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Enantioselective cyclization of enamide-ynes and application to the synthesis of the kopsifoline core

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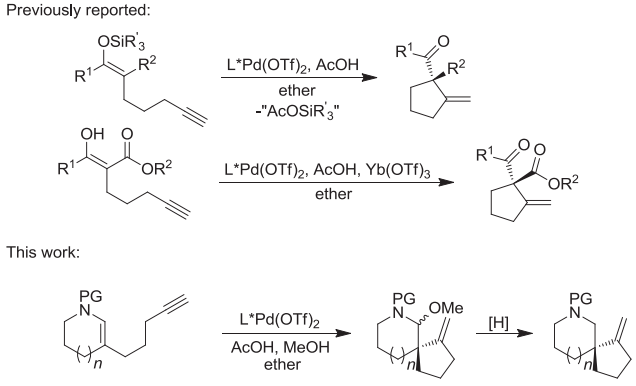
ABSTRACT

We report the palladium-catalyzed enantioselective cyclization of 1,6-enamidynes to form spirocyclic ring systems. We applied this methodology to the concise synthesis of the skeletal core of the kopsifoline alkaloids.

1. Introduction

The cyclization of 1,6-enynes stands out as a robust and atom-economical method among the myriad strategies for the synthesis of cyclopentanes. While the thermal Alder ene reaction of 1,6-enynes has been known for some time,[1] transition metal-catalyzed processes are substantially younger. Beginning with the seminal work of Trost,[2] a wide variety of catalyst systems have been employed across a truly impressive range of substrates.[3] As proof of its utility in the construction of complex molecules, dozens of natural product total syntheses that rely on a 1,6-enyne cyclization have been reported. Further extension of the metal-catalyzed cyclization paradigm has yielded a variety of 1,7- and 1,8-enyne cyclizations, as well as numerous methods that exploit metalated cyclization intermediates to further functionalize the cyclopentane skeleton.

Our group first reported a highly efficient Au(I)-catalyzed Conia-ene reaction in 2004,[4] which, along with work by Echavarren on the addition of enol ethers into alkynes, demonstrated that π-acids were highly competent catalysts for the addition of electron-rich alkenes into unactivated π-systems.[5] Further work in our group has led to the development of Pd(II)- and Au(I)-catalyzed enantioselective variants of these transformations.[6] The transformations that have previously been amenable to the chiral cationic Au(I) and Pd(II) developed by our group have utilized enols or silyl enol ethers as the nucleophilic alkene, with charge neutralization and product formation occurring upon loss of proton or silyl group. We reasoned that alternatively, product formation can occur by trapping of the oxocarbenium or iminium intermediate by an external alcohol nucleophile to give an acetal or aminal product (Scheme 1).



Scheme 1. Previously reported enantioselective 1,6-enyne cyclizations and enantioselective cyclization of 1,6-enamide-ynes.

Encouragingly, $PtCl_2$-catalyzed transformations involving similar substrates have recently been reported.[7] Herein we report the application of this strategy to 1,6-enamide-ynes in the preparation of enantioenriched spirocyclic nitrogen heterocycles. The method

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reported here enables the enantioselective generation of an all-carbon stereocenter β to nitrogen functionality. Given the prevalence of these motifs in alkaloid natural products, we embarked on a concise synthesis of the core of the kopsifoline family of alkaloids as a demonstration of the expedient access to molecular complexity that this methodology affords.

The kopsifolines are a family of monoterpenoid indole alkaloids isolated in 2004 from *Kopsia fruticosa*.[8] This novel class of compounds exhibits an unprecedented hexacyclic carbon skeleton. While similar to the aspidospermine natural products,[9] the kopsifolines introduce additional challenges to synthesis with an additional ring, and a total of three all-carbon quaternary stereocenters (Fig. 1). The congested, multiply bridging ring system presents a serious challenge to synthesis, and the lack of biological data further encourages synthetic investigation.

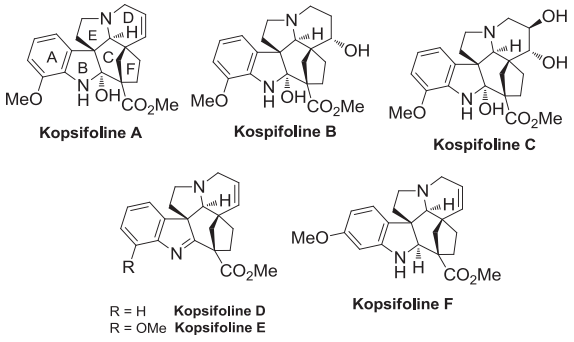
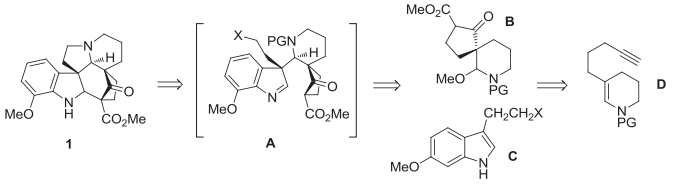


Fig. 1. Kopsifoline A–F.

Previously, Padwa and co-workers reported the racemic synthesis of the kopsifoline core in 13 steps through a dipolar cycloaddition approach.[10] The kopsifolines attracted our attention with the observation that the FD spiro ring system (ring labels shown on Kopsifoline A in Fig. 1) could potentially be forged through a Pd(II)-catalyzed enantioselective enyne cyclization. In our retrosynthesis, we envisioned that ring C could be constructed by an intramolecular Mannich cyclization of a β-ketoester onto in situ generated indole imine **A** (Scheme 2).[11] Imine **A** could in turn be formed from the reaction of the appropriately 3-substituted indole **C** with the imine generated from aminal **B**. Finally, we believed that spirocyclic aminal **B** could be formed enantioselectively using a cationic Pd(II)-catalyzed cyclization of enyne **D**.

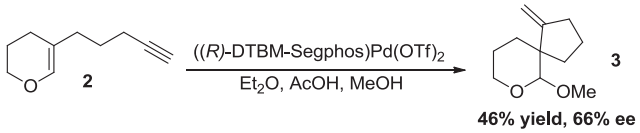


Scheme 2. Retrosynthetic analysis of kopsifoline core 1.

