An Asymmetric Formal Synthesis of Fasicularin

Michaël D. B. Fenster[b] and Gregory R. Dake*[a]

Abstract: An asymmetric formal synthesis of fasicularin (**1**) is described. This natural product, isolated from the extracts of the marine invertebrate *Nephteis fasicularis*, has shown modest cytotoxicity towards Vero cells. Fasicularin is among only two members of the cylindricine family of natural products, along with lepadiformine (**2**), to possess a *trans* A–B ring junction. Key steps of this approach to **1** involve a siloxy-epoxide semipinacol rearrangement of **5** to **6**, a B-alkyl Suzuki–Miyaura coupling reaction by using enol trifluoromethanesulfonate **19** and a substrate-directed hydrogenation reaction of **24**. This formal synthesis also highlights the difficulty in the incorporation of the thiocyanate functionality present in **1**.

Keywords: alkaloids · cross-coupling · semipinacol rearrangement · spirocycle

Introduction

Bioassay-guided screening of an extract of the marine invertebrate *Nephteis fasicularis* led to the isolation of fasicularin (**1**) in 1997 by Patil and co-workers (Figure 1).[1] Ultimately, **1** demonstrated selective activity in a yeast strain in which the RAD 52 gene, implicated in the recombination and repair of DNA double strand breaks, was deleted.[2] Modest cytotoxicity ($IC_{50} = 14\ mg\,mL^{-1}$) of **1** towards Vero cells was subsequently uncovered. Its intriguing tricyclic structure proved to be similar to that of a small family of recently isolated marine-derived natural products, lepidiformine (**2**) and the cylindricines.[3] Unlike the other members of the cylindricine family, **1** lacks oxygenation at its C4 position and is epimeric at C10, the spiro-ring junction adjacent to a nitrogen atom, thus resulting in a *trans*-1-azadecalin A–B ring system.

The tricyclic structure and potential pharmacological properties of **1** and its relatives in the cylindricine family have made them attractive targets for the synthetic organic chemistry community.[4–6] Interestingly, total synthesis proved to be vitally important in the ultimate structural and stereochemical assignment of **2**.[7] In considering a synthetic approach towards **1**, we were intrigued by the 1-azaspirobicyclic structure embedded within its tricyclic framework.

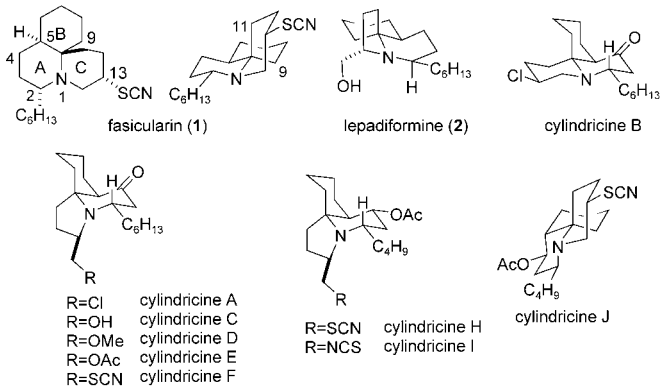

Figure 1.

The use of semipinacol rearrangement reactions in the context of total synthesis has become increasingly more important, perhaps because of the wider accessibility of enantiomerically and diastereomerically enriched starting materials for this process.[8] Our interest in **1** stemmed from the possibility of using a semipinacol rearrangement in order to construct the 1-azaspirobicyclic framework and set the stereochemical identity at C10 in a single operation. During the course of our investigations, two total syntheses that produce **1** in racemic form were disclosed.[4a,b] Each of these approaches established the spirocyclic center in **1** by using elegant cycloaddition strategies. An *N*-acylnitroso Diels–Alder

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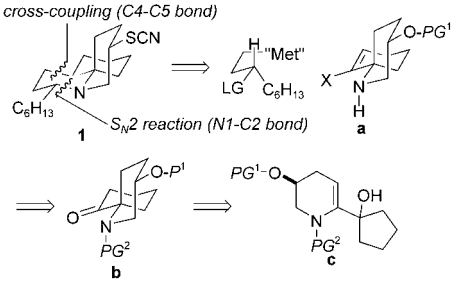
reaction was utilized in the Kibayashi approach,[4a] and a 2-amidoacrolein Diels–Alder cycloadduct formed the precursor to the spirocyclic ring system in the method of Funk and Maeng.[4b]

Our analysis is presented in Scheme 1. We considered that late stage annulation of the A-ring onto the 1-azaspirobicyclic system **a** might be possible. An intramolecular S_N2 reaction would be used to form the N1−C2 bond. The advantage of this approach—the ability to efficiently control the stereochemical outcome during the formation of the N1−C2 bond—outweighed its major drawback that the "annulation" fragment would have to be prepared in enantiomerically enriched form. At the outset, we believed a metal-catalyzed cross-coupling reaction could effectively form the C4−C5 bond. Simplification of **a** led to 1-azaspirocyclic ketone **b**, the key intermediate that we believed would be accessible through a semipinacol reaction on enesulfonamide **c**. The full details of the conversion of a 1-azaspirobicyclic compound similar to **b** to **1** (ultimately in a formal sense) is the subject of this report.

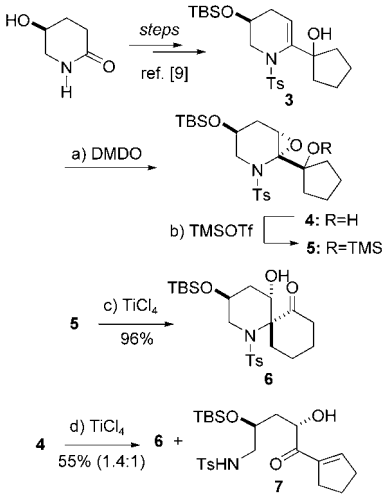


Scheme 1.

