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Synthesis of the Core Ring System of the Yuzurimine-Type *Daphniphyllum* Alkaloids by Cascade Condensation, Cyclization, Cycloaddition Chemistry

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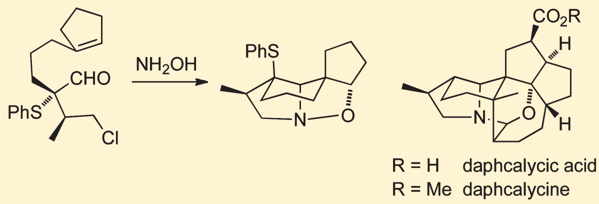
Supporting Information

ABSTRACT: Addition of hydroxylamine to substituted 4-chlorobutanals gives intermediate nitrones that undergo tandem cyclization and then intramolecular dipolar cycloaddition to give the core ring system of the yuzurimine-type natural products. Ring-opening of the isoxazolidines gives amino alcohols that can be converted to 1,3-oxazines, representing the tetracyclic core of alkaloids such as daphcalycic acid and daphcalycine.



The *Daphniphyllum* alkaloids are a structurally diverse family of natural products that are derived from evergreen shrubs and trees found in Japan and southeast Asia.[1−3] Many *Daphniphyllum* alkaloids have been discovered, and presently, there are over 200 of these alkaloids from more than 10 species of the genus *Daphniphyllum*. These alkaloids are generally classified by the structures of daphniphylline, secodaphniphylline, yuzurimine, daphnilactones A and B, and yuzurine, although other structural types are also known. The biosynthesis of these alkaloids arises from modification of squalene, and this has inspired the biomimetic synthesis of some of the members of these alkaloids.[4−8] Despite the large number of these alkaloids, there are only a few approaches to the core ring systems of these structurally complex compounds.[9−16]

We have recently reported a cascade of reactions involving condensation of an aldehyde and primary amine, in situ cyclization, then cycloaddition of the resulting 1,3-dipole.[17−22] This chemistry allows an efficient stereoselective access to tricyclic nitrogen-containing products. We therefore considered if this strategy could access the core of some of the *Daphniphyllum* alkaloids. In particular, the core tricyclic ring system of some of the yuzurimine alkaloids caught our attention. These alkaloids have two fused cyclopentane rings, one of which is spiro-fused to a cyclohexane ring, and some representative examples are shown in Figure 1. Daphcalycic acid[23] and daphcalycine[24] (and daphcalycinosidine A, in which R is an iridoid glucoside)[23] have a 1,3-oxazine ring, whereas other members of the yuzurimine type alkaloids, such as daphnioldhanin A[25] and daphlongamine D,[26] have a tertiary alcohol group. We are not aware of any reported syntheses or of any synthetic approaches toward these alkaloids.

The core ring system of these yuzurimine alkaloids and a retrosynthesis is shown in Scheme 1. The 1,3-oxazine (*N*,*O*-acetal) **1** and the amino alcohol **2** could be derived from the isoxazolidine **3**. Disconnection of the isoxazolidine **3** using a

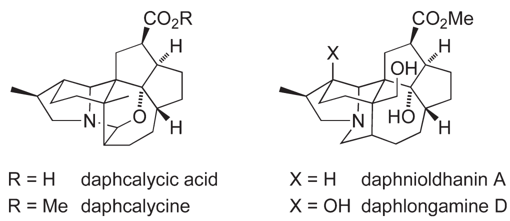


Figure 1. Some yuzurimine alkaloids.

dipolar cycloaddition for the forward direction suggests that we could use the aldehyde **4**. Condensation of this aldehyde with hydroxylamine should give the desired isoxazolidine **3** by a cascade of condensation to the oxime, cyclization to the nitrone, and dipolar cycloaddition.[27,28] This paper reports the results of this study and the first synthesis of the core ring system of the yuzurimine-type *Daphniphyllum* alkaloids.

We have recently reported that heating the aldehydes **5** with hydroxylamine hydrochloride and $^{i}Pr_2NEt$ in toluene gave the tricyclic products **6** or **7** (Scheme 2).[19] When two of the three rings in the new tricyclic product are five-membered then the all-*cis* stereoisomer is formed.[18] We therefore anticipated that the cascade chemistry with the aldehyde **4** would lead to the desired stereoisomer of the product **3**.

Initially, we prepared the related aldehyde **10**, starting from 6-heptenenitrile, using alkylation to give the alcohol **8**, conversion to the chloride **9**, and DIBAL-H reduction (Scheme 3). Disappointingly, no tricyclic product was obtained from heating aldehyde **10** with hydroxylamine, and instead, the pyrrole **12** and decomposed material were formed.

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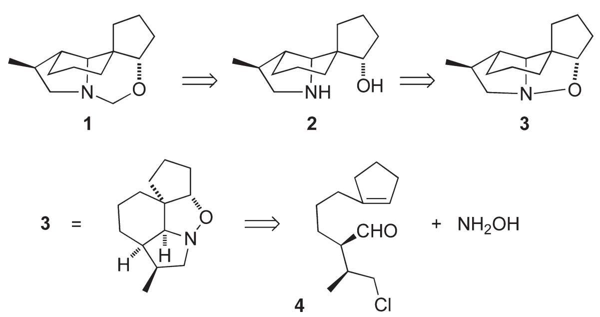
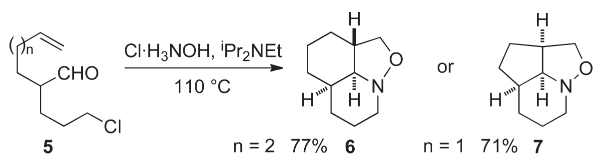
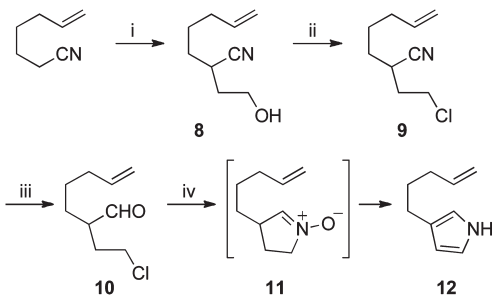
Scheme 1. Retrosynthetic Disconnection of the Core Ring System 1



Scheme 2. Previous Syntheses of Isoxazolidines[19]



Scheme 3. Model Studies with the Aldehyde 10[a]

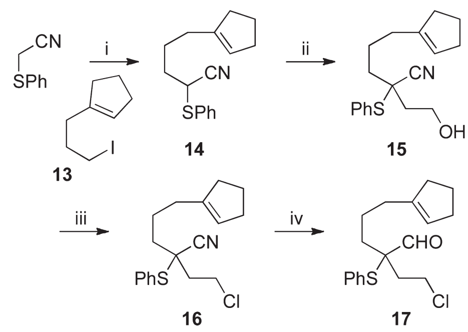


[a] Reagents and conditions: (i) LDA, $BrCH_2CH_2OTMS$, THF, −78 °C, then $HCl_{(aq)}$, 65%; (ii) PPh_3, *N*-chlorosuccinimide, THF, 67%; (iii) DIBAL-H, CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 72%; (iv) $NH_2OH \cdot HCl$, $^iPr_2NEt$, PhMe, 110 °C, 29%.

