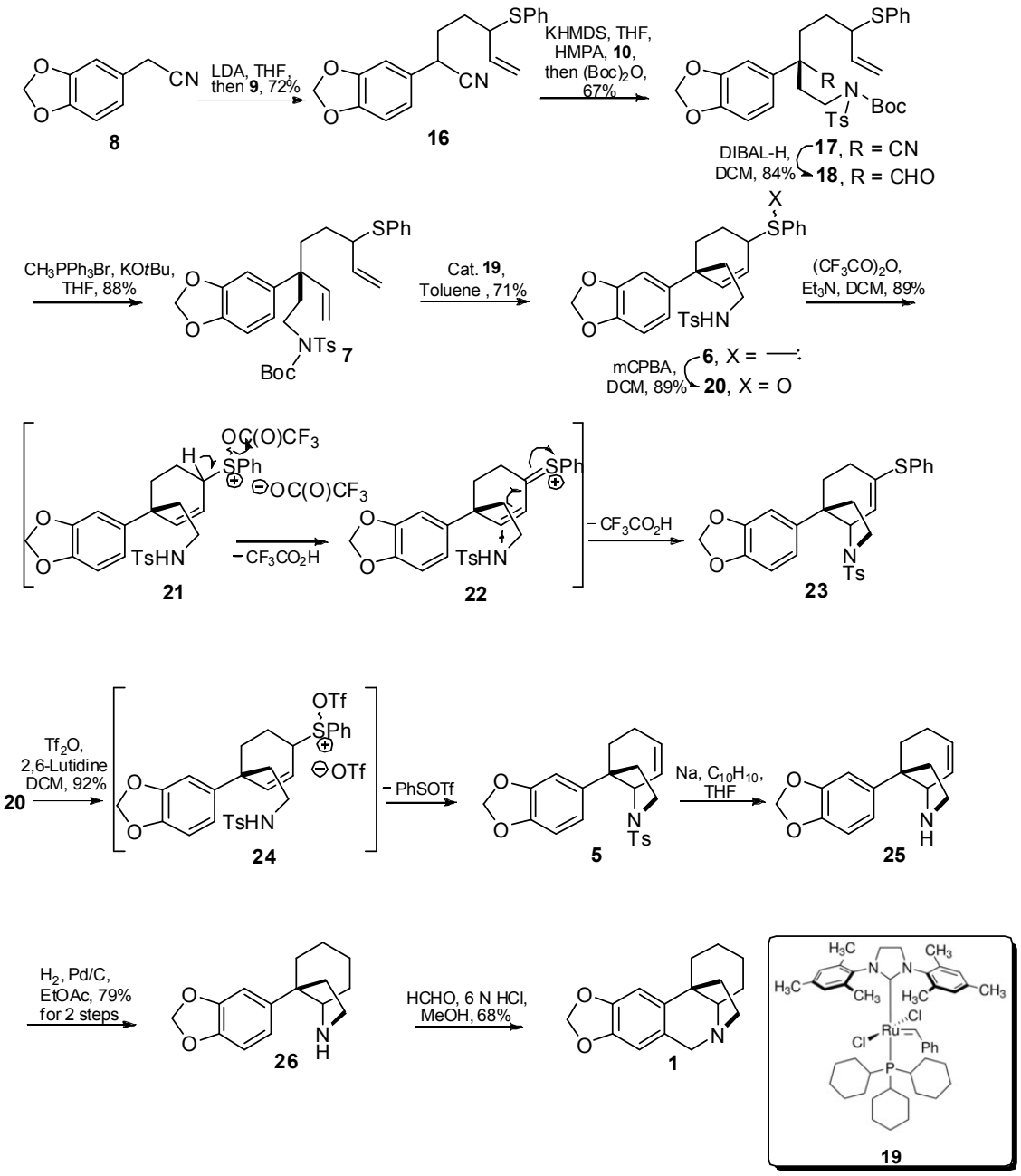
by initial detosylation using sodium naphthalinide[14] to yield the *cis*-arylhydroindole **25** which on reduction of the double bond furnished compound **26**. The secondary amine **26** on reaction with formalin under acidic conditions afforded crinane **1**, Scheme 4.