2. Results and discussion

2.1. Optimization and scope

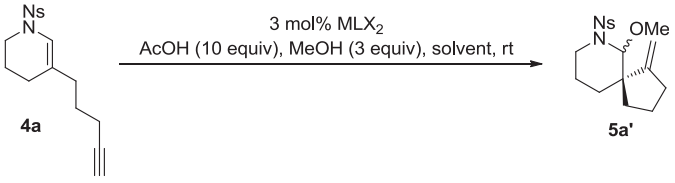
Initially, we investigated dihydropyran derived 1,6-alkoxyenynes, **2** under conditions developed for the cyclization of 1,6-silyloxyenynes, with the inclusion of excess methanol to trap the generated oxocarbenium ion. It was found that, indeed, exposure of **2** to (DTBM-Segphos)$Pd(OTf)_2$ resulted in the formation of the expected acetal product **3** as a mixture of diastereomers with modest yields and moderate enantioselectivities. Though encouraging, the enantioselectivity could not be improved beyond 66% ee despite extensive screening (Scheme 3). We hypothesized that the moderate level of enantioinduction stemmed from the lack of a sterically demanding group near the enol ether that would allow for efficient discrimination of the faces of the substrate. Thus we turned our attention to the analogous 1,6-enamide-yne system.



Scheme 3. Cyclization of dihydropyran substrate **2**.

We prepared *N*-nosyl enamide-yne **4a** as a model substrate and embarked on a survey of ligand choice and other reaction parameters (Table 1). We found that while chelating bisphosphinopalladium(II) triflates and tosylates furnished desired hemiaminal **5a′** in moderate to good yield (entries 1–3), catalysts bearing more coordinating benzoate or chloride ligands were inactive (entries 4 and 5). Although the product was obtained as a mixture of diastereomers, reduction of **5a′** to piperidine **5a** was conveniently carried out using triethylsilane, whose optical purity could be determined by chiral HPLC.

Table 1
Catalysts optimization



Entry	L	M	X	Solvent	Time (h)	**5a′** Yield	**5a** %ee[a]
1	Dppp	Pd	OTf	DCM	0.75	66	—
2	*rac*-BINAP	Pd	OTs	DCM	2	71	—
3	(*R*)-BINAP	Pd	OTf	DCM	3	42	25
4	*rac*-BINAP	Pd	Cl	DCM	48	NR	—
5	*rac*-BINAP	Pd	OBz	DCM	48	NR	—
6	(*R*)-DTBMSegphos	Pd	OTf	DCM	7	69	52
7	(*R*)-DTBMSegphos	Pd	OTf	Toluene	8	76	76
8	(*R*)-DTBMSegphos	Pd	OTf	MTBE	14	76	84
9	(*R*)-DTBMSegphos	Pd	OTf	Et_2O	20	77	84
10	(*R*)-Binaphane	Pd	OTf	Et_2O	2	71	90
11[b]	(*R*)-Binaphane	Pd	OTf	Et_2O	2	78	90
12	(*R*)-Binaphane	Pd	OTs	Et_2O	48	Decomp	—
13	(*R*)-DTBMSegphos	Pt	[c]	Et_2O	16	68	5
14	(*R*)-Binaphane	Pt	[c]	Et_2O	16	75	9

[a] ee measured after reduction of **5a′** to the corresponding piperidine **5a**.
[b] Catalyst (1 mol %) used, 2.93 mmol scale.
[c] Mixed complex PtLCl(OTf) generated by in situ mixture of $MLCl_2$ and AgOTf (3 mol % each). AgOTf (5 mol %) alone at 50 °C gave 10% conversion. Use of in situ generated $PtL(OTf)_2$ resulted in extensive olefin isomerization.

((*R*)-BINAP)$Pd(OTf)_2$ was found to give cyclization product with poor enantioselectivity (entry 3). By switching to a more sterically demanding chiral bisphosphine, improvement in both yield and enantioselectivity was observed (entry 6 vs 3). Out of a range of solvents screened, ethereal solvents MTBE and diethyl ether gave the best yield and enantioselectivity. Finally, change of ligand to ((*R*)-binaphane)$Pd(OTf)_2$ furnished the desired product in 90% ee, with no decrease in enantioselectivity observed when the reaction was performed on nearly 3 mmol scale, and catalyst loading was reduced to 1 mol %. Interestingly, while the corresponding platinum complexes were also competent catalysts, the levels of enantioinduction achieved by these catalysts were uniformly low (entries 13 and 14).[12]

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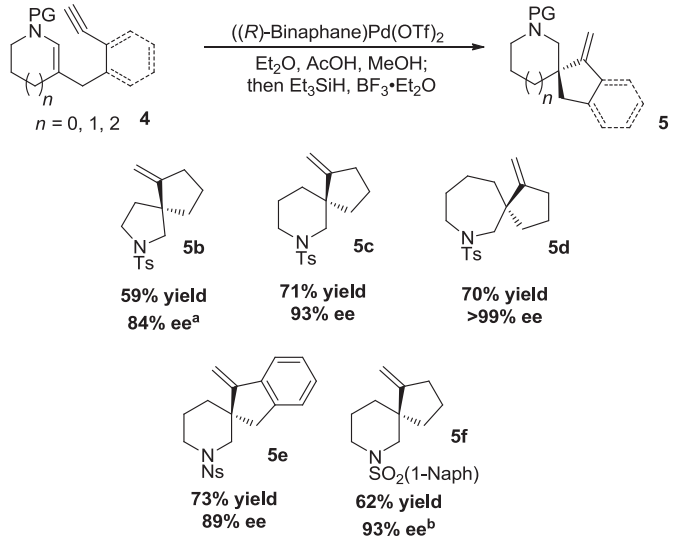
With these conditions in hand, we explored the substrate scope of the transformation. Exploration of enamide ring size revealed that five- and seven-membered rings were tolerated, with the seven-membered ring system giving desired product with exceptional enantioselectivity. The five-membered ring enamide afforded desired product **5b** with moderate enantioselectivity (78% ee) under standard conditions, which could be improved to 84% ee by switching the solvent to MTBE. A benzo-tethered alkyne afforded product **5e**[13] in good enantioselectivity, as did switching the protecting group to 1-naphthalenesulfonyl in **5f** (Scheme 4).



a. In MTBE in place of Et_2O
b. 3 mol % catalyst, 10 eq MeOH, 30 eq AcOH

Scheme 4. Substrate scope of 1,6-enamide-yne cyclization.