The pyrrole **12** may arise from the ability of the nitrone intermediate **11** to tautomerize followed by dehydration to the aromatic ring system. Alternatively, formation of the oxime then cyclization to a six-membered cyclic oxime (sometimes called a dihydro-1,2-oxazine), followed by tautomerism, fragmentation and recombination could lead to the pyrrole.[29] To prevent this process, we chose to block enamine formation with a phenylthio substituent alpha to the aldehyde. Hence, starting with phenylthioacetonitrile, alkylation with the known iodide **13**[30,31] gave the nitrile **14**. A second alkylation gave the alcohol **15** which was converted to the chloride **16** and, hence, after DIBAL-H reduction, the aldehyde **17** (Scheme 4).

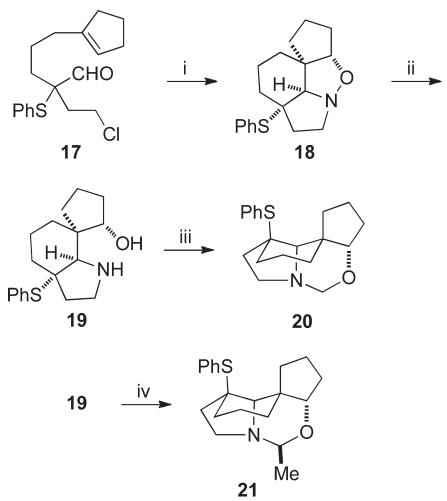
Heating the aldehyde **17** with hydroxylamine hydrochloride and $^iPr_2NEt$ in toluene under reflux gave the expected product **18** as a single stereoisomer (Scheme 5). Alternatively, heating at 60 °C gave the intermediate oxime (66% yield) that could be converted to the cycloadduct **18** in high (95%) yield. The stereochemistry of the product was determined by X-ray crystal structure analysis of the amino alcohol **19** (see the Supporting Information), formed after reductive ring-opening with zinc/acetic acid. This showed that the product had the desired stereochemistry which must have arisen from cycloaddition to the *cis*-fused product with suprafacial reaction of the cyclopentene dipolarophile.

Scheme 4. Synthesis of the Aldehyde 17[a]



[a] Reagents and conditions: (i) LDA, **13**, THF, −78 °C, 73%; (ii) LDA, $BrCH_2CH_2OTMS$, THF, −78 °C, then $HCl_{(aq)}$, 88%; (iii) PPh_3, *N*-chlorosuccinimide, THF, 83%; (iv) DIBAL-H, CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 56%.

Scheme 5. Cycloaddition Using the Aldehyde 17[a]

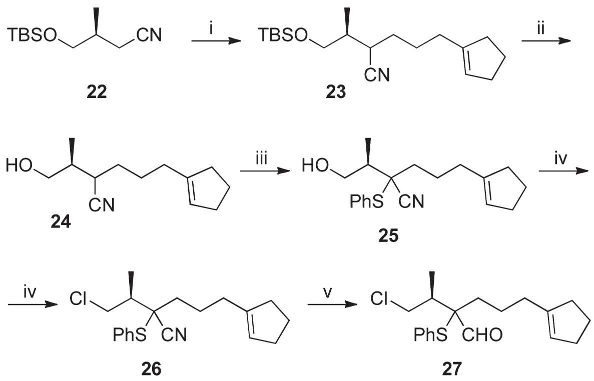


[a] Reagents and conditions: (i) $NH_2OH \cdot HCl$, $^iPr_2NEt$, PhMe, 110 °C, 60%; (ii) Zn, AcOH, H_2O, 90 °C, 91%; (iii) $(CH_2O)_n$, 5 mol % TsOH, $CHCl_3$, 80 °C, 70%; (iv) MeCHO, 5 mol % TsOH, $CHCl_3$, 80 °C, 57%.

The amino-alcohol **19** represents the core ring structure of some of the yuzurimine type alkaloids (see Figure 1). The 1,3-oxazine ring present in other yuzurimine type alkaloids was formed from amino-alcohol **19** by simple heating with paraformaldehyde and *p*-toluenesulfonic acid to give **20**, or with acetaldehyde to give **21**, which was formed as a single stereoisomer. The stereochemistry of the acetal **21** was determined by ^1H NOESY experiments. This chemistry therefore provides a method to prepare the tetracyclic core of the alkaloid daphcalycic acid (and its ester derivatives).

An attempt to remove the phenylthio group from the cycloadduct **18** using sodium amalgam (Na/Hg, MeOH, Na_2HPO_4, room temperature) gave only the amino alcohol **19** (75% yield). Rather than pursue alternative methods for desulfenylation, we decided to explore the preparation of the methyl-substituted derivative **4** containing a phenylthio substituent to block pyrrole formation.

Scheme 6. Synthesis of the Aldehyde 27[a]



[a] Reagents and conditions: (i) LDA, THF, **13**, −78 °C, 98%; (ii) Bu_4NF, THF, 82%; (iii) ^iPrMgCl, THF, −78 °C, PhSSPh, 92% (or $PhSSO_2Ph$, 85%); (iv) polymer-bound triphenylphosphine (diphenylphospinated polystyrene cross-linked with divinylbenzene), CCl_4, CH_2Cl_2, 90%; (v) DIBAL-H, CH_2Cl_2, −78 °C, then $HCl_{(aq)}$, 65%.

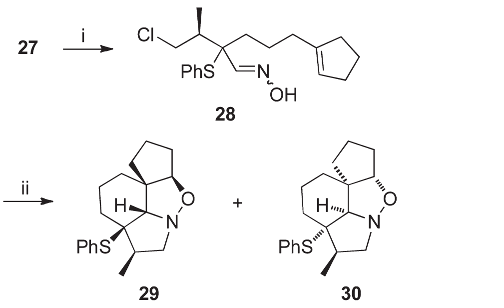
The nitrile **22** (Scheme 6) was prepared from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate using a known procedure.[32] Alkylation using LDA and the iodide **13** proceeded smoothly to give the nitrile **23** as a mixture of diastereoisomers (dr 2:1 by ^{1}H NMR spectroscopy, major isomer unknown). Treatment of the nitrile **23** with LDA followed by attempted sulfenylation with PhSSPh or $PhSSO_2Ph$ (or alkylation with MeI) gave only recovered starting material **23**. We therefore removed the silyl protecting group to give the nitrile **24**. This compound also failed to undergo sulfenylation using LDA, PhSSPh. However, following precedent from Fleming and co-workers,[33] treatment with ^iPrMgCl then sulfenylation gave the desired product **25**. Using $PhSSO_2Ph$ as the electrophile, the nitrile **25** was formed as a 1:1 (inseparable) mixture of diastereoisomers, whereas PhSSPh as the electrophile gave the nitrile **25** as a 2:1 mixture of diastereoisomers (major isomer unknown at this stage).