**Scheme 4.** Synthesis of crinane 1.

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## CONCLUSIONS

In conclusion, a stereoselective synthesis of crinane is disclosed taking advantage of chlorosulfide for C-C bond formation. The key steps include alkylation of a benzylic cyanide to introduce the quaternary carbon, ring-closing metathesis reaction and vinylogous Pummerer type reaction to form the octahydroindole core by C-N bond formation.

## EXPERIMENTAL

***tert*-Butyldimethyl(3-(phenylthio)propoxy)silane (12)**: To a solution of diphenyldisulfide (10.5 g, 48 mmol) in toluene (15 mL) at rt was added a solution of alcohol **11** (7.6 g, 40 mmol) in toluene (10 mL) followed by tri-*n*-butylphospine (11.9 mL, 48 mmol). The reaction mixture was stirred at ambient temperature for 8 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 5% EtOAc/hexane (v/v) as the eluent to afford sulfide **12** as a colorless oil (9 g, 32 mmol) in 80% yield. TLC: $R_f$ = 0.3 (ethyl acetate:hexanes, 1:9); IR (neat): 3059, 2930, 2857, 1475, 1099 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H), 7.29-7.24 (m, 2H), 7.17-7.13 (m, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.01 (t, *J* =7.2 Hz, 2H), 1.87-1.81 (m, 2H), 0.9 (s, 9H), 0.05 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 136.7, 128.8, 128.7, 125.6, 61.3, 32.2, 29.8, 25.9, 18.3, -5.4; MS (ESI) 283 $[M+H]^+$; HRMS (ESI) *m/z* Calcd. for $C_{15}H_{27}OSSi$: 283.1546, found 283.1544.

***tert*-Butyldimethyl((3-(phenylthio)pent-4-en-1-yl)oxy)silane (14)**: To a solution of sulfide **12** (2.80 g, 10 mmol) in anhydrous benzene (100 mL) was added *N*-chlorosuccinimide (1.5 g, 11.5 mmol) at ambient temperature and the mixture stirred for a period of 5 min. The resulting chloro sulfide solution in benzene (100 mL) was added to vinylmagnesium bromide (1 M in THF, 18 mL, 18 mmol) and stirring continued at ambient temperature for 2 h. The reaction was quenched by the addition of aqueous saturated

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ammonium chloride solution (50 mL). The layers were separated and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash column chromatography on silica gel using 4% EtOAc/hexane (v/v) as the eluent afforded allylic sulfide **14** (2.6 g, 8.5 mmol) in 85% yield. TLC: $R_f$ = 0.3 (ethyl acetate:hexanes, 1:9); IR (neat): 3077, 2930, 2858, 1470, 1099 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.41-7.16 (m, 5H), 5.76-5.62 (m, 1H), 4.99-4.86 (m, 2H), 3.87-3.60 (m, 3H), 1.99-1.72 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 138.4, 134.7, 132.3, 128.6, 126.9, 115.8, 60.1, 48.3, 37.0, 25.9, 18.2, -5.3, -5.4; MS (ESI): 309 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{17}H_{29}OSSi$: 309.1702, found 309.1717.

**3-(Phenylthio)pent-4-en-1-ol (15)**: To a solution of allylic sulfide **14** (6.2 g, 20 mmol) in MeOH (20 mL) was added CSA (232 mg, 1.0 mmol) at 0 °C. The resulting mixture was stirred at the same temperature for 30 min. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent to afford the alcohol **15** as a colorless oil (3.5 g, 18 mmol) in 90% yield. TLC: $R_f$ = 0.2 (ethyl acetate:hexanes, 2:8); IR (neat): 3445, 3076, 2932, 2881, 1477, 1048 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.43-7.37 (m, 2H), 7.31-7.21 (m, 3H), 5.79-5.65 (m, 1H), 5.00-4.88 (m, 2H), 3.86-3.67 (m, 3H), 1.99-1.81 (m, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 138.3, 134.0, 132.8, 128.6, 127.2, 115.9, 60.3, 49.0, 36.6; MS (ESI) 233 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{11}H_{14}O_2SNa$: 233.0606, found 233.0604. Note: The sulfide was oxidized to sulfoxide during analysis.