Results and Discussion

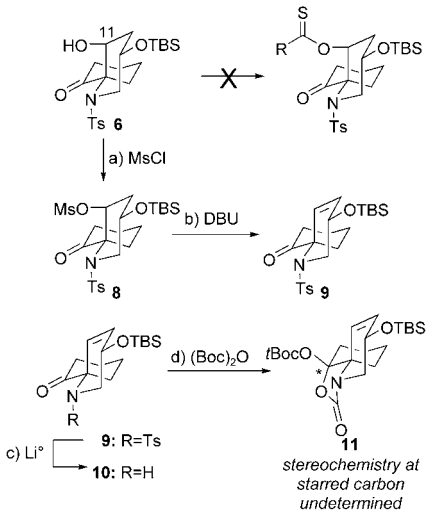
Formation and elaboration of 1-azaspirobicyclic ring system: As elaborated in detail elsewhere,[9] 5*S*-hydroxy-2-piperidone[10] could be elaborated to cyclopentanol **3** in five steps (Scheme 2). Attempts to coerce **3** to ring expand using Brønsted acids or *N*-bromosuccinimide were unsuccessful.[9a] Thus, a siloxy-epoxide semipinacol rearrangement was envisoned to install the critical stereogenic center adjacent to the nitrogen atom.[9,11–15] In the event, after efficient epoxidation and trimethylsilylation, the submission of trimethylsilyl ether **5** to the action of 1.1 equivalents of titanium tetrachloride in dichloromethane at −78 °C resulted in the formation of 1-azaspirobicyclic ketone **6** in 96% yield. A number of features of this reaction are noteworthy: a) the overall efficiency of the ring expansion reaction, especially the clean stereochemical outcome in the formation of the tertiary carbon (the spiro-ring junction) dictated by the epoxide; and b) the requirement of a trimethylsilyl ether for an effective process. Subjection of cyclopentanol **4** to identical conditions as that used for **5** resulted in a messy reaction from which **6** and ketone **7** could be recovered in a 1.4:1 ratio in 55% overall yield. The relative stereochemistry of **6** was established using X-ray crystallography.[15] With the key 1-spirobicyclic ketone **6** in hand, efforts for its elaboration to **1** began in earnest.

As some standard methods to generate a xanthate ester from the alcohol function at C11 in **6** (NaH, CS_2, MeI or KHMDS, CS_2, MeI or C_6F_5OCSCl, 4-DMAP) were unsuccessful,[16] an elimination–hydrogenation sequence was adopted for its removal (Scheme 3). Conversion of **6** to its methanesulfonate derivative **8** occurred uneventfully. We took advantage of the pseudoaxial orientation of this mesylate functional group, as the elimination using 27 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeded smoothly to give alkene **9** in 91% yield. Attempts to remove the *p*-toluenesulfonyl group proved more difficult. Methods employing either sodium amalgam[17] or photochemical conditions[18] yielded complex mixtures. Dissolved metal reduction conditions[19] by using lithium metal in ammonia provided sufficient quantities of the desired amine **10**, although the reaction was capricious, perhaps due to the presence of the ketone functional group (see below). Work to optimize this deprotection process was not undertaken as our attempts to carry out the subsequent step in our proposed construction—the re-protection of the amine function in **10** by using a carbamate protecting group uncovered the first insurmountable obstacle.



Scheme 2. a) DMDO, K_2CO_3, acetone, RT. b) TMSOTf (1.7 equiv), 2,6-lutidine (2.6 equiv), THF, RT, 15 min (83% over both steps). c) $TiCl_4$ (1.1 equiv), CH_2Cl_2, −78 °C, 30 min, 96%. d) $TiCl_4$ (1.1 equiv), CH_2Cl_2, −78 °C, 30 min, 55%.

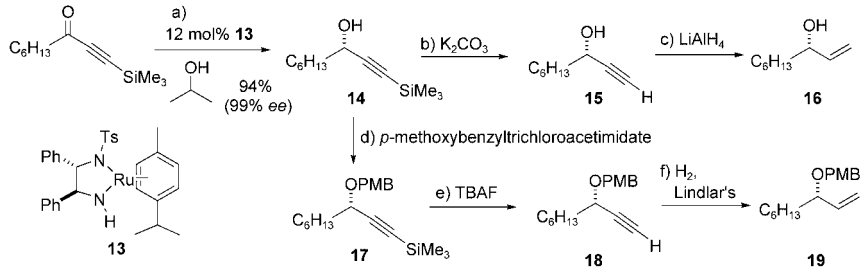
Amine **10** was subjected to 2.1 equivalents of di-*tert*-butylcarbonate and 4-DMAP in dichloromethane at room temperature to yield an unexpected product **11** in 93% yield. While inspection of the ^1H NMR spectrum of the product of this reaction clearly revealed a signal attributable to the *tert*-butyl group of the carbamate, attempts to engage the "carbonyl group" in further reactions were not successful. Analysis of the ^{13}C NMR spectrum of this compound suggested that the initially producted *tert*-butyl carbamate cyclized



Scheme 3. a) MsCl (2.4 equiv), 4-DMAP (4.0 equiv), CH_2Cl_2, RT, 30 min, 87%. b) DBU (27 equiv), toluene, reflux, 36 h, 91%. c) Li (72 equiv), NH_3/THF, −78°C, 5 min, 65% (79% brsm). d) $(Boc)_2O$ (2.1 equiv), 4-DMAP (3.1 equiv), CH_2Cl_2, RT, 30 min, 93%. e) Nitrobenzene, reflux, 97%.

Construction of annulation fragments: Known methods to generate chiral enantiomerically enriched propargyl alcohols were selected to install the needed chirality center within the annulation fragment. Our first experiments used *N*-methylephedrine mediated addition of alkynylzinc triflates to aldehydes as introduced by the Carriera group.[20] Although the addition of trimethylsilylacetylene to heptanal by using this protocol proceeded with acceptable enantioselectivity (~90% *ee*), in our hands the efficiency of the reaction was variable. Yields for this process ranged from 0–60%. Unsatisfied with the fickle nature of this reaction, attention was turned to the use of the Noyori transfer hydrogenation protocol that had been demonstrated to provide propargyl alcohols from ynones in high *ee*.[21]

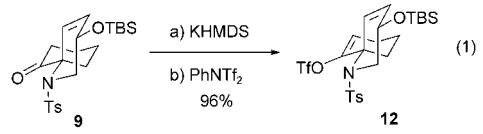
In the event, the reaction of 1-trimethylsilyl-1-nonyn-3-one and isopropanol in the presence of 12 mol% of Noyori's ruthenium(II) transfer hydrogenation catalyst **13** generated propargylic alcohol **14** in 94% yield with 99% *ee* (established using gas chromatography on a chiral column) (Scheme 4).[4c] This process was highly reproducible. Removal of the trimethylsilyl group from **14** to generate terminal alkyne