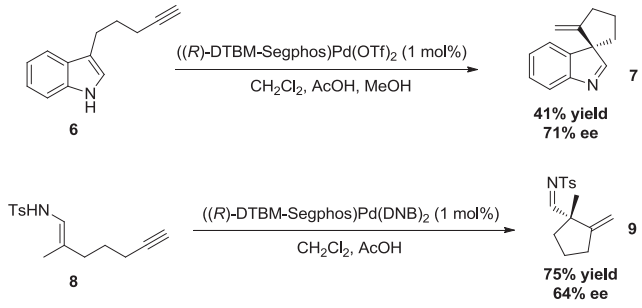
We speculated that the latent enamine found in the indole nucleus could be a competent substrate when appropriately tethered to an alkyne. Thus we prepared 3-substituted indole **6**. Although initial studies of **6** under standard reaction conditions resulted in the formation of many side products, we found that addition of substrate to a preformed solution of catalyst, AcOH, and MeOH in DCM resulted in much cleaner reaction. While ((*R*)-binaphane) $Pd(OTf)_2$ afforded spirocycle **7** in 50% ee, switching to ((*R*)-DTBM-Segphos)$Pd(OTf)_2$ afforded desired product with an improved enantioselectivity of 71% ee.[14]

Similarly, acyclic tosylenamide **8** cyclized to give imine **9** under standard conditions, although enantioselectivity was low (26% ee). Switching to ((*R*)-DTBM-Segphos)$Pd(OTf)_2$ improved enantioselectivity to 46% ee. Additional optimization revealed that methanol was unnecessary, and that more coordinating ligands on palladium (e.g., benzoate, 60% ee) gave further improvements in enantioselectivity. Accordingly, the 3,5-dinitrobenzoate complex gave product with good yield and in the highest enantioselectivity (64% ee) among the catalysts surveyed. While the selectivity achieved is still moderate, this result is remarkable nonetheless, given the significantly greater conformational freedom available to an acyclic substrate (Scheme 5).

2.2. Synthesis of the kopsifoline core

As a demonstration of the power of this newly developed method, we synthesized the core of kopsifoline alkaloids in 90% ee starting from commercially available δ-valerolactone in 12 steps.

As described in the previous section, tosyl protected cyclization product **5c′** could be obtained from 1,6-enamide-yne **4c** in 93% ee.



Scheme 5. Cyclization of indole and acyclic enamide substrates.

Ozonolysis of **5c′** afforded the corresponding ketone **10** in 95% yield. Initially, our investigation focused on reaction of **10** under Lewis acidic conditions with 3-methylindole. Unfortunately, under a variety of conditions, the desired aza-Mannich/intramolecular Mannich cascade could not be effected, and only pentacycle **11** could be obtained (Fig. 2). It appears that **11** formed from diversion of the desired aza-Mannich intermediate by facile Wagner–Meerwein shift of the newly introduced alkyl group from the indole 3-position to the 2-position.

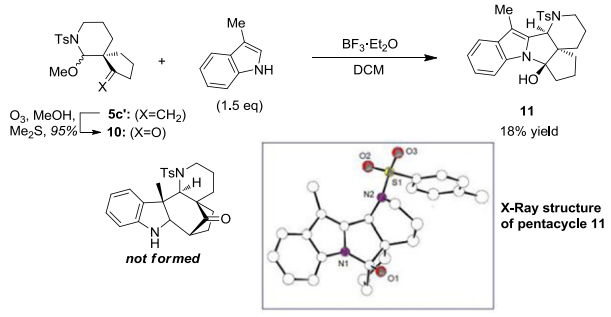
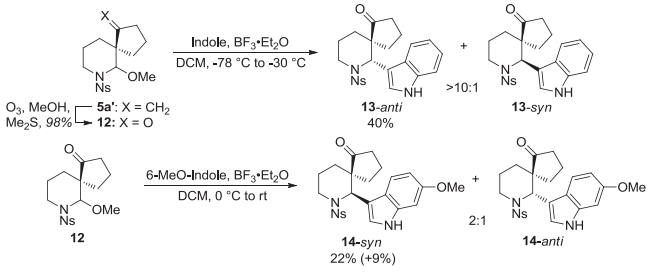


Fig. 2. Formation of undesired pentacycle **11**.

Thus, we turned our attention to 3-unsubstituted indoles, with the hope of introducing the C-5, C-6 ethylene bridge at a later stage, a strategy utilized by Natsume and co-workers in their synthesis of the *Aspidosperma* alkaloids.[15] Switching to the more easily removed nosyl protecting group, cyclization of 1,6-enamide-yne **4a** occurred under the conditions described earlier to give hemiaminal **5a′** in 78% yield, 90% ee. Ozonolytic cleavage of **5a** afforded ketone **12** in excellent yield.[16] Reaction of **12** with indole in the presence of $BF_3 \cdot Et_2O$ at −78 °C furnished a 3-alkylated indole as a single diastereomer; however, X-ray crystallography revealed that the undesired *anti*-isomer **13**-*anti* was formed.[17] Fortunately, subsequent experiments revealed that the desired isomer **13**-*syn* was preferred at higher temperatures (Scheme 6).

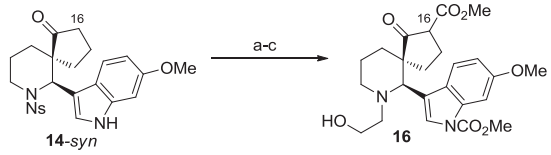


Scheme 6. Indolization of hemiaminal ketone **12**.

Similar reactivity was observed when 6-methoxyindole was employed as a nucleophile. Thus, while isomer **14**-*anti* was formed exclusively at −78 °C, the desired *syn*-isomer was favored (2:1) at warmer temperature. Moreover, resubjecting **14**-*anti* to the

reaction conditions furnished an additional 9% of the desired diastereomer **14**-*syn* for a total yield of 31% (Scheme 6).

Introduction of the C-16 ester was accomplished by treating ketone **14**-*syn* with 2 equiv of LHMDS followed by trapping with Mander's reagent to afford ester **15**. The nosyl group of **15** could be effectively cleaved with either K_2CO_3/PhSH or LiOH/mercaptoacetic acid;[18] however, the use of LiOH/mercaptoacetic acid was preferred as the deprotected amine could be isolated after extraction with aqueous sodium bicarbonate. The crude piperidine thus obtained was treated with ethylene oxide in methanol to give ethanolamine **16** in 56% yield over these two steps (Scheme 7).