**(5-Iodopent-1-en-3-yl)(phenyl)sulfone (9)**: To a solution of triphenylphosphine (5.8 g, 22.1 mmol) in dichloromethane (40 mL) at rt was added imidazole (1.5 g, 22.1 mmol), iodine (5.6 g, 22.1 mmol) and the mixture stirred for 2 min. The alcohol **15** (3.3 g, 17.0 mmol) in

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dichloromethane (10 mL) was then added to the reaction mixture and stirred at the same temperature. After 3 h, the reaction was quenched with an aq saturated sodium thiosulfate solution (20 mL). The volatiles were removed and the aq solution was extracted with $CHCl_3$ (80 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure to furnish the crude product. Purification of the crude residue via flash column chromatography on silica gel using 5% EtOAc/hexane (v/v) as the eluent afforded sulfide **9** (4.0 g, 13.2 mmol) in 78% yield. TLC: $R_f$ = 0.5 (ethyl acetate:hexanes, 1:9); IR (neat): 3075, 3004, 2924, 1582, 1476, 1208 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.44-7.38 (m, 2H), 7.33-7.24 (m, 3H), 5.73-5.58 (m, 1H), 5.08-4.94 (m, 2H), 3.76-3.65 (m, 1H), 3.41-3.28 (m, 1H), 3.27-3.15 (m, 1H), 2.24-2.00 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 137.0, 133.5, 133.1, 128.8, 127.4, 116.8, 52.4, 37.0, 3.4; MS (ESI): 304 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{11}H_{14}IS$: 304.9855, found 304.9858.

**2-(Benzo[d][1,3]dioxol-5-yl)-5-(phenylthio)hept-6-enenitrile** (**16**):

*n*-BuLi (2.5 M in hexane, 10.4 mL, 26 mmol) was added dropwise to a solution of diisopropylamine (3.8 mL, 27 mmol) in anhydrous THF (57 mL) cooled to –78 °C. The resulting yellow solution was stirred at this temperature for 1 h before a solution of 2-(benzo[*d*][1,3]dioxol-5-yl)acetonitrile **8** (4.3 g, 27 mmol) in anhydrous THF (32 mL) was slowly added via cannula. The mixture was allowed to warm to –40 °C and stirred for 20 min before it was recooled to –78 °C and iodo compound **9** (8.2 g, 27 mmol) in anhydrous THF (20 mL) was introduced and stirred for 1 h. The mixture was warmed to 0 °C and stirred further for a period of 2 h before the reaction was quenched with aq saturated $NH_4Cl$ solution (12 mL). 1 N HCl (10 mL) was then added to adjust the pH to 7. The layers were separated and the aq layer was extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, evaporated and the residue was purified by flash column

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chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford cyanide compound **16** as a yellow oil (6.5 g, 19.4 mmol) in 72% yield. TLC: $R_f$ = 0.3 (ethyl acetate:hexanes, 2:8); IR (neat): 3075, 2921, 2241, 1686, 1249 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.38-7.33 (m, 2H), 7.31-7.22 (m, 3H), 6.82-6.72 (m, 3H), 5.98 (s, 2H), 5.72-5.58 (m, 1H), 5.01-4.82 (m, 2H), 3.75-3.65 (m, 1H), 3.58-3.46 (m, 1H), 2.09-1.92 (m, 2H), 1.87-1.69 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 148.2, 147.4, 137.84, 137.8*, 133.7, 133.6*, 133.1, 128.7, 127.4, 120.7, 120.6*, 116.37, 116.3*, 108.6, 107.51, 107.5*, 101.4, 51.6, 51.5*, 36.6, 36.5*, 33.4, 33.2*, 31.1, 31.0*; MS (ESI): 376 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{20}H_{19}NO_3SNa$: 376.0978, found 376.0981. Note: The $^{13}C$ signals for one of the epimers is denoted by an asterisk mark. The sulfide was oxidized to sulfoxide during analysis.