Scheme 4. a) **13** (12 mol%), 2-propanol, RT, 103 h, 94%, (>99% *ee*). b) K_2CO_3 (3.0 equiv), MeOH, RT, 5 h, 94%. c) $LiAlH_4$ (5.1 equiv), Et_2O, RT, 10 d, 97%. d) *p*-methoxybenzyl trichloroacetimidate, PPTs (31 mol%), CH_2Cl_2, RT, 46 h, 73% (97% brsm). e) TBAF (1.1 equiv), THF, RT, 15 min, 95%. f) H_2 (1 atm), $Pd/CaCO_3$ (Pb poisoned) (11 mol%), EtOH, −6°C, 1.75 h, 93%.

into the adjacent ketone functional group. The alkoxide anion produced from this cyclization then reacted with a second equivalent of di-*tert*-butylcarbonate to give functionalized oxazolidinone **11**. Heating **11** in nitrobenzene converted it back to **10** (97% yield), supporting the structural assignment. Use of one equivalent of di-*tert*-butylcarbonate led only to the formation of **11** in 37% yield with 50% of recovered **10**. Other acylating agents such as trichloroethyloxycarbonyl chloride gave similar results. Although the *p*-toluenesulfonyl protecting group in **9** had been shown to be somewhat difficult to remove cleanly, this complication in the reprotection of **10** forced us to modify the protecting group strategy.

Having decided to delay the removal of the *p*-toluenesulfonyl group in **9** until later in the synthesis, the ketone function in **9** was smoothly converted to enol trifluoromethanesulfonate **12** by using 2.1 equivalents of potassium hexamethyldisilazide and 2.3 equivalents of *N*-phenyltrifluoromethanesulfonimide in 96% yield [Eq. (1)]. Use of one equivalent of base and triflating reagent lowered the yield of **12** to 81%. The next task was the enantioselective preparation of a suitably functionalized annulation fragment.



(1)

15 occurred smoothly using potassium carbonate in methanol (94%). The triple bond in **15** could be reduced smoothly to allyl alcohol **16** by using conventional conditions ($LiAlH_4$, Et_2O, 97%). Protection of the alcohol function in **14** as a PMB ether was best undertaken using acidic conditions (PPTs) with *para*-methoxybenzyl trichloroacetamidate,[22] as anionic conditions (base and *para*-methoxybenzyl chloride) appeared to give a product resulting from a Brook rearrangement.[23] Removal of the trimethylsilyl group in **17** (TBAF, THF, 95%) followed by hydrogenation over Lindlar's catalyst at temperatures below −6°C gave alkene **19** in 94% yield. Overreduction of alkyne **18** was observed if the reaction temperature for the hydrogenation warmed above the specified temperature. With potential annulation fragments **15**, **16**, **18** and **19** in hand, attention was turned on the crucial carbon–carbon bond forming reaction.

Cross-coupling experiments: The enol triflate function within **12** is relatively hindered, and we were concerned that it would not react efficiently with an appropriate organome-

tallic reagent under standard cross coupling conditions. To test this notion with a small organometallic reagent, a Sonogashira-type coupling of alkyne **15** or **18** was initially attempted in order to probe the sensitivity of the triflate to cross-coupling conditions.[24] The results are summarized in Equation (2) and Table 1.

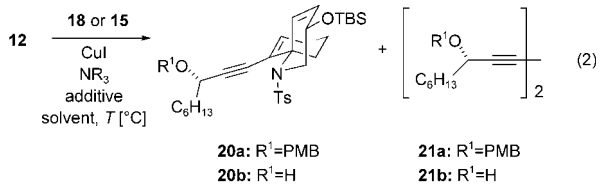


Table 1. Sonogashira coupling of **12** with Alkynes **15** or **18**.

Entry	Alkyne	NR_3	Additive	T [°C]	Solvent	atm	Yield [%] **20**[a]	Yield [%] **12**[a]	Yield [%] **21**[a]
1	**18**	$PrNH_2$	none	25	PhH	N_2	0	97	35
2	**18**	NEt_3	TBAI	50	DMF	N_2	3	82	30
3	**18**	NEt_3	TBAI	60	DMF	Ar	51	42	23
4	**15**	NEt_3	TBAI	60	DMF	Ar	60	30	nd[b]

[a] Isolated yield. [b] nd = not determined.

Adjustment of reaction parameters such as solvent and the inert atmosphere were crucial to obtain the desired cross-coupling product **20**. The isolated yields of the enyne products were moderate even under optimized conditions. A major difficulty was the dimerization of the terminal alkyne under these conditions.[25] Although stringent precautions were undertaken to exclude trace amounts of oxygen from the reaction conditions, this side reaction could not be avoided. The moderate yields of this cross-coupling process combined with the requirement to reduce the alkyne functionality at a later stage suggested that we attempt a more direct approach. We were pleased to find that the enol triflate function within **12** could be engaged in a cross-coupling event, and thus we turned to a B-alkyl Suzuki-Miyaura cross-coupling reaction as a suitable alternative.[26]

Allyl alcohol **16** was therefore hydroborated by using the 9-BBN dimer under the conditions defined by Shibasaki,[27] and then the resulting organoborane was treated with **12** under cross-coupling conditions described by Johnson and Braun using a catalytic amount of either tetrakis(triphenylphosphine)palladium(0) or (1,1′-diphenylphosphineferrocene)palladium dichloride [Eq. (3), Table 2, entries 1 and 2].[28] The Johnson–Braun reaction conditions have been reported to significantly accelerate Suzuki cross-coupling reactions, allowing them to take place at room temperature. In these reactions absolutely no cross-coupling product **22a** was observed-only alkene **23** was formed, presumably via a path involving a β-hydride elimination reaction of an organopalladium intermediate. Fortunately, repeating the above sequence with the PMB ether **19** as the alkene starting material resulted in the formation of the desired cross-coupling product **22b** in good yields (entries 3–7). Tetrakis(triphenylphosphine) palladium(0) was an inferior precatalyst compared with (1,1′-diphenylphosphineferrocene)palladium dichloride. The catalyst loadings could be reduced to 10 or 5 mol % without a substantial decrease in the effectiveness of the process. Our concerns regarding the efficiency of the cross-coupling with this hindered enol triflate appeared to be warranted as no reaction was observed for this process until the reaction was warmed to 60 °C, even when using the Johnson–Braun conditions.