We expected that, using the same procedure as before, the nitrile **25** could be converted to the aldehyde **27**. The product **26**, from chlorination of **25** (dr 2:1) with *N*-chlorosuccinimide and PPh_3 was inseparable from the byproduct Ph_3PO and the mixture was detrimental to the following reduction step. Therefore, the chlorination was conducted using polymer-supported phosphine and CCl_4.[34] Finally, reduction of the nitrile **26** with DIBAL-H gave the desired aldehyde **27**. This was formed as an inseparable mixture of diastereoisomers (dr 7:3).

Heating the mixture of diastereoisomeric aldehydes **27** with hydroxylamine hydrochloride at 60 °C gave the intermediate oximes **28** that were heated under reflux in toluene to give two separable cycloadducts **29** and **30** (ratio 7:3) (Scheme 7). The stereochemistry of the minor isomer **30** was established by single-crystal X-ray analysis (see the Supporting Information). The stereochemistry of the major isomer **29** was determined by ^{1}H NMR spectroscopy (NOESY).

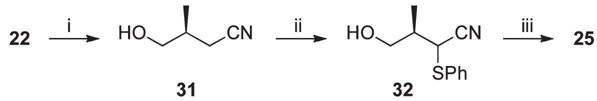
The formation of the isomer **30** as the minor product indicates that the sulfenylation reaction of the magnesium (di)anion of nitrile **24** with PhSSPh took place to give predominantly the undesired diastereoisomer of the nitrile **25** (dr 2:1). Therefore, we attempted an inverse order of alkylation, where the phenylthio group was added before the alkyl halide. Nitrile **31**, prepared by desilylation of nitrile **22**, was converted to the nitrile **32** (dr 3:1, major isomer unknown) (Scheme 8). Subsequent alkylation using ^iPrMgCl (and the iodide **13**) was unsuccessful and gave the product **24** (60% yield, dr 2:1), formed by desulfenylation then alkylation. Using LDA and iodide **13**, the product **25** was formed; however, the diastereoisomer ratio was low (dr 2:1) and the major diastereoisomer was the same (as judged by ^{1}H NMR spectroscopy) as that formed from nitrile **24** (Scheme 6).

Scheme 7. Cycloaddition Using the Aldehyde 27[a]



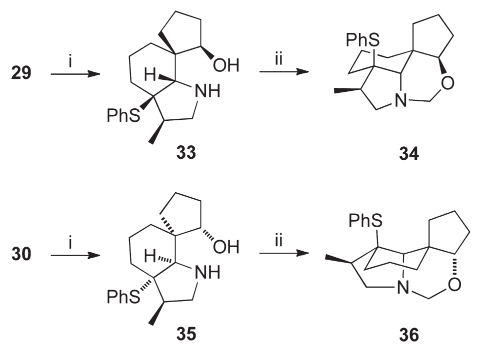
[a] Reagents and conditions: (i) $NH_2OH\cdot HCl$, $^iPr_2NEt$, PhMe, 60 °C, 16 h, 72%; (ii) PhMe, 110 °C, 16 h, 80%.

Scheme 8. Alternative Synthesis of Nitrile 25[a]



[a] Reagents and conditions: (i) Bu_4NF, THF, 90%; (ii) ^iPrMgCl, THF, −78 °C, PhSSPh, 80%; (iii) LDA, THF, **13**, −78 °C, 83%.

Scheme 9. Completion of the Synthesis of the Core Ring System[a]



[a] Reagents and conditions: (i) Zn, AcOH, H_2O, 90 °C, 99% for **33**, 95% for **35**; (ii) $(CH_2O)_n$, 5 mol % TsOH, $CHCl_3$, 65 °C, 79% for **34**, 61% for **36**.

The separated cycloadducts **29** and **30** were converted to the amino alcohols **33** and **35** and hence to the 1,3-oxazines **34** and **36** (Scheme 9). The formation of the 1,3-oxazine **36** represents the desired framework of the core of some of the yuzurimine alkaloids, including daphcalycic acid and daphcalycine.

In summary, we have shown that a cascade of condensation, cyclization then intramolecular dipolar cycloaddition reactions can be used to construct the tricyclic core of the yuzurimine alkaloids, including the spirocyclic cyclohexane and cyclopentane rings. This tricyclic arrangement can be converted easily to the tetracyclic core containing a 1,3-oxazine ring. A phenylthio group was used to prevent pyrrole formation. The cascade chemistry, in particular the cycloaddition step, is stereoselective for a single stereoisomer of the tricyclic product. The results could form the basis for a synthesis of this type of *Daphniphyllum* alkaloid.

EXPERIMENTAL SECTION

2-(2-Hydroxyethyl)hept-6-enenitrile 8. *n*-Butyllithium (9.60 mL, 24 mmol, 2.5 M) was added to diisopropylamine (3.55 mL, 25 mmol) in THF (25 mL) at −78 °C. After 10 min, heptenenitrile (2.57 mL, 20 mmol) then 2-bromoethyl trimethylsilyl ether (4.30 g, 22 mmol) were added, and the mixture was warmed to room temperature. After 16 h, HCl (2 M, 10 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (9:1 to 0:1), gave nitrile **8** (1.96 g, 65%) as an oil: IR ν_{max} (film)/cm^{-1} 3270, 2940, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* 17, 10, 6.5 Hz, 1H), 5.11−4.98 (m, 2H), 3.86 (t, *J* 5.5 Hz, 2H), 2.91−2.80 (m, 1H), 2.19−2.07 (m, 2H), 1.90−1.80 (m, 2H), 1.75−1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 122.1, 115.3, 59.3, 34.7, 33.0, 31.4, 28.0, 26.2; HRMS (ES) found 154.1232, $C_9H_{16}NO$ requires MH$^+$ 154.1236.