***tert*-Butyl-(3-(benzo[d][1,3]dioxol-5-yl)-3-cyano-6-(phenylthio)oct-7-en-1-yl)(tosyl)carbamate (17)**: To a solution of sulfide **16** (6.0 g, 18 mmol) in anhydrous THF (36 mL) and HMPA (12 mL) cooled to –60 °C was added KHMDS (0.5 M in toluene, 46.8 mL, 23.4 mmol) via syringe. The reaction was stirred for 30 min and recooled to –78 °C. The solution of *N*-tosyl aziridine **10** (4.6 g, 23.4 mmol) in anhydrous THF (16 mL) and HMPA (8 mL) was added dropwise. The reaction was stirred at same temperature for 2 h and allowed to gradually warm to 0 °C over a period of 2 h. The reaction mixture was quenched by adding $(Boc)_2O$ (8.7 mL, 37.8 mmol) and stirred at same temperature. After 2 h the reaction mixture was diluted with EtOAc (100 mL) and water (100 mL). The layers were separated and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, evaporated and the residue was purified by flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford compound **17** as a colorless oil (7.6 g, 12.0 mmol) in 67% yield. TLC: $R_f$ = 0.5 (ethyl acetate:hexanes, 2:8); IR (neat): 2979, 2930, 1736, 1488, 1156 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.67-7.59 (m, 2H) 7.41-7.34 (m, 2H), 7.32-7.22 (m, 5H), 7.02-6.93 (m, 2H), 6.84-6.77 (m, 1H), 6.02-5.98 (s, 2H), 5.75-5.59 (m,

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1H), 5.03-4.85 (m, 2H), 3.63-3.51 (m, 1H), 3.37-3.20 (m, 2H), 3.18-3.01 (m, 2H), 2.63-2.47 (m, 1H), 2.45-2.27 (m, 4H), 1.96-1.77 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 165.5, 148.4, 148.1, 143.5, 137.6, 135.7, 133.5, 133.1, 129.5, 128.5, 127.5, 127.3, 127.2, 119.7, 117.9, 116.6, 116.5*, 108.5, 106.3, 101.6, 84.6, 52.2, 49.1, 47.1, 47.0*, 45.1, 36.8, 36.7*, 32.8, 27.5, 21.4; MS (ESI): 657 $[M+Na]^+$; HRMS (ESI): *m/z* Calcd. for $C_{34}H_{38}N_2O_6S_2Na$: 657.2063, found 657.2067. Note: The $^{13}$C signals for one of the epimers is denoted by an asterisk mark.