Setting the C5 stereochemistry: With the critical C4–C5 bond formed, the *p*-toluenesulfonyl and *p*-methoxybenzyl groups in **22b** were simultaneously cleaved by using lithium metal in liquid ammonia to produce amine **24** in 83 % yield [Eq. (4)]. This deprotection sequence was reproducible and occurred without complications, in sharp contrast to the experience with ketone **9**. Cyclodehydration occurred uneventfully by using triphenylphosphine and diethylazodicarboxylate to generate tricycle **25** in 92 % yield.[29]

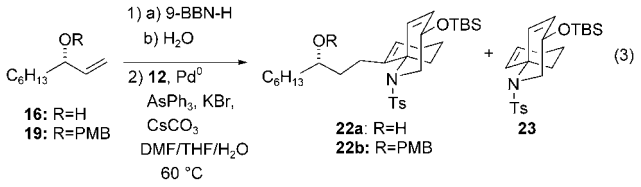
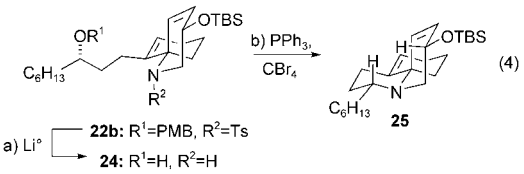


Table 2. B-Alkyl Suzuki–Miyaura coupling of **12**.

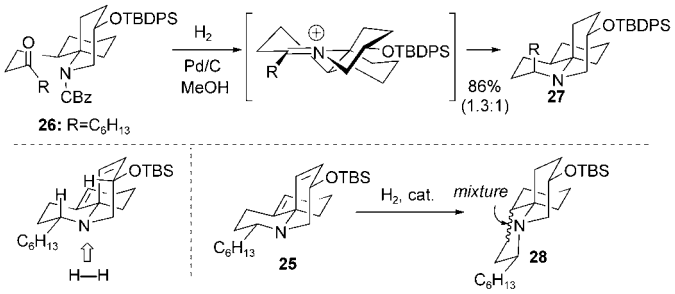
Entry	Substrate	Pd source[a]	Loading [mol %]	Yield [%] **22**[b]	Yield [%] **23**[b]
1	**16**	A	20	0	74
2	**16**	B	20	0	60
3	**19**	A	20	61	16
4	**19**	B	20	82	14
5	**19**	A	5	48	20
6	**19**	B	5	75	13
7	**19**	B	10	84	8

[a] A = Tetrakis(triphenylphosphine)palladium(0), B = (1,1′-diphenylphosphineferrocene)palladium dichloride. [b] Isolated yield.



In the Kibayashi approach, the reductive amination of **26** was initially used to form the tricyclic system of **1** (Scheme 5).[4a] These experiments resulted in the slight preferential formation of the undesired isomer **27**. Considering this result, we expected that hydrogenation of the alkenes within

25 might also occur from the "bottom" face, thus setting the *trans*-junction in the azadecalin system of **1**. Unfortunately, in the event, hydrogenation of **25** over palladium on carbon generated a mixture of epimers (favoring the undesired isomer). Similar results were obtained by using an analogue in which the *tert*-butyldimethylsilyl ether was removed.



Scheme 5.

Consideration of (Dreiding) molecular models suggested an option (Figure 2). Although both faces of tricycle **25** may be sterically encumbered, resulting in low diastereoselectivity in the hydrogenation reaction, a bicyclic system similar to **24** could occur preferentially from the "bottom" face. Specifically, the hexyl side that is projected below the plane of the A–B decalin ring in **25** is not present in bicycle **24**, opening up its "bottom" face. In addition, a directing effect of the amine nitrogen group could also result in preferred hydrogenation from the bottom face of the bicyclic ring system in **24**.[30]

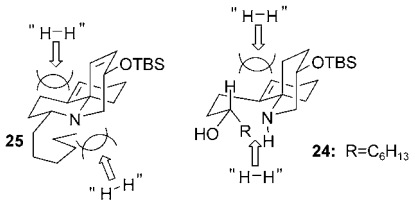


Figure 2.

A summary of hydrogenation screening experiments on **24** is presented in Equation (5) and Table 3. Somewhat surprisingly, hydrogenations over Wilkinson's catalyst, Crabtree's catalyst or ruthenium dioxide gave no reaction (entries 1–3), possibly because of the ability of the amine in **24** to ligate and inactivate the metal catalyst. Hydrogenation over platinum oxide (used in a stoichiometric amount) did yield the desired diastereomer **29** in a modest ratio (2.3:1) (entry 4). A catalytic reaction was possible by using palladium-on-carbon in ethanol, although this reaction failed when using cyclohexane as solvent (entries 5 and 6). The diastereoselectivity of this process was slightly better (4.7:1), and performing the reaction under higher pressures of hydrogen did not improve matters significantly (entry 7). Fortunately, the use of rhodium-on-carbon in ethanol gave the best selectivity, resulting in a 10.5:1 ratio of diastereomers favoring **29** in 76% isolated yield (entry 8). Hydrogenations with this catalyst system in methanol and ethyl acetate were also attempted, but these reactions generated significant amounts of unknown by-products. The diastereoselectivity of those reactions could not be determined as signals resulting from these by-products complicated the ^{1}H NMR spectrum of the crude reaction mixtures.

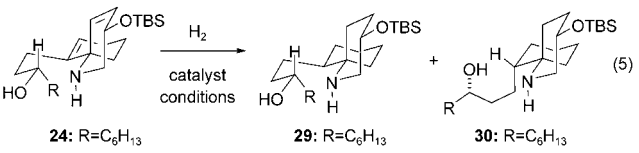


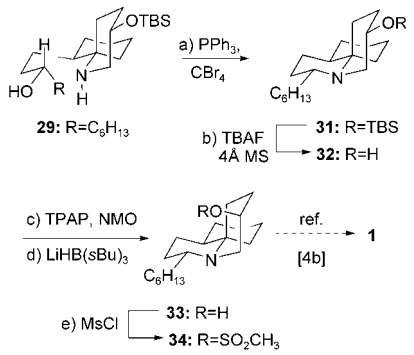
Table 3. Hydrogenations of **24**.