2-(2-Chloroethyl)hept-6-enenitrile 9. Alcohol **8** (1.90 g, 12.4 mmol) was added to PPh_3 (4.88 g, 18.6 mmol) and *N*-chlorosuccinimide (1.80 g, 13.6 mmol) in THF (25 mL) at 0 °C, and the mixture was warmed to room temperature. After 16 h, the solvent was evaporated, and water was added. The mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), evaporated, filtered over Celite, and washed with petroleum ether, and the solvent was evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (97:3), gave nitrile **9** (1.43 g, 67%) as an oil: IR ν_{max} (film)/cm^{-1} 2960, 2235, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* 17, 10, 6.5 Hz, 1H), 5.12−4.98 (m, 2H), 3.78−3.66 (m, 2H), 2.96−2.86 (m, 1H), 2.21−2.07 (m, 3H), 2.05−1.94 (m, 1H), 1.75−1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 121.0, 115.6, 41.7, 35.0, 33.0, 31.1, 28.9, 26.2; HRMS (ES) found 172.0893, $C_9H_{15}N^{35}Cl$ requires MH$^+$ 172.0896.

2-(2-Chloroethyl)hept-6-enal 10. DIBAL-H (10 mL, 10 mmol, 1.0 M in hexanes) was added to nitrile **9** (1.40 g, 8.2 mmol) in CH_2Cl_2 (40 mL) at −78 °C. After 1.5 h, aqueous HCl (2 M, 5 mL) was added. After 30 min, the mixture was warmed to room temperature, extracted with Et_2O (6 × 25 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (99:1), gave aldehyde **10** (1.02 g, 72%) as an oil: IR ν_{max} (film)/cm^{-1} 2935, 1725, 1640, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 5.80 (ddt, *J* 17, 10, 6.5 Hz, 1H), 5.08−4.96 (m, 2H), 3.66−3.52 (m, 2H), 2.65−2.56 (m, 1H), 2.26−2.15 (m, 1H), 2.15−2.05 (m, 2H) 1.92−1.80 (m, 1H), 1.79−1.64 (m, 1H), 1.58−1.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 137.9, 115.2, 48.9, 42.5, 33.6, 31.2, 27.9, 26.0; HRMS (ES) found 175.0890, $C_9H_{16}O^{35}Cl$ requires MH$^+$ 175.0883.

3-(Pent-4-enyl)-1*H*-pyrrole 12. The aldehyde **10** (0.50 g, 2.86 mmol), hydroxylamine hydrochloride (0.30 g, 4.29 mmol), and diisopropylethylamine (1.50 mL, 8.58 mmol) in PhMe (30 mL) were heated under reflux. After 1.5 h, the mixture was adsorbed onto silica. Purification by column chromatography, eluting with petroleum ether−EtOAc (19:1), gave pyrrole **12** (0.14 g, 29%) as an oil: IR ν_{max} (film)/cm^{-1} 3370, 2925, 1680, 1640, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 6.76 (q, *J* 2.5 Hz, 1H), 6.62 (d, *J* 1 Hz, 1H), 6.18−6.11 (m, 1H), 5.89 (ddt, *J* 17, 10, 6.5 Hz, 1H), 5.14−4.96 (m, 2H), 2.56 (t, *J* 7.5 Hz, 2H), 2.16 (q, *J* 7.5 Hz, 2H), 1.73 (quin, *J* 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 124.2, 117.7, 115.0, 114.4, 108.6, 33.6, 30.4, 26.4; HRMS (ES) found 135.1053, $C_9H_{13}N$ requires MH$^+$ 135.1048.

5-Cyclopentenyl-2-(phenylthio)pentanenitrile 14. *n*-Butyllithium (1.36 mL, 3.7 mmol, 2.5 M in hexanes) was added to diisopropylamine (0.52 mL, 3.4 mmol) in THF (5 mL) at −78 °C. After 10 min, phenythioacetonitrile (0.42 mL, 3.23 mmol) and then iodide **13**[30] (0.80 g, 3.39 mmol) were added, and the mixture was warmed to room temperature. After 3 h, saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (99:1), gave nitrile **14** (0.61 g, 73%) as an oil: IR ν_{max} (film)/cm^{-1} 2940, 2840, 2235, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.59 (m, 2H), 7.46−7.38 (m, 3H), 5.40−5.35 (m, 1H), 3.73 (t, *J* 7 Hz, 1H), 2.36−2.28 (m, 2H), 2.28−2.20 (m, 2H), 2.18−2.11 (m, 2H), 1.94−1.81 (m, 4H), 1.80−1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 134.5, 130.5, 129.5 (overlapping signals), 124.5, 119.3, 37.1, 34.9, 32.4, 32.1, 30.2, 25.0, 23.4; HRMS (ES) found 258.1314, $C_{16}H_{20}NS$ requires MH$^+$ 258.1316.

5-Cyclopentenyl-2-(2-hydroxyethyl)-2-(phenylthio)pentanenitrile 15. In the same way as **8**, *n*-butyllithium (0.96 mL, 2.4 mmol, 2.5 M in hexanes), diisopropylamine (0.37 mL, 2.63 mmol), nitrile **14** (0.59 g, 2.29 mmol), and 2-bromoethyl trimethylsilyl ether (0.58 g, 2.98 mmol) gave, after purification by column chromatography, eluting with petroleum−EtOAc (17:3), nitrile **15** (0.59 g, 88%) as an oil: IR ν_{max} (film)/cm^{-1} 3340, 2945, 2845, 2250, 1650, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.66 (m, 2H), 7.52−7.40 (m, 3H), 5.39−5.34 (m, 1H), 3.96 (q, *J* 6.5 Hz, 2H), 2.36−2.27 (m, 2H), 2.26−2.18 (m, 2H), 2.17−1.99 (m, 4H), 1.96−1.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.1, 130.4, 129.3, 129.0, 124.5, 121.4, 59.1, 47.6, 39.1, 37.2, 34.5, 32.4, 30.6, 23.4, 22.9; HRMS (ES) found 302.1575, $C_{18}H_{24}NOS$ requires MH$^+$ 302.1579.

2-(2-Chloroethyl)-5-cyclopentenyl-2-(phenylthio)pentanenitrile 16. In the same way as **9**, PPh_3 (0.78 g, 3.0 mmol), *N*-chlorosuccinimide (0.29 g, 2.2 mmol), and alcohol **15** (0.58 g, 1.9 mmol) gave, after purification by column chromatography, eluting with petrol−EtOAc (99:1), nitrile **16** (0.51 g, 83%) as an oil: IR ν_{max} (film)/cm^{-1} 2945, 2840, 2250, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 2H), 7.54−7.41 (m, 3H), 5.40−5.36 (m, 1H), 3.76 (td, *J* 10.5, 6 Hz, 1H), 3.70 (td, *J* 10.5, 6 Hz, 1H), 2.37−2.18 (m, 6H), 2.12 (bs, 2H), 1.93−1.59 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 137.1, 130.6, 129.5, 128.5, 124.5, 120.0, 48.2, 39.4, 38.9, 36.7, 34.9, 32.4, 30.5, 23.4, 22.9; HRMS (ES) found 320.1241, $C_{18}H_{23}NS^{35}Cl$ requires MH$^+$ 320.1240.