***tert*-Butyl-(3-(benzo[d][1,3]dioxol-5-yl)-3-formyl-6-(phenylthio)oct-7-en-1-yl)(tosyl)carbamate (18)**: To a solution of cyanide **17** (6.8 g, 10.8 mmol) in anhydrous $CH_2Cl_2$ (40 mL) cooled to –78 $^oC$, maintained under nitrogen atmosphere was added DIBAL-H (1.5 M in Toluene, 16.2 mL, 24.3 mmol) dropwise during 15 min and the mixture stirred further for a period of 30 min at 0 $^oC$. The reaction mixture was quenched using an aq saturated solution of sodium potassium tartrate (5 mL) and extracted with $CH_2Cl_2$ (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $Na_2SO_4$ and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford aldehyde **18** (5.7 g, 9.01 mmol) in 84% yield. TLC: $R_f$ = 0.2 (ethyl acetate:hexanes, 2:8); IR (neat): 2978, 2929, 1724, 1487, 1156 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.58-7.52 (m, 2H), 7.33-7.29 (m, 2H), 7.22-7.16 (m, 5H), 6.73 (dd, *J* = 8.2, 3.1 Hz, 1H), 6.58 (t, *J* = 2.3 Hz, 1H), 6.52 (td, *J* = 8.2, 2.0 Hz, 1H) 5.91-5.88 (m, 2H), 5.66-5.55 (m, 1H), 4.94-4.88 (m, 1H), 4.86-4.80 (m, 1H), 3.58-3.47 (m, 1H), 3.30-3.12 (m, 2H), 3.08-2.92 (m, 2H), 2.32 (s, 3H), 2.30-2.14 (m, 2H), 1.90-1.74 (m, 2H), 1.43 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 200.9, 150.7, 148.6, 147.2, 144.3, 138.33, 138.3*, 137.2, 134.5, 134.4*, 132.74, 132.7*, 131.1, 129.3, 128.74, 128.7*, 127.9, 127.2, 127.17*, 121.0, 116.4, 116.2*, 108.7, 107.9, 101.4, 84.5, 84.46*, 56.0, 55.9*, 52.6, 52.5*, 43.2, 43.15*, 31.9, 31.8*,

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29.8, 28.3, 28.2*, 28.0, 21.7; MS (ESI): 638 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{34}H_{40}NO_7S_2$: 638.2241, found 638.2249. Note: The $^{13}C$ signals for one of the epimers is denoted by an asterisk mark.

***tert*-Butyl-(3-(benzo[d][1,3]dioxol-5-yl)-6-(phenylthio)-3-vinyloct-7-enyl)(tosyl)carbamate (7)**: To a solution of methyltriphenylphosphonium iodide (4.3 g, 12 mmol) in anhydrous THF (48 mL) cooled to 0 °C, was added *t*-BuOK (1.4 g, 12.4 mmol) slowly and after being stirred at the same temperature for 10 min, it was warmed to rt rapidly, stirred for 25 min, then cooled to –78 °C and the solution of aldehyde **18** (5.1 g, 8 mmol) in anhydrous THF (12 mL) was added slowly. The reaction mixture was stirred at the same temperature for 1 h, then gradually warmed to rt and stirred for 8 h. The reaction was quenched by adding ice pieces and the mixture was diluted with EtOAc (50 mL). The layers were separated and the organic layer was washed with $H_2O$ (50 mL), brine (50 mL), dried over anhydrous $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 2.5% EtOAc/hexane (v/v) as the eluent to afford diene as a colorless oil **7** (4.4 g, 7.0 mmol) in 88% yield. TLC: $R_f$ = 0.5 (ethyl acetate:hexanes, 3:7); IR (neat): 2977, 2927, 1726, 1160 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.77-7.71 (m, 2H), 7.35-7.15 (m, 7H), 6.85-6.73 (m, 3H), 6.00-5.87 (m, 3H), 5.71-5.57 (m, 1H), 5.31-5.21 (m, 2H), 4.96-4.80 (m, 2H), 3.79-3.57 (m, 2H), 3.55-3.41 (m, 1H), 2.42 (s, 3H), 2.33-2.09 (m, 2H), 1.98-1.78 (m, 2H), 1.65-1.49 (m, 2H), 1.43 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 150.7, 147.6, 145.7, 143.9, 143.6, 143.56*, 138.6, 138.56*, 138.4, 138.36*, 137.3, 134.6, 134.57*, 132.5, 132.4*, 129.1, 128.5, 127.7, 126.8, 120.0, 115.8, 115.7, 114.0, 107.7, 100.8, 84.0, 52.7, 52.6*, 46.4, 44.0, 37.4, 37.2*, 36.2, 28.5, 28.4*, 27.8, 21.5; MS (ESI): 636 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{35}H_{42}NO_6S_2$: 636.2448, found 636.2440. Note: The $^{13}C$ signals for one of the epimers is denoted by an asterisk mark.