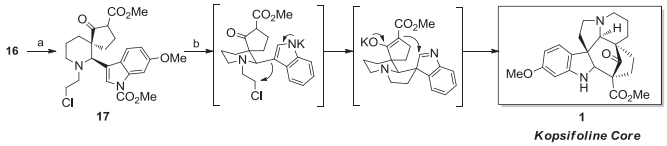


a) LHMDS, $NCCO_2Me$, 71%;
b) LiOH, $HSCH_2CO_2H$, DMF; c) ethylene oxide, MeOH, 56% over 2 steps

Scheme 7. Synthesis of cyclization precursor **16**.

Activation of the primary hydroxyl group using methanesulfonyl chloride and potassium carbonate furnished primary chloride **17** that was directly treated under basic conditions in order to induce alkylation at the indole C-3. Initial results with various bases in mixtures of THF/HMPA resulted in formation of **1** in poor yields (<15%). Subsequently, we found that treatment of **17** with potassium *tert*-butoxide in a 5:1 mixture of THF/DMSO at −78 °C induced the cyclization cascade to afford kopsifoline core **1** as one diastereomer in 40% yield from alcohol **16**.

The formation of a single diastereomer presumably results from the fact that the intramolecular Mannich reaction can only take place when the imine is formed on the same face of the piperidine ring as the ketoester. Thus, while the S_N2 reaction between the indole and the alkyl chloride may occur on either face of the indole, productive Mannich closure can only occur in one diastereomer (Scheme 8).



a) K_2CO_3, MsCl, CH_2Cl_2; b) *t*-BuOK, THF:DMSO 5:1, -78 °C, 40% over two steps

Scheme 8. Presumed mechanism of cyclization cascade to kopsifoline core **1**.

3. Conclusions

To summarize, we have developed a palladium-catalyzed methodology for the enantioselective synthesis of β-amino spirocycles.[19] This method enabled a facile, enantioselective synthesis of the kopsifoline core in 12 steps from valerolactam in 90% ee. The rapid assembly of this natural product core demonstrates the efficiency of our approach in the synthesis of stereochemically complex natural product system.

4. Experimental

4.1. General information

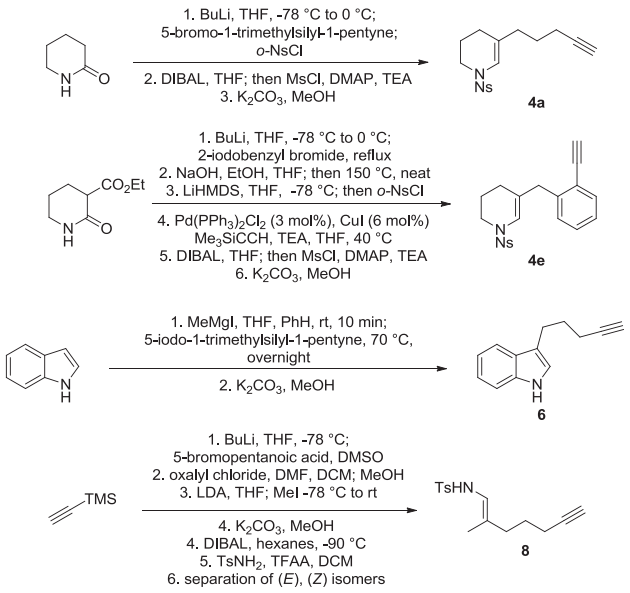
Unless otherwise noted, reagents were obtained from commercial sources and used without further purification. All reactions were carried out under N_2 using Schlenk line techniques, unless otherwise stated. Dry and degassed THF, dichloromethane, diethyl ether, toluene, triethylamine, and dimethylformamide were obtained by passage through activated alumina columns under argon. All other dried solvents were obtained by storage over 3 Å or 4 Å molecular sieves overnight. Palladium complexes were prepared as reported by Sodeoka and co-worker.[20] TLC analysis of reaction mixtures was performed on Merck silica gel 60 F_{254} TLC plates and visualized by UV, I_2/silica, and/or ceric ammonium molybdate stain. Flash chromatography was carried out with ICN SiliTech 32-63 D 60 Å silica gel. Standard aqueous workup refers to extraction with the indicated solvent, followed by drying of the combined organic layers with sodium sulfate (magnesium sulfate when extracting with diethyl ether), gravity filtration, and removal of solvent by rotary evaporation. ^1H and ^{13}C NMR spectra were recorded with Bruker AV-300, AVQ-400, AVB-400, AV-500, DRX-500, and AV-600 spectrometers and were referenced to ^1H (residual) and ^{13}C signals of the deuterated solvents, respectively.[21] Mass spectral and microanalytical data were obtained via the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley.

4.2. General procedure for the Pd catalyzed cyclization of 1, 6-enamide-yne 4

A solution of substrate (0.02 mmol), acetic acid (0.1 mL), methanol (30 μL), and ((*R*)-binaphane)$Pd(OH_2)_2(OTf)_2$ (1 mol %) in diethyl ether (1 mL) was stirred until the reaction was complete as determined by TLC.[6b] The reaction was neutralized with saturated sodium bicarbonate (1 mL). The organic phase was separated and concentrated before being redissolved in dichloromethane (1 mL) and filtered through a plug of silica to remove catalyst. To this solution were then added triethylsilane (2.2 equiv) and boron trifluoride etherate (1.1 equiv) and the reaction mixture was stirred for 20 min at room temperature. Purification on silica gel gave the desired products **5** (Scheme 9).

4.3. Synthesis of substrates

Substrates were prepared as illustrated below:



Scheme 9. Synthesis of substrates.