2-(2-Chloroethyl)-5-cyclopentenyl-2-(phenylthio)pentanal 17. In the same way as **10**, DIBAL-H (3.12 mL, 3.12 mmol, 1.0 M in hexanes) and nitrile **16** (0.50 g, 1.56 mmol) gave, after purification by column chromatography, eluting with petroleum ether−EtOAc (99:1), aldehyde **17** (0.28 g, 56%) as an oil: IR ν_{max} (film)/cm^{-1} 2945, 1715, 1475, 1440; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.46−7.31 (m, 5H), 5.40−5.36 (m, 1H), 3.80 (td, *J* 10.5, 5.5 Hz, 1H), 3.58 (td, *J* 10.5, 5.5 Hz, 1H), 2.37−2.28 (m, 2H), 2.27−2.07 (m, 5H), 2.06−1.95 (m, 1H), 1.94−1.82 (m, 2H), 1.80−1.54 (m, 3H), 1.47−1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 143.1, 137.1, 130.0, 129.3, 128.3, 124.5, 62.5, 39.5, 35.0, 32.4, 32.3, 31.1, 30.1, 23.4, 22.3; HRMS (ES) found 323.1237, $C_{18}H_{24}OS^{35}Cl$ requires MH$^+$ 323.1236.

Cycloadduct 18. Aldehyde **17** (0.27 g, 0.84 mmol), hydroxylamine hydrochloride (0.09 g, 1.26 mmol), and diisopropylethylamine (0.67 mL, 2.52 mmol) in PhMe (8 mL) were heated to 60 °C. After 1.5 h, the mixture was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (49:1), gave the intermediate oxime (0.19 g, 66%) as an oil (1:1 mixture of isomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.53 (m, 2H), 7.49−7.37 (m, 3H), 6.84 (d, *J* 1.5 Hz, 0.5H), 6.84 (d, *J* 1.5 Hz, 0.5H), 5.39−5.36 (m, 1H), 3.70−3.60 (m, 1H), 3.18−3.07 (m, 1H), 2.44−2.37 (m, 2H), 2.36−2.29 (m, 2H), 2.28−2.21 (m, 2H), 2.17−2.09 (m, 2H), 1.93−1.54 (m, 6H). This oxime (0.18 g, 0.53 mmol) in PhMe (5.5 mL) was heated under reflux. After 16 h, the mixture was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (99.5:0.5), gave cycloadduct **18** (0.15 g, 95%) as an oil: IR ν_{max} (film)/cm^{-1} 2935, 2855, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.51 (m, 2H), 7.44−7.31 (m, 3H), 4.11 (d, *J* 5 Hz, 1H), 3.46 (td, *J* 12.5, 6 Hz, 1H), 3.39−3.32 (m, 1H), 3.31 (s, 1H), 2.22 (td, *J* 12.5, 6 Hz, 1H), 2.06−1.95 (m, 2H), 1.94−1.80 (m, 3H), 1.79−1.66 (m, 3H), 1.64−1.54 (m, 2H), 1.51−1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 132.7, 128.9, 128.7, 87.9, 79.6, 59.4, 59.0, 55.7, 43.1, 37.2, 36.3, 33.8, 33.0, 24.3, 19.0; HRMS (ES) found 302.1568, $C_{18}H_{24}NOS$ requires MH$^+$ 302.1579.

(2*R*,3a′*R*,7a′*S*)-3a′-(Phenylthio)octahydrospiro[cyclopentane-1,7′-indol]-2-ol 19. Zn powder (0.26 g, 4.0 mmol) was added to cycloadduct **18** (0.30 g, 1.0 mmol) in AcOH (1.6 mL) and H_2O (3.3 mL), and the mixture was heated at 100 °C. After 3 h, the mixture was cooled to room temperature, filtered, washed with CH_2Cl_2, and evaporated. Aqueous NH_4OH (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$), and evaporated to give alcohol **19** (0.27 g, 91%), which was recrystallized from CH_2Cl_2−petroleum ether as cubes: mp 96−98 °C; IR ν_{max} (film)/cm^{-1} 3335, 1445, 1250; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.49 (m, 2H), 7.39−7.29 (m, 3H), 3.78 (d, *J* 4.5 Hz, 1H), 3.06−2.92 (m, 3H), 2.33−2.23 (m, 1H), 2.13−1.57 (m, 9H), 1.49−1.39 (m, 1H), 1.37−1.25 (m, 2H), 1.17 (td, *J* 13.5, 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 133.0, 128.6, 128.5, 82.4, 68.0, 56.3, 47.8, 43.3, 42.6, 34.1, 31.6, 31.4, 29.5, 22.5, 18.4; HRMS (ES) found 304.1730, $C_{18}H_{26}NOS$ requires MH$^+$ 304.1735. Anal. Calcd for $C_{18}H_{25}NOS$: C, 71.24; H, 8.30; N, 4.62; S, 10.57. Found: C, 71.44; H, 8.10; N, 4.70; S, 10.45.

Acetal 20. Paraformaldehyde (20 mg, 0.65 mmol) and TsOH·H_2O (1.5 mg, 0.05 mmol) were added to amino alcohol **19** (50 mg, 0.16 mmol) in $CHCl_3$ (3 mL), and the mixture was heated to 65 °C. After 16 h, the mixture was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (99.5:0.5), gave acetal **20** (35 mg, 70%) as an oil: IR ν_{max} (film)/cm^{-1} 2925, 2860, 2800, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.50 (m, 2H), 7.39−7.30 (m, 3H), 4.39 (d, *J* 7 Hz, 1H), 3.94 (d, *J* 7 Hz, 1H), 3.77 (t, *J* 9 Hz, 1H), 3.01 (td, *J* 8, 3 Hz, 1H), 2.47 (ddd, *J* 13, 8, 5 Hz, 1H), 2.36−2.19 (m, 3H), 2.09−1.55 (m, 9H), 1.55−1.42 (m, 2H), 1.30−1.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.9, 128.7, 128.4, 84.0, 79.4, 67.3, 56.0, 46.9, 42.1, 39.4, 34.6, 34.1, 33.2, 25.4, 20.4, 19.9; HRMS (ES) found 316.1723, $C_{19}H_{26}NOS$ requires MH$^+$ 316.1735.