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***N*-(2-(1-(Benzo[d][1,3]dioxol-5-yl)-4-(phenylthio)cyclohex-2-en-1-yl)ethyl)-4-methylbenzenesulfonamide (6):** The solution of diene **7** (3.8 g, 6 mmol) in anhydrous toluene (10 mL) was degassed by bubbling $N_2$ for 15 min. Grubbs II generation catalyst **19** (150 mg, 0.18 mmol, 3 mol%) was added, the reaction mixture was refluxed for 12 h and then allowed to attain ambient temperature. Toluene was removed under reduced pressure. The crude reaction mixture was purified via flash column chromatography on silica gel using 3% EtOAc/hexane (v/v) as the eluent to afford sulfide **6** as a colourless oil (2.2 g, 4.3 mmol) in 71% yield. TLC: $R_f$ = 0.5 (ethyl acetate:hexanes, 3:7); IR (neat): 3283, 3021, 2927, 1484, 1158 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.64-7.56 (m, 2H), 7.33-7.28 (m, 2H), 7.24-7.12 (m, 5H), 6.63-6.37 (m, 3H), 5.91-5.82 (m, 3H), 5.74-5.61 (m, 1H), 4.48-4.40 (m, 1H), 3.74-3.60 (m, 1H), 2.87-2.61 (m, 2H), 2.37-2.31 (s, 3H), 2.03-1.96 (m, 1H), 1.86-1.76 (m, 2H), 1.75-1.67 (m, 1H), 1.62-1.33 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 147.7*, 147.6, 145.74*, 145.7, 143.3, 139.62*, 139.5, 136.7, 134.7, 134.0*, 133.8, 132.7, 131.4, 129.6, 129.5*, 128.9*, 128.8, 127.2, 127.0, 126.9*, 120.0, 119.8*, 107.8, 107.1, 100.9, 44.0, 43.5*, 41.8, 41.7*, 41.6*, 41.5, 39.3*, 39.2, 36.2, 32.6*, 25.7, 24.6*, 21.5; MS (ESI): 524 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{30}NO_5S_2$: 524.1560, found 524.1561. Note: The $^{13}C$ signals for one of the epimers is denoted by an asterisk mark. The sulfide was oxidized to sulfoxide during analysis.

***N*-(2-(1-(Benzo[d][1,3]dioxol-5-yl)-4-(phenylsulfinyl)cyclohex-2-en-1-yl)ethyl)-4-methylbenzenesulfonamide (20):** To a solution of allylic sulfide **6** (2.0 g, 4.0 mmol) in dichloromethane (20 mL) cooled to –40 ºC was added *m*CPBA (870 mg, 4.0 mmol) and the reaction mixture stirred at the same temperature for another 1 h. The mixture was diluted with dichloromethane (10 mL) and the layers separated. The combined organic layers were washed successively with aq saturated $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure to furnish the crude

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compound which was purified by column chromatography using 30% ethyl acetate/hexanes (v/v) as the eluent to afford the sulfoxide **20** (1.86 g, 3.6 mmol) in 89% yield as a liquid. TLC: $R_f$ = 0.2 (ethyl acetate:hexanes, 4:6); IR (neat): 3272, 2930, 2924, 1156 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.80-7.75 (m, 2H), 7.72-7.49 (m, 5H), 7.32-7.27 (m, 2H), 6.74-6.56 (m, 3H), 6.25 (d, *J* = 10.5 Hz, 1H), 5.94-5.90 (m, 2H), 5.53 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.28-3.16 (m, 1H), 3.06-2.91 (m, 2H), 2.41 (m, 3H), 2.22-2.08 (m, 2H), 2.00-1.79 (m, 4H); MS (ESI): 524 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{30}NO_5S_2$: 524.1560, found 524.1574.