4.4. Characterization of substrates and products

*4.4.1. 6-Methoxy-1-methylene-7-oxaspiro[4.5]decane (**3**).* A solution of vinyl ether **1** (18.0 mg, 0.12 mmol), acetic acid (80 μL), methanol (20 μL), and (*R*)-DTBMSegphosPd$(OTf)_2$ (1.1 mg, 1 mol %) in 2 mL diethyl ether was stirred for 2 h at room temperature. The reaction was neutralized with saturated aqueous sodium

bicarbonate (5 mL) and extracted with diethyl ether. Flash chromatography (hexanes/ethyl acetate 50:1) gave acetal **3** as a volatile oil (9 mg, 46%). Chiraldex G-TA; 90 °C hold 0 min, then 5 °C/min to 150 °C; 2.0 mL/min He carrier gas, t_M=9.5 min, t_m=8.9 min, 66% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.94 (s, 1H), 4.15 (s, 1H), 3.92 (m, 1H), 3.54 (m, 1H), 3.38 (s, 3H), 2.47 (m, 2H), 1.97 (m, 1H), 1.68 (m, 1H), 1.66–1.48 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.7, 107.5, 105.5, 64.5, 56.5, 49.0, 34.7, 33.7, 33.6, 23.2, 22.6.

*4.4.2. 6-Methylene-2-tosyl-2-azaspiro[4.4]nonane (**5b**).* The racemic product has been characterized previously.[7a] Yield 59%. HPLC Chiralcel AD column (95:5 hexanes/ethanol, 1.0 mL/min): t_M=16.1 min, t_m=20.9 min: 84% ee.

*4.4.3. 1-Methylene-7-tosyl-7-azaspiro[4.5]decane (**5c**).* The racemic product has been characterized previously.[7a] Yield 71%. HPLC Chiralcel AD column (95:5 hexanes/ethanol, 1.0 mL/min): t_M=9.2 min, t_m=10.9 min: 93% ee.

*4.4.4. 1-Methylene-7-tosyl-7-azaspiro[4.6]undecane (**5d**).* The racemic product has been characterized previously.[7a] Yield 70%. Chiralcel AD column (98:2 hexanes/ethanol, 1.0 mL/min): t_M=12.2 min, t_m=14.7 min: >99% ee.

*4.4.5. 5-(2-Ethynylbenzyl)-1-(2-nitrophenylsulfonyl)-1,2,3,4-tetrahydropyridine (**4e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 1H, J=7.6 Hz), 7.58–7.74 (m, 3H), 7.48 (d, 1H, J=8.0 Hz), 7.25–7.31 (m, 1H), 7.23–7.17 (m, 1H), 6.58 (s, 1H), 3.52 (s, 2H), 3.47 (m, 2H), 3.01 (s, 1H), 1.94 (t, 2H, J=6.4 Hz), 1.74 (quint, 2H, J=6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 133.6, 132.9, 131.7, 130.4, 129.0, 126.3, 124.0, 122.0, 120.7, 82.3, 81.2, 43.8, 39.5, 24.3, 21.1. HRMS (FAB): calcd for $[C_{20}H_{19}N_2O_4S]^+$: 383.1060, found: 383.1070.

*4.4.6. 1-Methylene-1′-((2-nitrophenyl)sulfonyl)-1,3-dihydrospiro[indene-2,3′-piperidine] (**5e**).* Yield 73%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.88 (m, 1H), 7.60–7.75 (m, 3H), 7.48–7.42 (m, 1H), 7.10–7.30 (m, 3H), 5.60 (s, 1H), 4.97 (s, 1H), 3.91–4.05 (m, 1H), 3.57 (d, J=12.0 Hz, 1H), 2.60–2.90 (m, 3H), 1.55–2.00 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 143.1, 139.6, 133.6, 131.9, 131.6, 131.1, 129.2, 126.9, 125.8, 124.1, 121.0, 103.7, 55.9, 46.5, 46.4, 41.0, 35.0, 22.6.

*4.4.7. 1-(Naphthalen-1-ylsulfonyl)-5-(pent-4-yn-1-yl)-1,2,3,4-tetrahydropyridine (**4f**).* ^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.87–8.03 (m, 3H), 7.76 (dd, J=8.7, 1.7 Hz, 1H), 7.57–7.68 (m, 2H), 6.60 (s, 1H), 3.32–3.40 (m, 2H), 2.04–2.15 (m, 4H), 1.96–2.02 (m, 1H), 1.79 (t, J=6.1 Hz, 2H), 1.52–1.64 (m, 4H). ^{13}C NMR (126 MHz): 135.0, 134.9, 132.3, 129.4 (two peaks), 128.9, 128.5, 128.1, 127.7, 122.6, 120.6, 120.2, 84.1, 69.0, 43.8, 34.0, 26.3, 24.4, 21.0, 17.6. HRMS (ESI$^+$): calcd for $[C_{20}H_{21}O_2NS+H]^+$: 340.1366, found: 340.1368.

*4.4.8. 1-Methylene-7-(naphthalen-1-ylsulfonyl)-7-azaspiro[4.5]decane (**5f**).* Yield 62%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31–8.32 (m, 1H), 7.97 (t, J=7.5 Hz, 2H), 7.92 (d, J=7.8 Hz, 1H), 7.73 (dd, J=8.6, 1.8 Hz, 1H), 7.59–7.68 (m, 2H), 4.91 (t, J=2.0 Hz, 1H), 4.66 (t, J=2.2 Hz, 1H), 3.77–3.84 (m, 1H), 3.44 (d, J=11.4 Hz, 1H), 2.26–2.50 (m, 3H), 2.10–2.16 (m, 1H), 2.06 (d, J=11.5 Hz, 1H), 1.62–1.83 (m, 4H), 1.39–1.52 (m, 2H), 1.21–1.35 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 134.9, 133.9, 132.4, 129.4, 129.3, 128.8, 128.0, 127.6, 123.1, 105.8, 55.0, 46.7, 45.6, 35.8, 35.3, 33.9, 22.9, 22.6. HRMS (ESI$^+$): calcd for $[C_{20}H_{23}O_2NS+H]^+$: 342.1522, found: 342.1531. HPLC Chiralcel AD column (99:1 hexanes/isopropanol, 1.0 mL/min): t_M=28.6 min, t_m=35.7 min: 93% ee.