Entry	Catalyst	Loading [mol%]	*p* [atm]	Solvent	Ratio **29**:**30**[a]	Yield [%]
1	$[(PPh_3)_3RhCl]$	20	27	CH_2Cl_2	n/a[b]	no rxn
2	Crabtree's	22	1	CH_2Cl_2	n/a[b]	no rxn
3	RuO_2	26	1	EtOH	n/a[b]	no rxn
4	PtO_2	120	1	EtOH	2.3:1	nd[c]
5	Pd/C	21	1	EtOH	4.7:1	nd[c]
6	Pd/C	21	1	c-C_6H_{12}	n/a[b]	no rxn
7	Pd/C	21	41	EtOH	4.8:1	nd[c]
8	Rh/C	20	1	EtOH	10.5:1[d]	76%[e]

[a] Based on ^{1}H NMR. [b] n/a = not applicable. [c] nd = not determined. [d] Based on isolated yield. [e] Isolated yield.

Completion of the formal synthesis: With the stereochemistry at C-5 established, the cyclization of the A-ring was performed as previously described (PPh_3, DEAD) to obtain **31**.[29] The removal of the *tert*-butyldimethylsilyl group required the use of TBAF in the presence of 4 Å molecular sieves, yielding **32** in 80% yield.[31] The sieves were a crucial additive, as their omission led to the formation of a number of uncharacterizable by-products. Attempts to invert the stereochemistry of the secondary alcohol function within **32** using a Mitsunobu procedure was unsuccessful as a mixture of inversion and retention products were obtained.[32] Thus, oxidation using TPAP-NMO[33] followed by reduction using lithium tri(*sec*-butyl)borohydride generated alcohol **33** (Scheme 6), a late stage intermediate in both the Kibayashi and the Funk constructions of **1**.[4a,b] Transformation of the hydroxyl functional group to a thiocyanate moiety remained to be done.[34]

This reaction sequence, as performed by Kibayashi and Funk, produces **1** in a small amount (~20%) as the minor component in a mixture of at least three compounds. An elimination product and the isothiocyanate corresponding to **1** are also produced during this reaction sequence. In addition, this reaction sequence has been reported to be capricious. Neither the Funk team nor our group could effectively reproduce the conditions reported by Kibayashi (HSCN, PPh_3, DEAD, benzene) to convert **33** to **1**. Funk had consequently developed an alternate set of conditions to carry out



Scheme 6. a) PPh_3 (3.3 equiv), CBr_4 (3.3 equiv), NEt_3 (3.3 equiv), CH_2Cl_2, 0 °C→RT, 5 h, 84 %. b) TBAF (3.1 equiv), 4 Å molecular sieves, CH_2Cl_2, RT, 30 min, 82 %. c) TPAP (11 mol %), NMO (1.4 equiv), 4 Å molecular sieves, CH_2Cl_2, RT, 2 h, 79 %. d) $LiHB(sBu)_3$ (1.7 equiv), THF, −78 °C, 1 h, 67 %. e) MsCl (1.9 equiv), NEt_3 (2.1 equiv), 4-DMAP (0.64 equiv), CH_2Cl_2, 0 °C, 3.5 h, 84 %.

this procedure. Following their method, alcohol **33** was converted to mesylate **34**. Although the reaction of **34** with tetrabutylammonium thiocyanate was attempted several times, only minute amounts of **1** could be observed in the crude reaction mixture. Despite our efforts using column chromatography or high pressure liquid chromatography, we were unable to obtain an analytically pure sample of **1**. A useful solution to this problem remains as a challenge to the synthetic organic chemistry community.

Unlike the previous approaches, our approach, if completed, would have stood as the first asymmetric synthesis of **1**. Unfortunately, as original samples of **1** from the isolate are no longer available and because optical rotation data of **1** was not acquired due to a lack of sample,[35] no data is available for comparison to synthetic material. For this reason, we did not pursue other approaches to install the thiocyanate moiety in **1**.

Conclusion

The details of our synthetic approach towards **1** have been presented. This approach differs markedly from earlier strategies as a cycloaddition reaction was not used to install the critical spirocyclic ring system. Key transformations in this approach are a siloxy-epoxide semipinacol rearrangement, a B-alkyl Suzuki–Miyaura reaction in a complex molecular setting, and a substrate-directed hydrogenation reaction to install the stereochemistry at C-5. The stereogenic centres in our route (except for C-2) were established by stereochemical relay of the C-13 stereogenic center, which was derived from the inexpensive chiral pool reagent, L-glutamic acid. Approaches to other members of the cylindricine family using this synthetic strategy are currently ongoing in our laboratories.

Experimental Section

General methods: All reactions were performed under a nitrogen atmosphere in flame-dried glassware. The glass syringes, Teflon cannulae and stainless steel needles used for handling anhydrous solvents and reagents were oven dried, cooled in a desiccator, and flushed with dry nitrogen prior to use. Plastic syringes were flushed with dry nitrogen before use. Thin-layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Optical rotations of samples were measured using either a Perkin–Elmer model MC-241 or a Jasco model P1010 polarimeter. Infrared (IR) spectra were obtained using a Perkin-Elmer 1710 FT-IR spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded in deuterochloroform using either a Bruker WH-400, Bruker AV-400, or a Bruker AV-300 spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterochloroform using a Bruker AV-400 or a Bruker AV-300 spectrometer. Chemical shifts are reported in parts per million (ppm) and are referenced to the centerline of deuterochloroform (δ 7.24 ppm ^{1}H NMR; 77.0 ppm ^{13}C NMR). Coupling constants (J values) are given in Hertz (Hz). The carbon–fluoride coupling constants are represented as follows: $J_{C,F}$. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were recorded on either a Kratos-AEI model MS 50 spectrometer (for EI), a Kratos MS 80 spectrometer (for CI or DCI), a Micromass LCT (for ESI), or a Bruker Esquire~LC (for ESI). Microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer Model 1106 or a Fisions CHN-O Elemental Analyzer Model 1108. All solvents and reagents were purified and dried using established procedures. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, toluene, triethylamine, 2,6-lutidine, trimethylsilyl trifluoromethanesulfonate were distilled from calcium hydride under an atmosphere of dry nitrogen. *N*,*N*-Dimethylformamide (DMF) was purified by drying over 4 Å molecular sieves. Solutions of methyllithium in diethyl ether, *n*-butyllithium in hexanes were obtained from the Aldrich Chemical Co. and were standardized using the procedure of Kofron and Baclawski.[36] All other reagents were commercially available and were used without further purification.