**(3a*R*,7a*R*)-3a-(Benzo[*d*][1,3]dioxol-5-yl)-1-tosyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (5)**: Trifluoromethanesulfonic anhydride (0.21 mL, 1.3 mmol) was added to a mixture of the solution of sulfoxide **20** (523 mg, 1.0 mmol) and 2,6-lutidine (0.18 mL, 1.6 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at –78 $^oC$. A bright yellow color was observed instantaneously and the reaction was completed in 2 min as evidenced by TLC. Ice-cold water (15 mL) was added and the cooling bath was removed, allowing the mixture to warm to room temperature. The two layers were separated and the aq phase was extracted with dichloromethane (3 x 20 mL). The combined organic layer were washed successively with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 20% ethyl acetate/hexanes (v/v) as the eluent to afford the sulfonamide compound **5** (365 mg, 0.92 mmol) in 92% yield as a liquid. TLC: $R_f$ = 0.4 (ethyl acetate:hexanes, 3:7); IR (neat): 3006, 2924, 1596, 1160 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.61-6.47 (m, 3H), 6.19-6.11 (m, 1H), 5.95-5.87 (m, 3H), 4.12-4.07 (m, 1H), 3.60-3.49 (m, 1H), 3.41-3.30 (m, 1H), 2.37 (s, 3H), 2.15-1.94 (m, 2H), 1.82-1.72 (m, 2H), 1.66-1.58 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 147.6, 145.8, 143.0, 139.0, 135.0, 129.4, 129.2, 127.9, 127.2, 118.7, 107.8, 106.6, 100.9, 61.7, 47.8, 46.0, 34.7, 32.1, 21.9, 21.4; MS (ESI): 398 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{22}H_{24}NO_4S$: 398.1421, found 398.1422.

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DOI: 10.1039/C6OB01966H



**(3a*R*,7a*R*)-3a-(Benzo[d][1,3]dioxol-5-yl)octahydro-1*H*-indole (26)**:

To a solution of sulfonamide **5** (135 mg, 0.45 mmol) in DME (1.8 mL) was added a solution of sodium naphthalenide (0.8 M, 5.6 mL, 4.5 mmol) dropwise at –78 $^{o}$C until the deep green color of nahthalenide remained. The reaction mixture was stirred at the same temperature for 30 min, then gradually warmed to rt and stirred for 1 h. The reaction was quenched by adding ice pieces and the mixture was diluted with EtOAc (50 mL). The layers were separated and the organic layer was washed with $H_2O$ (50 mL), brine (50 mL), dried over anhydrous $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure to afford crude allylic amine **26** which was used in the next step without furtehr purification. To a solution of the above crude product (110 mg, 0.45 mmol) in EtOAc (3 mL) was added 10% Pd/C (20 mg) and the reaction mixture was stirred under hydrogen atmosphere at ambient temperature overnight. The reaction mixture was filtered through a small pad of Celite and washed with EtOAc (2 X 10 mL). The combined organic layers were washed successively with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 30% ethyl acetate/hexanes (v/v) as the eluent to afford the amine **27** (87 mg, 0.35 mmol) in 79% yield as a liquid. TLC: $R_f$ = 0.2 (ethyl acetate:hexanes, 3:7); IR (neat): 3277, 3075, 2921, 1249 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): δ 6.91-6.69 (m, 3H), 5.93 (s, 2H), 3.50-2.26 (m, 2H), 3.24-2.95 (m, 2H), 2.10-1.14 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 147.6, 145.2, 140.7, 119.4, 107.7, 107.5, 100.8, 60.9, 47.9, 42.9, 41.2, 33.8, 26.0, 22.0, 21.0; MS (ESI): 246 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{15}H_{20}NO_2$: 246.1489, found 246.1484.