*4.4.9. 2-Methylenespiro[cyclopentane-1,1′-indene] (**7**).* Yield 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.60 (d, J=8 Hz, 1H), 7.34 (dt, J=7, 2.1 Hz, 1H), 7.26 (m, 2H), 4.82 (t, J=2.3 Hz, 1H), 4.35 (t, J=2.3 Hz, 1H), 2.71 (m, 2H), 2.00–2.20 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 155.3, 149.2, 144.2, 127.7, 126.4, 122.0, 120.8, 107.9, 68.1, 34.7, 33.8, 25.1. HRMS (EI): calcd for $[C_{13}H_{13}N]^+$: 183.1048, found 183.1047. HPLC Chiralcel AD column (98:2 hexanes/isopropanol, 1.0 mL/min): t_M=10.5 min, t_m=9.8 min: 71% ee.

*4.4.10. 4-Methyl-N-((1-methyl-2-methylenecyclopentyl)methylene) benzenesulfonamide (**9**).* Yield 75%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.78 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H), 5.05 (br s, 1H), 4.69 (br s, 1H), 2.30–2.55 (m, 2H), 2.43 (s, 3H), 2.09 (m, 1H), 1.80–1.60 (m, 3H), 1.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.4, 154.8, 144.2, 135.0, 129.7, 127.9, 109.8, 51.8, 37.6, 33.4, 23.6, 22.9, 21.6. HRMS (EI): calcd for $[C_{15}H_{19}NO_2S]^+$: 277.1137, found 277.1143. HPLC Chiralcel AD column (95:5 hexanes/ethanol, 1.0 mL/min): t_M=10.2 min, t_m=9.5 min: 64% ee.

4.5. Procedures and characterization of intermediates for the synthesis of the kopsifoline core

*4.5.1. 1-((2-Nitrophenyl)sulfonyl)-5-(pent-4-yn-1-yl)-1,2,3,4-tetrahydropyridine (**4a**).* The title compound was synthesized in four steps from valerolactam (33% overall yield) in analogy to procedures previously reported.[7a]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, J=7.0, 1.5 Hz, 1H), 7.70 (m, 2H), 7.61 (dd, J=7.0, 1.5 Hz, 1H), 3.50 (m, 2H), 2.15 (m, 4H), 1.98 (t, J=2.5 Hz, 1H), 1.94 (t, J=6.0 Hz, 2H), 1.78 (quint, J=6.0 Hz, 2H). 1.65 (quint, J=7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 133.7, 131.6, 130.4, 124.0, 120.7, 119.4, 84.0, 68.8, 43.9, 34.0, 26.2, 24.4, 21.2, 17.7. HRMS (FAB): calcd for $[C_{16}H_{19}N_2O_4S]^+$: 334.09873, found 334.09824.

*4.5.2. 6-Methoxy-1-methylene-7-((2-nitrophenyl)sulfonyl)-7-azaspiro[4.5]decane (**5a′**, major diastereomer).* To a solution of **3a** (980 mg, 2.93 mmol) in diethyl ether (200 mL), acetic acid (19 mL) and methanol (3.2 mL) was added ((*R*)-binaphane)Pd(OTf)$_2$(OH$_2$)$_2$ (35 mg, 1 mol%). After 21 h the reaction was carefully quenched with slow addition of saturated sodium bicarbonate solution (250 mL). Concentration afforded the crude product as a 10:1 mixture of diastereomers, which were separated by flash chromatography (5:1 hexanes/ethyl acetate) to give the title product (840 mg, 78%) as a light yellow oil.

$[\alpha]_D$ +32.3 ($CHCl_3$, *c* 1.0 g/100 mL). HPLC Chiralcel AD column (99:01 hexanes/isopropanol, 1.0 mL/min): t_M=21.5 min, t_m=24.1 min: 90% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (m, 1H), 7.58–7.71 (m, 3H), 4.98 (m, 2H), 4.56 (s, 1H), 3.70 (dd, J=12.0, 3.9 Hz, 1H), 3.19 (dt, J=12.6, 3.6 Hz, 1H), 3.15 (s, 3H), 2.38 (m, 2H), 2.02 (dt, J=12.6, 4.8 Hz, 1H), 1.18–1.82 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 148.2, 134.5, 133.6, 132.0, 130.3, 124.4, 109.5, 89.1, 57.9, 50.3, 41.2, 35.5, 33.8, 29.7, 22.8, 22.2. HRMS (FAB): calcd for $[C_{16}H_{19}N_2O_4S]^+$ (loss of methoxide): 335.10655, found: 335.10643.

*4.5.3. 6-Methoxy-7-((2-nitrophenyl)sulfonyl)-7-azaspiro[4.5]decan-1-one (**12**, major diastereomer).* A solution of **5a′** (750 mg, 2.05 mmol) in methanol (50 mL) was subjected to a stream of ozone at −78 °C for 5 min. Dimethyl sulfide was added, and the solution was allowed to come to room temperature. Concentration yielded a colorless oil, which was taken into dichloromethane (100 mL), washed with water (3×200 mL), and dried over $MgSO_4$. Concentration gave the title product (740 mg, 98%) as a white foam.

$[\alpha]_D$ +41.7 ($CHCl_3$, *c* 0.75 g/100 mL). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J=7.0 Hz, 1H), 7.71 (m, 2H), 7.63 (d, J=7.0, 1H), 4.88 (s, 1H), 3.77 (br d, J=12.0 Hz, 1H), 3.19 (dt, J=13.0, 3.5 Hz, 1H), 3.06 (s, 3H), 2.45 (m, 1H), 2.24 (m, 3H), 1.91 (m, 2H), 1.50–1.52 (m, 3H), 1.17 (d, J=13.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.6, 147.8, 133.9, 131.8, 130.2, 124.2, 85.1, 56.6, 53.4, 40.9, 37.1, 32.3, 25.4, 21.8, 17.6.

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HRMS (FAB): calcd for $[C_{15}H_{17}N_2O_5S]^+$ (loss of methoxide): 337.08582, found: 337.08601.