Epoxide 5: Excess dimethyldioxirane solution in acetone was added to alcohol **3** (1.08 g, 2.39 mmol, 1.0 equiv) and potassium carbonate (3.40 g, 24.6 mmol, 10 equiv) until the reaction was complete by TLC. The mixture was poured into a saturated solution of aqueous ammonium chloride, extracted with dichloromethane, and the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was dissolved in THF (60 mL) and a solution of freshly distilled trimethylsilyl trifluoromethanesulfonate (720 μL, 3.97 mmol, 1.7 equiv) and 2,6-lutidine (720 μL, 6.22 mmol, 2.6 equiv) in THF (60 mL) were added. The mixture was stirred at RT for 15 min. The organic layer was washed sequentially with a saturated solution of aqueous sodium bicarbonate and a saturated solution of aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered and evaporated in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:15; 1 % triethylamine) on silica gel afforded a white solid (1.07 g, 83 %). M.p. 94–95 °C (methanol/hexanes); $[\alpha]_D^{26} = -12.3$ (c = 0.23 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 3.39–3.19 (m, 1H), 3.29 (d, J = 3.1 Hz, 2H), 2.70 (dd, J = 13.4, 9.9 Hz, 1H), 2.40 (s, 3H), 2.25 (dd, J = 15.6, 6.4 Hz, 1H), 2.16–2.00 (m, 1H), 1.97–1.83 (m, 2H), 1.81–1.68 (m, 3H), 1.67–1.53 (m, 3H), 0.75 (s, 9H), 0.16 (s, 9H), −0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 137.4, 129.6, 128.5, 86.0, 72.4, 63.0, 55.6, 51.1, 40.0, 35.9, 33.0, 25.6, 23.5, 21.8, 21.5, 17.8, 2.0, −5.0; IR (KBr): $\tilde{\nu}$ = 2954, 2859, 1353, 1250, 1164, 839 cm^{-1}; elemental analysis calcd (%) for $C_{26}H_{45}NO_5SSi_2$ (539.9): C 57.84, H 8.40, N 2.59; found: C 57.96, H 8.51, N 2.68.

Ketone 6: A 1.0 M dichloromethane solution of titanium tetrachloride (180 μL, 0.18 mmol, 1.1 equiv) was added at −78 °C to a solution of epoxide **5** (89 mg, 0.17 mmol, 1.0 equiv) in dichloromethane (8.0 mL). The mixture was stirred at −78 °C for 0.5 h and then warmed to RT and

poured into a saturated solution of sodium chloride. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:3) on silica gel yielded a white solid (75 mg, 96%). M.p. 137–138°C (methanol); $[\alpha]_D^{26} = -8.6$ (c = 0.25 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.13–4.00 (m, 1H), 4.04 (d, J = 2.4 Hz, 1H), 3.58 (s, 1H), 3.32 (dd, J = 12.0, 8.0 Hz, 1H), 3.06–2.86 (m, 2H), 2.64–2.53 (m, 1H), 2.52–2.44 (m, 1H), 2.41 (s, 3H), 2.10–1.97 (m, 2H), 1.88–1.54 (m, 5H), 0.81 (s, 9H), −0.04 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.9, 143.6, 137.6, 129.6, 127.7, 69.9, 69.5, 62.0, 47.7, 40.9, 35.1, 33.7, 26.9, 25.7, 21.5, 20.2, 17.9, −4.9; IR (KBr): $\tilde{\nu}$ = 3505, 2941, 2858, 1718, 1329, 1149 cm^{-1}; elemental analysis calcd (%) for for $C_{23}H_{37}NO_5SSi$ (467.7): C 59.07, H 7.97, N 2.99; found: C 59.29, H 8.09, N 3.09.

Methanesulfonic ester 8: Methanesulfonyl chloride (190 μL, 2.45 mmol, 2.4 equiv) was added to a solution of **6** (475 mg, 1.01 mmol, 1.0 equiv) and 4-dimethylaminopyridine (499 mg, 4.08 mmol, 4.0 equiv) in dichloromethane (35 mL). The mixture was stirred at RT for 0.5 h and poured into a saturated solution of sodium chloride. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 8:5) on silica gel yielded a foam (527 mg, 87%). $[\alpha]_D^{25} = -19.7$ (c = 0.19 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 5.14–5.09 (m, 1H), 4.19–4.08 (m, 1H), 3.41 (dd, J = 14.3, 5.2 Hz, 1H), 3.09 (s, 3H), 3.06 (dd, J = 14.3, 9.5 Hz, 1H), 3.00–2.88 (m, 1H), 2.70–2.59 (m, 1H), 2.53–2.30 (m, 2H), 2.42 (s, 3H), 2.06–1.95 (m, 1H), 1.87–1.59 (m, 5H), 0.81 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 143.7, 137.7, 129.7, 127.5, 69.9, 62.2, 48.0, 40.8, 39.1, 27.6, 25.6, 21.4, 20.6, 17.8, −5.0; IR (KBr): $\tilde{\nu}$ = 2955, 2859, 1720, 1338, 1178 cm^{-1}; HRMS (DCI+, ammonia/isobutane): m/z: calcd for $C_{24}H_{40}NO_7S_2Si$: 546.2015; found: 546.2017 $[M+H]^+$.

Alkene 9: A solution of **8** (590 mg, 0.980 mmol, 1.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.0 mL, 26 mmol, 27 equiv) in toluene (40 mL) was heated to reflux and stirred for 36 h. The mixture was cooled to RT and poured into water. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:5) on silica gel yielded a white solid (402 mg, 91%). M.p. 102–103°C (ethyl acetate/hexanes); $[\alpha]_D^{24} = +65.4$ (c = 0.20 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.82 (dd, J = 10.4, 1.8 Hz, 1H), 5.74 (d, J = 10.5 Hz, 1H), 4.05–3.95 (m, 1H), 3.31 (ddd, J = 12.2, 6.8, 1.0 Hz, 1H), 2.87 (dd, J = 12.1, 8.8 Hz, 1H), 2.80–2.59 (m, 2H), 2.51–2.28 (m, 2H), 2.40 (s, 3H), 2.04–1.86 (m, 2H), 1.81–1.61 (m, 2H), 0.75 (s, 9H), −0.13 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.6, 143.6, 137.2, 132.5, 129.4, 128.3, 126.0, 68.8, 64.7, 46.8, 39.8, 37.0, 25.6, 23.6, 22.3, 21.5, 18.0, −5.1, −5.2; IR (KBr): $\tilde{\nu}$ = 2933, 1725, 1597, 1331, 1159 cm^{-1}; elemental analysis calcd (%) for $C_{23}H_{35}NO_4SSi$ (449.7): C 61.33, H 7.84, N 3.11; found: C 61.47, H 7.84, N 3.29.