Acetal 21. Acetaldehyde (0.04 mL, 0.65 mmol) and TsOH·H_2O (1.5 mg, 0.05 mmol) were added to amino alcohol **19** (50 mg, 0.16 mmol) in $CHCl_3$ (3 mL), and the mixture was heated to 65 °C. After 16 h, the mixture was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (99.5:0.5), gave acetal **21** (30 mg, 57%) as an oil: IR ν_{max} (film)/cm^{-1} 2930, 2880, 2800, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.48 (m, 2H), 7.38−7.29 (m, 3H), 3.97 (q, *J* 7 Hz, 1H), 3.78 (t, *J* 8.5 Hz, 1H), 3.05−2.98 (m, 1H), 2.55−2.45 (m, 1H), 2.29−2.18 (m, 3H), 2.13−2.03 (m, 1H), 2.00−1.71 (m, 4H), 1.70−1.55 (m, 4H), 1.54−1.38 (m, 2H), 1.30−1.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 132.9, 128.6, 128.4, 84.8, 83.9, 67.7, 56.2, 47.3, 41.9, 39.4, 34.3, 33.9, 33.1, 26.0, 20.4, 20.2, 19.9; HRMS (ES) found 330.1889, $C_{20}H_{28}NOS$ requires MH$^+$ 330.1892.

2-((*S*)-1-(*tert*-Butyldimethylsilyloxy)propan-2-yl)-5-cyclopentenylpentanenitrile 23. *n*-Butyllithium (5.52 mL, 13.8 mmol, 2.5 M in hexanes) was added to diisopropylamine (2.13 mL, 15.1 mmol) in THF (15 mL) at −78 °C. After 10 min, nitrile **22**[32] (2.80 g, 13.1 mmol) and then iodide **13**[30] (4.65 g, 19.7 mmol) were added, and the mixture was warmed to room temperature. After 16 h, saturated aqueous ammonium chloride solution (25 mL) was added, the mixture was extracted with Et_2O (3 × 60 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (99:1), gave nitrile **23** (4.11 g, 98%) as an oil (dr 2:1): IR ν_{max} (film)/cm^{-1} 2930, 2860, 2250, 1460, 1260; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39−5.35 (m, 1H), 3.68−3.44 (m, 2H), 3.01−2.90 (m, 0.65H), 2.79−2.67 (m, 0.35H), 2.35−2.28 (m, 2H), 2.27−2.20 (m, 2H), 2.16−2.09 (m, 2H), 2.02−1.43 (m, 7H), 1.01 (t, *J* 7 Hz, 3H), 0.93−0.90 (m, 9H), 0.09−0.07 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 143.6, 124.1, 122.1, 120.9, 65.6, 65.0, 37.6, 37.3, 34.9, 33.9, 33.1, 32.4, 30.6, 30.4, 29.9, 27.9, 25.6, 25.7, 23.4, 18.2, 14.3, 12.6, −5.5; HRMS (ES) found 322.2556, $C_{19}H_{36}NOSi$ requires MH$^+$ 322.2566.

5-Cyclopentenyl-2-((*S*)-1-hydroxypropan-2-yl)pentanenitrile 24. Tetrabutylammonium fluoride (7.8 mL, 7.8 mmol, 1.0 M in THF) was added to ether **23** (1.00 g, 3.11 mmol, dr 2:1) in THF (30 mL) with 4 Å molecular sieves. After 1 h, the mixture was filtered and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (3:1), gave alcohol **24** (0.53 g, 82%) as an oil (dr 2:1): IR ν_{max} (film)/cm^{-1} 3360, 2950, 1460; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40−5.35 (m, 1H), 3.75−3.55 (m, 2H), 3.01−2.94 (m, 0.65H), 2.73−2.66 (m, 0.35H), 2.36−2.28 (m, 2H), 2.27−2.20 (m, 2H), 2.18−2.10 (m, 2H), 2.03−1.46 (m, 7H), 1.09 (d, *J* 7 Hz, 1H), 1.05 (d, *J* 7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 143.6, 124.1, 120.7, 65.5, 65.0, 37.3, 37.2, 34.9, 34.2, 33.3, 32.4, 30.5, 30.0, 28.4, 25.7, 25.6, 23.4, 14.6, 12.6; HRMS (ES) found 208.1695, $C_{13}H_{22}NO$ requires MH$^+$ 208.1701.

5-Cyclopentenyl-2-((*R*)-1-hydroxypropan-2-yl)-2-(phenylthio)pentanenitrile 25. ^{i}PrMgCl (2.40 mL, 4.80 mmol, 2.0 M in THF) was added to nitrile **24** (0.20 g, 0.97 mmol) in THF (2 mL) at −78 °C. After 5 min, the mixture was warmed to room temperature. After 30 min, the mixture was cooled to −78 °C, diphenyl disulfide (1.05 g, 4.80 mmol) in THF (2 mL) was added, and the mixture was warmed to room temperature. After 16 h, saturated aqueous ammonium chloride solution (10 mL) was added, the mixture was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), and evaporated. Purification by column chromatography, eluting with petroleum ether−EtOAc (4:1), gave nitrile **25** (0.28 g, 92%) as an oil (dr 2:1): IR ν_{max} (film)/cm^{-1} 3420, 2945, 2850, 2250, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.60 (m, 2H), 7.54−7.34 (m, 3H), 5.39−5.31 (m, 1H), 4.11−3.98 (m, 1H), 3.78−3.69 (m, 1H), 2.34−2.26 (m, 2H), 2.26−2.17 (m, 2H), 2.11−2.01 (m, 2H), 1.91−1.58 (m, 7H), 1.28 (d, *J* 7 Hz, 1H), 1.25 (d, *J* 7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 143.4, 143.3, 137.3, 137.0, 130.3, 129.3, 128.8, 124.4, 120.5, 64.6, 64.3, 52.8, 40.4, 40.2, 35.0, 34.9, 34.5, 34.0, 32.4, 30.7, 23.4, 23.1, 22.6, 12.8, 12.6; HRMS (ES) found 316.1732, $C_{19}H_{26}NOS$ requires MH$^+$ 316.1735.