*4.5.4. (5R,6S)-6-(1H-Indol-3-yl)-7-((2-nitrophenyl)sulfonyl)-7-azaspiro[4.5]decan-1-one (**13**-anti).* To a solution of **12** (236 mg, 0.64 mmol) and indole (112 mg, 0.96 mmol) in dichloromethane (7 mL) at −78 °C was added boron trifluoride etherate (0.09 mL, 0.70 mmol). The reaction was warmed to −30 °C and stirred for 30 min. The reaction was quenched with saturated sodium bicarbonate solution, extracted with dichloromethane, and dried over $MgSO_4$. Flash chromatography (1:1 hexanes/ethyl acetate) gave the title product (115 mg, 40%).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.52 (br, 1H), 7.60 (br d, *J*=6.9 Hz, 1H), 7.40−6.90 (br m, 8H), 5.56 (br s, 1H), 3.87 (br m, 1H), 3.40 (br s, 1H), 1.40−2.50 (br m, 10H). ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 218.6, 134.9, 134.0, 132.7, 131.0, 129.7, 127.9, 123.6, 122.6, 120.3, 118.8, 111.8, 111.3, 52.0, 42.4, 37.7, 36.0, 26.6, 21.1, 18.0. HRMS (ESI$^+$): calcd for $[C_{23}H_{23}N_3O_5S+H]^+$: 454.1437, found: 454.1428.

Relative stereochemistry of the title product as determined via X-ray crystallography (Fig. 3).

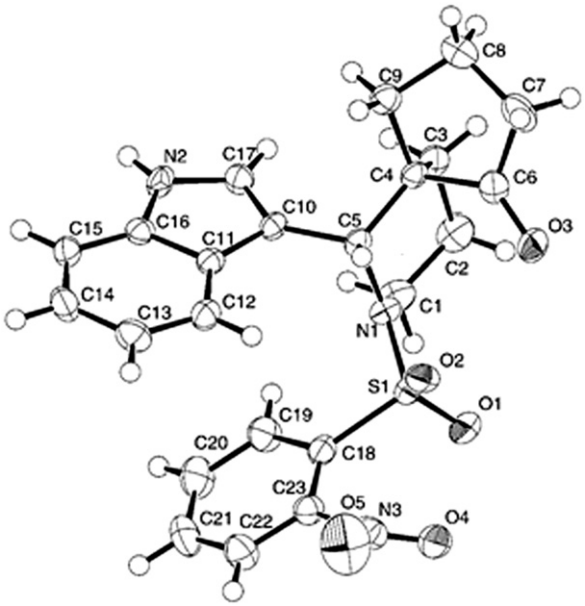

Fig. 3. X-ray structure of **13**-*anti*.

*4.5.5. (5R,6R)-6-(6-Methoxy-1H-indol-3-yl)-7-((2-nitrophenyl)sulfonyl)-7-azaspiro[4.5]decan-1-one (**14**-syn).* To a solution of **12** (750 mg, 2.04 mmol) and 6-methoxyindole (540 mg, 3.67 mmol) in dichloromethane (45 mL) at 0 °C was added boron trifluoride etherate (0.51 mL, 4.06 mmol). The ice bath was removed and the reaction was allowed to stir for 15 min. The reaction was quenched with saturated sodium bicarbonate solution, extracted with dichloromethane, and dried over $MgSO_4$. Flash chromatography (8:5 hexanes/ethyl acetate) gave the desired *syn*-isomer (220 mg, 22%), as well as a mixture of *syn*- and *anti*-isomers (320 mg, 33%). A solution of *anti*-isomer was treated with 1.0 equiv boron trifluoride etherate at room temperature for 15 min and worked up as described above to yield additional desired product (90 mg, 9%) for a total yield of 31%. The relative stereochemistry was assigned by analogy to the corresponding indole adduct (vide supra).

$[\alpha]_D$ −13.0 ($CHCl_3$, *c* 0.15 g/100 mL). ^{1}H NMR (400 MHz, CD_3CN) δ 9.13 (br, 1H), 7.46 (d, *J*=7.6 Hz, 1H), 7.36 (d, *J*=8.0 Hz, 1H), 7.32 (d, *J*=2.4 Hz, 1H), 7.23 (d, *J*=8 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 6.96 (t, *J*=8.0 Hz, 1H), 6.80 (d, *J*=2.0 Hz), 6.61 (dd, *J*=8.4, 2.0 Hz, 1H), 5.45 (s, 1H), 3.78 (m, 1H), 3.76 (s, 3H), 3.36 (m, 1H), 2.57 (m, 1H), 2.28 (td, *J*=14, 4.4 Hz, 1H), 1.65−2.20 (m, 7H), 1.34 (br d, *J*=14 Hz, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 216.6, 156.4, 135.3, 133.2, 132.6, 131.0, 129.2, 123.6, 122.3, 122.0, 117.9, 109.7, 109.5, 94.2, 55.1, 53.2, 50.7, 41.9, 36.5, 33.7, 28.7, 26.1, 21.7, 17.5. HRMS (FAB): calcd for $[C_{24}H_{25}N_3O_3S]^+$: 483.1464, found: 483.1465.

*4.5.6. Methyl 6-methoxy-3-((5R,6R)-2-(methoxycarbonyl)-7-((2-nitrophenyl)sulfonyl)-1-oxo-7-azaspiro[4.5]decan-6-yl)-1H-indole-1-carboxylate (**15**).* To a solution of LHMDS (124 mg, 0.74 mmol) in THF (8 mL) at −78 °C was added a solution of **14**-*syn* (90 mg, 0.186 mmol) and HMPA (68 μL, 0.39 mmol) in THF (8 mL). After stirring for 1 h, methyl cyanoformate (74 μL, 0.93 mmol) was added and the reaction was warmed to room temperature. The reaction was quenched with 10% sodium bicarbonate solution, extracted with dichloromethane, washed with brine, and dried over $MgSO_4$. Flash chromatography (3:2 hexanes/ethyl acetate) gave the title product (79 mg, 71%) as a 2:1:1 keto, *epi*-keto and enol isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br, 0.25H, enol), 7.12−7.70 (m), 6.84−7.00 (m), 6.70−7.80 (m), 5.53 (s, 0.5H), 5.42 (s, 0.25H), 5.21 (s, 0.25H), 4.04 (m), 3.99 (s), 3.94 (d, *J*=12.4 Hz), 3.70 (s), 3.65 (s), 3.45 (m), 3.30 (m), 3.28 (s), 3.21 (t, *J*=10 Hz), 2.91 (dd, *J*=13.2, 6.4 Hz), 2.28−2.80 (m), 1.45−1.95 (m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.0, 209.6, 175.4, 171.2, 169.9, 169.6, 168.6, 158.4, 158.2, 151.2, 151.1, 148.0, 147.5, 134.9 (br), 133.4, 133.1, 133.0, 132.9, 132.8, 131.1, 131.0, 130.7, 130.3, 129.4, 129.2, 124.7, 124.0, 123.8, 123.7, 123.5, 122.7, 122.5, 121.3, 119.5, 118.4, 118.2, 117.5, 114.7, 114.6, 112.6, 112.1, 101.7, 99.3, 98.8, 77.4, 77.3, 77.1, 76.7, 64.4, 60.4, 55.7, 55.0, 54.0, 53.9, 53.7, 53.4, 52.6, 52.4, 51.7, 51.6, 51.3, 50.8, 49.8, 42.8, 42.1, 41.8, 33.6, 33.0, 32.7, 30.7, 28.0, 27.0, 26.9, 23.4, 23.0, 22.5, 21.8, 21.6, 21.3, 21.1, 19.1, 14.2, 13.7. HRMS (FAB): calcd for $[C_{28}H_{29}N_3O_{10}S]^+$: 599.1574, found: 599.1558.