Amine 10: Lithium (23 mg, 3.3 mmol, 72 equiv) was washed three times with HPLC grade pentane and dissolved in ammonia (8.0 mL) at −78°C. A solution of **9** (20.8 mg, 0.046 mmol, 1.0 equiv) in THF (8.0 mL) was added. The mixture was stirred at −78°C for 5 min and quenched by the cautious dropwise addition of ethanol. A saturated solution of aqueous ammonia chloride was added and the mixture was allowed to warm to RT while open to the atmosphere to allow the ammonia to evaporate. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:5) on silica gel yielded (+)-(3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(toluene-4-sulfonyl)-1-azaspiro[5.5]undec-4-en-7-one (**9**) as a white solid (3.7 mg, 18%) and (+)-(3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-1-azaspiro[5.5]undec-4-en-7-one (**10**) as a white solid (8.8 mg, 65%). M.p. 56–57°C (methanol); $[\alpha]_D^{25} = +136$ (c = 0.20 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (dd, J = 10.4, 1.5 Hz, 1H), 5.86 (dd, J = 10.4, 2.9 Hz, 1H), 3.96–3.90 (m, 1H), 2.96 (dd, J = 13.4, 4.6 Hz, 1H), 2.69 (dd, J = 13.6, 6.3 Hz, 1H), 2.65–2.59 (m, 1H), 2.48–2.38 (m, 1H), 2.16–2.06 (m, 2H), 1.99–1.61 (m, 5H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.8, 132.9, 130.4, 64.3, 64.0, 47.3, 40.9, 38.4, 27.8, 25.9, 21.4, 18.2, −4.6; IR (KBr): $\tilde{\nu}$ = 3320, 2929, 1708, 1454 cm^{-1}; HRMS (CI, ammonia/methane): calcd for $C_{16}H_{30}NO_2Si$: 296.2046; found: 296.2046 $[M+H]^+$.

Carbamate 11: 4-Dimethylaminopyridine (79.6 mg, 0.651 mmol, 3.1 equiv) was added in one portion followed by the addition of a solution of di-*tert*-butylcarbonate (93.8 mg, 0.430 mmol, 2.1 equiv) in dichloromethane (5.0 mL) to a solution of **10** (61.9 mg, 0.209 mmol, 1.0 equiv) in dichloromethane (5.0 mL). The mixture was stirred at RT for 0.5 h. A saturated solution of aqueous sodium bicarbonate was added. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:5) on silica gel yielded a clear oil (85.1 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (d, J = 10.7 Hz, 1H), 5.65 (dd, J = 10.5, 2.3 Hz, 1H), 4.41–4.33 (m, 1H), 4.08 (ddd, J = 13.1, 6.7, 0.9 Hz, 1H), 2.75 (dd, J = 13.1, 9.5 Hz, 1H), 2.27 (ddd, J = 14.5, 5.5, 3.4 Hz, 1H), 2.01–1.89 (m, 1H), 1.81–1.57 (m, 4H), 1.55–1.45 (m, 2H), 1.41 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 150.1, 134.1, 124.8, 106.7, 82.8, 62.8, 62.6, 43.3, 31.6, 27.5, 25.7, 18.0, 16.8, 15.4, −4.7, −4.8; IR (NaCl): $\tilde{\nu}$ = 2956, 1786, 1760 cm^{-1}; HRMS (CI, ammonia/methane): m/z: calcd for $C_{22}H_{41}N_2O_6Si$: 457.2734; found: 457.2733 $[M+H_2O]^+$.

Enol trifluoromethanesulfonate 12: A 0.52 M toluene solution of potassium bis(trimethylsilyl)amide (265 μL, 0.138 mmol, 2.1 equiv) was added to a cold (−78°C) solution of **9** (29.3 mg, 0.0652 mmol, 1.0 equiv) in THF (1.6 mL). The mixture was stirred at −78°C for 0.75 h. A solution of *N*-phenylbis(trifluoromethanesulfonimide) (52.5 mg, 0.147 mmol, 2.3 equiv) in THF (1.6 mL) was added and the mixture was stirred at −78°C for 1 h. The mixture was warmed to RT and poured into a saturated solution of aqueous ammonium chloride. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:12; 1% triethylamine) on silica gel yielded a clear oil (36.4 mg, 96%). $[\alpha]_D^{22.6} = +99.6$ (c = 0.261 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 5.91–5.88 (m, 1H), 5.86 (d, J = 10.1 Hz, 1H), 5.63 (d, J = 10.1, 2.0 Hz, 1H), 3.96–3.89 (m, 1H), 3.27 (ddd, J = 12.2, 5.2, 1.2 Hz, 1H), 2.82 (dd, J = 12.2, 9.5 Hz, 1H), 2.63 (td, J = 12.8, 3.7 Hz, 1H), 2.48–2.37 (m, 2H), 2.40 (s, 3H), 2.34–2.21 (m, 2H), 1.95–1.85 (m, 1H), 1.81–1.65 (m, 1H), 0.74 (s, 9H), −0.16 (s, 3H), −0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.2, 144.0, 136.8, 134.4, 129.4, 128.7, 127.9, 120.6, 118.4 (q, $J_{C,F}$ = 317 Hz), 64.4, 61.8, 47.2, 34.8, 25.6, 24.0, 21.5, 19.5, 18.0, −5.3; IR (CCl_4): $\tilde{\nu}$ = 2931, 2859, 1416, 1337, 1164 cm^{-1}; elemental analysis calcd (%) for $C_{24}H_{34}F_3NO_6S_2Si$ (581.7): C 49.55, H 5.89, N 2.41; found: C 49.89, H 6.18, N 2.27.