2-((*S*)-1-Chloropropan-2-yl)-5-cyclopentenyl-2-(phenylthio)pentanenitrile 26. The alcohol **25** (0.63 g, 2.0 mmol, dr 2:1) was added to polymer-bound triphenylphosphine (1.30 g, 4.0 mmol, ∼3 mmol·g^{-1}, 2% cross-linked with divinylbenzene) and CCl_4 (4.90 mL, 40 mmol) in CH_2Cl_2 (4 mL) at 0 °C, and the mixture was warmed to room temperature. After 3 d, the mixture was filtered, washed with CH_2Cl_2, evaporated, and adsorbed onto silica. Purification by column chromatography, eluting with petroleum ether−EtOAc (99:1), gave nitrile **26** (0.60 g, 90%) as an oil (dr 2:1): IR ν_{max} (film)/cm^{-1} 2945, 2850, 2250, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.64 (m, 2H), 7.54−7.40 (m, 3H), 5.40−5.34 (m, 1H), 4.12 (dd, *J* 11, 2.5 Hz, 0.65H), 4.02 (dd, *J* 11, 2.5 Hz, 0.35H), 3.50 (t, *J* 11 Hz, 0.35H), 3.43 (t, *J* 11 Hz, 0.65H), 2.36−2.27 (m, 2H), 2.27−2.18 (m, 2H), 2.15−2.05 (m, 2H), 1.93−1.66 (m, 6H), 1.64−1.51 (m, 1H), 1.37 (d, *J* 6.5 Hz, 1H), 1.32 (d, *J* 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 143.1, 137.4, 137.1, 130.6, 130.5, 129.4, 128.4, 124.6, 119.8, 53.8, 53.3, 46.5, 46.0, 41.2, 34.9, 34.9, 33.9, 33.7, 32.4, 30.6, 30.6, 23.4, 23.3, 22.5, 13.5, 13.2; HRMS (ES) found 334.1408, $C_{19}H_{25}NS^{35}Cl$ requires MH$^+$, 334.1396.

2-((*S*)-1-Chloropropan-2-yl)-5-cyclopentenyl-2-(phenylthio)pentanal 27. In the same way as **10**, DIBAL-H (4.20 mL, 4.2 mmol, 1.0 M in hexanes) and nitrile **26** (0.70 g, 2.10 mmol, dr 2:1) gave, after purification by column chromatography, eluting with petrol−EtOAc

(99:1), gave aldehyde **27** (0.46 g, 65%) as an oil (dr 7:3): IR ν_{max} (film)/cm^{-1} 2940, 2845, 1715, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 0.3H), 9.44 (s, 0.7H), 7.46−7.31 (m, 5H), 5.38−5.31 (m, 1H), 4.09 (dd, *J* 10.5, 3 Hz, 0.7H), 3.87 (dd, *J* 10.5, 3 Hz, 0.3H), 3.59−3.51 (m, 0.3H), 3.47−3.40 (m, 0.7H), 2.39−2.26 (m, 2H), 2.26−2.16 (m, 2H), 2.08−1.96 (m, 2H), 1.87 (quin, *J* 7.5 Hz, 2H), 1.79−1.67 (m, 1H), 1.65−1.35 (m, 4H), 1.32 (d, *J* 7 Hz, 0.9H), 1.26 (d, *J* 7 Hz, 2.1H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 194.1, 193.2, 143.5, 137.5, 137.2, 130.0, 129.4, 128.9, 128.2, 124.3, 65.9, 47.3, 47.2, 38.9, 38.3, 35.0, 32.4, 31.6, 29.5, 23.4, 22.4, 22.3, 13.4; HRMS (ES) found 337.1394, $C_{19}H_{26}OS^{35}Cl$ requires MH^+ 337.1393.

2-((*S*)-1-Chloropropan-2-yl)-5-cyclopentenyl-2-(phenylthio)-pentanal Oxime 28. Aldehyde **27** (0.44 g, 1.31 mmol, dr 7:3), hydroxylamine hydrochloride (0.14 g, 1.97 mmol), and diisopropylethylamine (0.69 mL, 3.93 mmol) were heated in PhMe (13 mL) at 60 °C. After 16 h, the solvent was evaporated and the mixture was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (49:1), gave oxime **28** (0.33 g, 72%) as an oil (dr 7:3): IR ν_{max} (film)/cm^{-1} 3280, 2930, 1455, 1275; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.47 (m, 2H), 7.44−7.32 (m, 3H), 6.88 (s, 0.3H), 6.70 (s, 0.7H), 5.38 (s, 0.3H), 5.34 (m, 0.7H), 3.80 (dd, *J* 13.5, 8.5 Hz, 1H), 3.51−3.42 (m, 1H), 2.81−2.70 (m, 1H), 2.37−2.16 (m, 4H), 2.15−2.03 (m, 2H), 1.94−1.58 (m, 5H), 1.55−1.41 (m, 1H), 1.31 (d, *J* 7.5 Hz, 2.1H), 1.13 (d, *J* 7.5 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 143.5, 139.4, 137.5, 137.2, 129.7, 129.6, 129.5, 129.3, 129.2, 124.3, 68.5, 68.0, 64.5, 63.3, 38.8, 38.5, 36.8, 34.9, 33.4, 32.4, 31.3, 31.0, 23.4, 23.2, 13.1, 11.9; HRMS (ES) found 316.1725, $C_{19}H_{26}NOS$ requires MH^+ 316.1735.

Cycloadducts 29 and 30. The oxime **28** (0.32 g, 0.91 mmol, dr 7:3) was heated in PhMe (9 mL) under reflux. After 16 h, the solvent was evaporated and the residue was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (99.5:0.5), gave cycloadducts **29** and **30** (0.23 g, 80%) (ratio 7:3) partially separated.

29 (107 mg) as an oil: $[\alpha]^{21}_D$ −3.5 (*c* 0.09, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2930, 2860, 1460, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.50 (m, 2H), 7.41−7.33 (m, 3H), 4.06 (d, *J* 6 Hz, 1H), 3.70 (s, 1H), 3.39 (dd, *J* 13, 6.5 Hz, 1H), 3.23 (t, *J* 13 Hz, 1H), 2.70−2.64 (m, 1H), 2.15 (dd, *J* 14, 1.5 Hz, 1H), 1.92−1.76 (m, 3H), 1.72−1.62 (m, 1H), 1.59−1.33 (m, 5H), 1.27−1.17 (m, 1H), 1.12 (d, *J* 7 Hz, 3H), 1.00 (td, *J* 13, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 132.5, 128.8, 128.7, 87.8, 79.6, 62.9, 62.3, 59.7, 42.8, 40.4, 33.6, 33.5, 33.2, 24.1, 19.2, 10.5; HRMS (ES) found 316.1732, $C_{19}H_{26}NOS$ requires MH^+ 316.1735.

29 and **30** (98 mg) (1:1 mixture) as an oil.

30 (28 mg) as an oil, which crystallized on standing to give cubes: mp 89−91 °C; $[\alpha]^{21}_D$ +4.3 (*c* 0.25, $CHCl_3$);IR ν_{max} (film)/cm^{-1} 2930, 2860, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.48 (m, 2H), 7.43−7.30 (m, 3H), 4.31−4.25 (m, 1H), 3.34 (dd, *J* 11.5, 7.5 Hz, 1H), 3.26 (s, 1H), 2.81 (t, *J* 11.5 Hz, 1H), 2.36−2.17 (m, 2H), 1.94−1.69 (m, 7H), 1.66−1.52 (m, 4H), 1.01 (d, *J* 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 130.9, 129.2, 128.9, 87.2, 77.4, 61.6, 57.2, 56.1, 42.9, 42.0, 35.0, 27.1, 24.3, 23.4, 16.7, 10.7; HRMS (ES) found 316.1737, $C_{19}H_{26}NOS$ requires MH^+ 316.1735. Anal. Calcd for $C_{19}H_{25}NOS$: C, 72.34; H, 7.99; N, 4.44; S, 10.16. Found: C, 72.44; H, 7.97; N, 4.46; S, 10.00.