**(4a*R*,11b*R*)-1,2,3,4,4a,6-Hexahydro-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridine (1)**:

To a solution of amine **27** (48 mg, 0.2 mmol) in MeOH (1.2 mL) was added formaldehyde (37% aq solution, 1.0 mL). After 10 min, the reaction mixture was treated with HCl (6 M, 2.5 mL) at rt. The mixture was warmed to 50 °C and stirred for 9 h. After cooling to rt, the

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reaction mixture was basified by the addition of solid $K_2CO_3$ and then extracted with $CH_2Cl_2$ (2 X 5 mL). The combined organic layer were washed successively with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 25% ethyl acetate/hexanes (v/v) as the eluent to afford the crinane **1** (32 mg, 0.13 mmol) in 68% yield as a liquid. TLC: $R_f$ = 0.6 (ethyl acetate:hexanes, 3:7); IR (neat): 3075, 3004, 2924, 1208 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.45 (s, 1H), 5.88 (s, 2H), 4.33 (d, *J* = 16.8 Hz, 1H), 3.74 (d, *J* = 16.8 Hz, 1H), 3.36-3.28 (m, 1H), 2.85-2.75 (m, 2H), 2.37-2.31 (m, 1H), 2.24-2.16 (m, 1H), 1.81-1.45 (m, 6H), 1.29-1.18 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 146.1, 145.4, 141.8, 125.3, 106.0, 103.1, 100.5, 67.2, 61.7, 51.7, 42.7, 37.5, 28.7, 27.2, 24.1, 21.5; MS (ESI): 258 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{16}H_{20}NO_2$: 258.1489, found 258.1484.

**3a-(Benzo[*d*][1,3]dioxol-5-yl)-6-(phenylthio)-1-tosyl-2,3,3a,4,5,7a-hexahydro-1*H*-indole (23):** Trifluoroacetic anhydride (0.21 mL, 1.3 mmol) was added to a solution of the mixture of sulfoxide **20** (523 mg, 1.0 mmol) and $Et_3N$ (0.18 mL, 1.6 mmol) in anhydrous $CH_2Cl_2$ (20 mL) at –0 $^oC$. The reaction mixture was stirred at the same temperature for 1 h and the cooling bath was removed, allowing the mixture to warm to room temperature. The reaction mixture was diluted with dichloromethane (3 x 20 mL). The combined organic layers were washed successively with water (10 mL), brine (10 mL), dried over $Na_2SO_4$ and the solvent evaporated under reduced pressure to furnish the crude compound which was purified by column chromatography using 20% ethyl acetate/hexanes (v/v) as the eluent to afford the sulfide **23** (0.44 g, 0.89 mmol) in 89% yield as a liquid.TLC: $R_f$ = 0.2 (ethyl acetate:hexanes, 3:7); IR (neat): 2925, 2854, 1721, 1159 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.37- 7.27 (m, 5H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.49 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.30-6.27 (m, 1H), 5.92 (d, *J* = 1.5 Hz, 1H), 5.91

View Article Online
DOI: 10.1039/C6OB01966H



(d, $J$ = 1.5 Hz, 1H), 4.23 (d, $J$ = 4.1 Hz, 1H), 3.57-3.50 (m, 1H), 3.45-3.38 (m, 1H), 2.46-2.39 (m, 1H), 2.38 (s, 3H), 2.12-1.99 (m, 3H), 1.89-1.76 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 147.6, 146.0, 143.1, 138.3, 136.4, 135.1, 132.8, 132.3, 129.4, 129.1, 127.6, 127.4, 127.2, 118.7, 107.9, 106.6, 101.0, 62.8, 47.4, 46.1, 35.0, 33.1, 26.5, 21.4; MS (ESI): 506 $[M+H]^+$; HRMS (ESI): *m/z* Calcd. for $C_{28}H_{28}NO_4S_2$: 506.1454, found 506.1458.

**Supplementary Information**

Spectroscopic characterization data.

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8 Attempted regioselective 1,4-addition of thiophenol to methyl sorbate followed by LAH reduction to secure alcohol **15** was unsuccessful. A complex mixture of products resulted from the thiophenol addition reaction.

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View Article Online
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11 It was observed that the reduction of the nitrile to the aldehyde and subsequent Wittig olefination reaction proceeded more cleanly when the sulfonamide was further protected as its carbamate.

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**Table of Contents**