*4.5.7. Methyl 3-((5R,6R)-7-(2-hydroxyethyl)-2-(methoxycarbonyl)-1-oxo-7-azaspiro[4.5]decan-6-yl)-6-methoxy-1H-indole-1-carboxylate (**16**).* A solution of **15** (176 mg, 0.294 mmol), mercaptoacetic acid (0.1 mL, 1.5 mmol), lithium hydroxide (71 mg, 3.0 mmol), and DMF (1 mL) was stirred for 1 h. The reaction mixture was poured into 30% saturated sodium bicarbonate solution (50 mL) and extracted with dichloromethane (5×20 mL). The organic layer was washed with 30% saturated sodium bicarbonate solution and the aqueous layer was further extracted with dichloromethane (2×20 mL). The combined organics were dried over $MgSO_4$ before being concentrated to afford the crude piperidine.

This crude material was dissolved in methanol (8 mL) and added to a solution of ethylene oxide (5 mL) in methanol (10 mL) at −78 °C. The reaction was warmed to room temperature and stirred for 3 h. Concentration and flash chromatography (270:10:0.6:0.6 DCM/MeOH/H_2O/NH_4OH with further elution with 90:10:0.6:0.6) gave the desired ethanolamine (75 mg, 56% yield) as a predominantly 2:1 mixture of diastereomers.

$[\alpha]_D$ +41.3 (CH_2Cl_2, *c* 2.2 g/100 mL). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.77 (br, 1H), 7.43 (m, 1H), 7.26 (m, 1H), 6.89 (m, 1H), 4.00 (s, 3H major), 3.99 (s, 3H minor), 3.86 (s, 3H major), 3.85 (s, 3H minor), 3.68 (s, 3H major), 3.45 (s, 3H, minor), 3.50−3.75 (m), 3.08−3.35 (m), 2.80−2.90 (m), 2.63 (m, 1H), 1.54−2.30 (m), 1.44 (m, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 212.2, 211.9, 169.9, 168.2, 158.3, 158.1, 151.3, 135.7 (br), 123.4 (br), 119.6 (br), 119.1, 117.8 (br), 111.8 (br), 111.7 (br), 99.2 (br), 62.4 (br), 57.8, 57.7, 56.8, 55.7, 55.5, 54.6 (br), 53.8, 52.1, 51.9, 50.6 (br), 35.0, 34.6, 33.4 (br), 32.3 (br), 24.3, 22.9, 22.8, 22.3, 21.3, 20.9. HRMS (FAB): calcd for $[C_{24}H_{31}N_2O_7]^+$ (protonated): 459.2131, found 459.2142.

*4.5.8. (3aR,3a^{1}R,6S,11bS)-methyl 9-methoxy-15-oxo-2,3,3a^1,4,5,6,6a,7,12,13-decahydro-1H-3a,6-methanoindolizino[1′,8′:2,3,4]cyclohepta[1,2-b]indole-6-carboxylate (**1**).* To a suspension of ethanolamine **16** (31 mg, 0.0676 mmol) and potassium carbonate (93 mg, 0.68 mmol) was added methanesulfonyl chloride (13 μL, 0.169 mmol). The

reaction vessel was covered with aluminum foil and the reaction mixture was stirred at room temperature for 16 h before being poured into water and extracted three times with dichloromethane. The combined organics were washed with 10% sodium bicarbonate in brine, and this aqueous phase was back extracted twice with dichloromethane. The combined organics were dried over $MgSO_4$ and concentrated to give the crude chloride, which was used in the next step without further purification.

To a solution of potassium *tert*-butoxide (10 mg, 0.089 mmol) and DMSO (0.5 mL) in THF (7 mL) was added crude chloride **17** (13.5 mg, 0.0283 mmol) in THF (3 mL) at −78 °C. The resulting slurry was stirred for 20 min before being allowed to warm to room temperature. The reaction mixture was quenched with 10% sodium bicarbonate solution and extracted with dichloromethane. The combined organics were washed once with brine and dried over $MgSO_4$. Concentration followed by column chromatography (100:1 DCM/MeOH) gave the title product as a film (4.3 mg, 40% over two steps).

$[\alpha]_D$ +14.3 (CH_2Cl_2, *c* 0.3 g/100 mL). ^1H NMR (400 MHz, C_6D_6) δ 6.78 (d, J=8.4 Hz, 1H), 6.34 (dd, J=8.4, 2.2 Hz, 1H), 5.90 (d, J=2.2 Hz, 1H), 4.67 (s, 1H), 3.90 (br s, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 2.84 (m, 1H), 2.74 (t, J=8.4 Hz, 1H), 2.56 (m, 1H), 2.40 (s, 1H), 2.06–2.22 (m, 2H), 1.96 (m, 2H), 1.72 (m, 2H), 1.56 (dd, J=12.4, 7.6 Hz, 1H), 1.46 (td, J=14.8, 6.8 Hz, 1H), 1.29 (m, 1H), 1.18 (td, J=14.8, 6.8 Hz, 1H), 0.91 (td, J=14.8, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 208.7, 171.7, 160.9, 151.3, 127.7, 122.0, 103.2, 94.1, 80.5, 76.0, 64.8, 54.6, 53.9, 52.8, 51.7, 51.3, 48.3, 44.3, 28.8, 28.1, 21.7, 20.3. HRMS (FAB): calcd for $[C_{22}H_{26}N_2O_4+Li]^+$: 389.2053, found: 389.2049.

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