(3*R*)-4-Hydroxy-3-methyl-2-(phenylthio)butanenitrile 32. In the same way as **25**, nitrile **31**[35] (0.30 g, 3.03 mmol), ^{i}PrMgCl (4.55 mL, 9.10 mmol, 2.0 M in THF), and PhSSPh (1.99 g, 9.10 mmol) gave, after purification by column chromatography, eluting with petroleum ether−EtOAc (4:1), nitrile **32** (0.50 g, 80%) as an oil (dr 3:1): IR ν_{max} (film)/cm^{-1} 3420, 2945, 2850, 2250, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.57 (m, 2H), 7.42−7.32 (m, 3H), 4.15 (d, *J* 5.5 Hz, 0.75H), 3.98 (d, *J* 5.5 Hz, 0.25H), 3.83−3.72 (m, 1H), 3.62−3.55 (m, 1H), 2.31−2.14 (m, 2H), 1.21 (d, *J* 7 Hz, 0.75H), 1.18 (d, *J* 7 Hz, 2.25H); ^{13}C NMR (100 MHz, $CDCl_3$, some peaks coalesce and/or are not observed) δ 134.0, 133.7, 131.7, 131.6, 129.5, 129.3, 129.2, 119.2, 118.2, 64.4, 64.0, 40.9, 40.2, 38.4, 38.3, 14.1, 13.5; HRMS (ES) found 208.0788, $C_{11}H_{14}NOS$ requires MH^+ 208.0796.

(1*S*,2*R*,3′*R*,3a′*R*,7a′*S*)-3′-Methyl-3a′-(phenylthio)octahydrospiro[cyclopentane-1,7′-indol]-2-ol 33. In the same way as **19**, cycloadduct **29** (0.10 g, 0.32 mmol) and Zn powder (0.08 g, 1.27 mmol) at 70 °C for 2 h gave alcohol **33** (0.10 g, 99%) as an oil, which was used without further purification: IR ν_{max} (film)/cm^{-1} 3360, 2930, 2870, 1435; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.41 (m, 2H), 7.36−7.24 (m, 3H), 3.83 (d, *J* 4 Hz, 1H), 3.39 (dd, *J* 11, 6 Hz, 1H), 3.07 (s, 1H), 2.75 (dd, *J* 11, 6 Hz, 1H), 2.31−2.21 (m, 1H), 2.04−1.59 (m, 8H), 1.48−1.39 (m, 1H), 1.36−1.12 (m, 3H), 1.28 (d, *J* 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 133.0, 128.8, 127.7, 82.1, 65.5, 61.8, 52.2, 47.9, 43.4, 34.7, 31.7, 31.1, 29.9, 21.9, 18.9, 18.3; HRMS (ES) found 318.1888, $C_{19}H_{28}NOS$ requires MH^+ 318.1892.

Acetal 34. In the same way as **20**, alcohol **33** (0.09 g, 0.28 mmol), paraformaldehyde (0.034 g, 1.12 mmol), and TsOH·H_2O (3 mg, 0.01 mmol) gave, after purification by column chromatography, eluting with CH_2Cl_2−MeOH (99.5:0.5), acetal **34** (0.07 g, 79%) as an oil: $[\alpha]^{21}_D$ −100 (*c* 0.5, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2925, 1475, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.37 (m, 2H), 7.33−7.21 (m, 3H), 4.40 (d, *J* 6.5 Hz, 1H), 3.99 (d, *J* 6.5 Hz, 1H), 3.70 (t, *J* 8 Hz, 1H), 3.40 (t, *J* 7.5 Hz, 1H), 2.55−2.44 (m, 1H), 2.24 (s, 1H), 2.18 (q, *J* 7.5 Hz, 1H), 2.04 (td, *J* 13, 3.5 Hz, 1H), 1.96−1.85 (m, 2H), 1.85−1.71 (m, 4H), 1.70−1.59 (m, 1H), 1.59−1.42 (m, 2H), 1.40−1.32 (m, 1H), 1.27 (d, *J* 7.5 Hz, 3H), 1.22 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.2, 132.8, 128.6, 126.7, 84.6, 79.9, 65.4, 56.7, 56.6, 42.5, 41.9, 34.7, 33.1, 32.8, 26.0, 20.8, 20.2, 20.1; HRMS (ES) found 330.1890, $C_{20}H_{28}NOS$ requires MH^+, 330.1892. Anal. Calcd for $C_{20}H_{27}NOS$: C, 72.90; H, 8.26; N, 4.25; S, 9.73. Found: C, 72.84; H, 8.56; N, 4.12; S, 9.66.

Acetal 36. In the same way as **33**, cycloadduct **30** (23 mg, 0.073 mmol) and Zn powder (19 mg, 0.29 mmol) gave the alcohol **35** (23 mg, 0.07 mmol), which was not characterized but was taken on directly. Paraformaldehyde (9 mg, 0.29 mmol) and TsOH·H_2O (0.70 mg, 0.003 mmol) were added to **35** in $CHCl_3$ (1.5 mL), and the mixture was heated to 65 °C. After 16 h, the mixture was adsorbed onto silica. Purification by column chromatography, eluting with CH_2Cl_2−MeOH (99.5:0.5), gave acetal **36** (14 mg, 58% over two steps) as an oil: $[\alpha]^{21}_D$ +90 (*c* 0.5, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2925, 2855, 1440; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.52 (m, 2H), 7.44−7.30 (m, 3H), 4.32 (d, *J* 7 Hz, 1H), 3.95 (d, *J* 7 Hz, 1H), 3.71 (t, *J* 8 Hz, 1H), 2.67−2.51 (m, 2H), 2.45 (t, *J* 8 Hz, 1H), 2.41−2.32 (m, 2H), 2.08−1.43 (m, 10H), 1.32−1.20 (m, 1H), 0.73 (d, *J* 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 131.9, 129.0, 128.6, 84.5, 79.6, 66.4, 57.8, 54.0, 43.3, 40.7, 34.1, 33.0, 28.1, 26.1, 20.4, 20.0, 13.2; HRMS (ES) found 330.1877, $C_{20}H_{28}NOS$ requires MH^+ 330.1892.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Crystallographic information files (CIFs) and ORTEP diagrams for the amino alcohol **19** and the cycloadduct **30** (CCDC reference nos. 806620 and 806619, respectively) and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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