(−)-(3*S*)-1-Trimethylsilylnon-1-yn-3-ol (14): To a solution of 1-trimethylsilylnon-1-yn-3-one (1.21 g, 5.75 mmol, 1.0 equiv) in isopropanol (55 mL) was added (η^6-*p*-cymene)[(1S,2S)-*N*-*p*-toluenesulfonyl 1,2-diphenylethey-lenediamine]ruthenium(II) (**13**) (64.1 mg, 0.107 mmol, 0.019 equiv) in one portion and the mixture was stirred at RT for 9.5 h. Subsequently additional amounts of **13** were added, each in one portion and the mixture was stirred for the respective period: Compound **13** (57.6 mg, 0.0960 mmol, 0.017 equiv) for 22.5 h; compound **13** (75.4 mg, 0.126 mmol, 0.022 equiv) for 25 h; compound **13** (57.4 mg, 0.0957 mmol, 0.017 equiv) for 45.5 h; compound **13** (78.0 mg, 0.130 mmol, 0.023 equiv) for 55 h; compound **13** (84.1 mg, 0.0140 mmol, 0.024 equiv) stirred for another 48 h. The solvent was removed by evaporation in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 1:12) on silica gel gave a pale yellow oil (1.15 g, 94%). $[\alpha]_D^{19.9} = -0.19$ (c = 1.28 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (dd, J = 12.2, 6.7 Hz, 1H), 1.95 (d, J = 5.8 Hz, 1H), 1.73–1.57 (m, 2H), 1.47–1.35 (m, 2H), 1.34–1.20 (m,

6H), 0.85 (t, $J=6.7$ Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 107.0, 89.2, 62.9, 62.8, 37.7, 31.7, 28.8, 25.0, 22.5, 14.0, 0.20, −0.17, −0.51; IR (NaCl): $\tilde{\nu}=3338$, 2932, 2860, 2173 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{24}OSi$ (212.4): C 67.86, H 11.39; found: C 67.56, H 11.66.

(3*S*)-Non-1-yn-3-ol (15): A solution of (−)-(3*S*)-1-trimethylsilylnon-1-yn-3-ol (**14**) (419 mg, 1.97 mmol, 1.0 equiv) and potassium carbonate (823 mg, 5.95 mmol, 3.0 equiv) in methanol (40 mL) was stirred at RT for 5 h and then poured into a saturated solution of aqueous sodium chloride and extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 2:11) on silica gel afforded a pale yellow oil (261 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 (t, $J=6.2$ Hz, 1H), 2.43 (d, $J=2.1$ Hz, 1H), 1.89 (br s, 1H), 1.73–1.64 (m, 2H), 1.48–1.38 (m, 2H), 1.35–1.22 (m, 6H), 0.86 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 85.0, 72.8, 62.3, 37.6, 31.7, 28.9, 24.9, 22.5, 14.0; IR (KBr): $\tilde{\nu}=3379$, 3311, 2929, 2859 cm^{-1}.

(3*S*)-Non-1-en-3-ol (16): Lithium aluminum hydride (550 mg, 14.5 mmol, 5.1 equiv) was added in three portions with 10 min intervals to a cold (0 °C) solution of (3*S*)-non-1-yn-3-ol (**15**) (400 mg, 2.85 mmol, 1.0 equiv) in diethyl ether (40 mL). The mixture was warmed to RT and allowed to stir for 10 d. The mixture was cooled to 0 °C and quenched by cautious addition of water (2.2 mL). Magnesium sulfate was added and the mixture was stirred at RT for 1 h. The mixture was filtered and the solvent was evaporated in vacuo to afford a clear oil (393 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddd, $J=17$, 11, 6.0 Hz, 1H), 5.19 (d, $J=17$ Hz, 1H), 5.07 (d, $J=11$ Hz, 1H), 4.19–3.95 (m, 1H), 1.78–0.99 (m, 11H), 0.85 (t, $J=7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 114.4, 73.2, 37.0, 31.7, 29.2, 25.2, 22.5, 14.0; IR (NaCl): $\tilde{\nu}=3352$, 2929, 1644 cm^{-1}.

(−)-(3*S*)-[3-(4-Methoxybenzyloxy)-non-1-ynyl]-trimethylsilane (17): A solution of 4-methoxybenzyl trichloroacetimidate (764 mg, 2.70 mmol, 1.6 equiv) in dichloromethane (25 mL) was added to a solution of (−)-(3*S*)-1-trimethylsilylnon-1-yn-3-ol (**14**) (353 mg, 1.66 mmol, 1.0 equiv) in dichloromethane (50 mL). Pyridium *p*-toluenesulfonate (130 mg, 0.517 mmol, 0.31 equiv) was added in one portion and the mixture was stirred at RT for 46 h. The mixture was poured into a saturated solution of aqueous sodium bicarbonate. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 1:12) on silica gel yielded the starting material as a pale yellow oil (88.8 mg, 25%) and a clear oil (405 mg, 73%). $[\alpha]_D^{19.9}=-118.07$ (c = 2.48 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27 (d, $J=8.5$ Hz, 2H), 6.86 (d, $J=8.5$ Hz, 2H), 4.70 (d, $J=11.6$ Hz, 1H), 4.43 (d, $J=11.6$ Hz, 1H), 4.02 (t, $J=6.6$ Hz, 1H), 3.79 (s, 3H), 1.78–1.61 (m, 2H), 1.48–1.36 (m, 2H), 1.30–1.21 (m, 6H), 0.86 (t, $J=6.7$ Hz, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 130.2, 129.6, 113.7, 105.2, 90.3, 70.0, 68.7, 55.1, 35.6, 31.7, 28.9, 25.2, 22.5, 14.0, 0.0; IR (NaCl): $\tilde{\nu}=2956$, 2859, 2168, 1613, 1515, 1250 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{32}O_2Si$ (332.6): C 72.23, H 9.70; found: C 72.27, H 9.94.

(−)-(1*S*)-1-(1-Ethynylheptyloxymethyl)-4-methoxybenzene (18): Tetrabutylammonium fluoride (1.40 mL, 1.40 mmol, 1.1 equiv) was added to a solution of (−)-(3*S*)-[3-(4-methoxybenzyloxy)-non-1-ynyl]-trimethylsilane (**17**) (405 mg, 1.22 mmol, 1.0 equiv) in THF (50 mL). The mixture was stirred at RT for 15 min and then poured into water. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by evaporation in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 1:30) on silica gel yielded a clear oil (301 mg, 95%). $[\alpha]_D^{22.4}=-110.22$ (c = 0.230 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, $J=8.5$ Hz, 2H), 6.86 (d, $J=8.5$ Hz, 2H), 4.71 (d, $J=11.3$ Hz, 1H), 4.42 (d, $J=11.3$ Hz, 1H), 4.02 (td, $J=6.6$, 2.1 Hz, 1H), 3.78 (s, 3H), 2.43 (d, $J=2.1$ Hz, 1H), 1.80–1.63 (m, 2H), 1.47–1.37 (m, 2H), 1.33–1.21 (m, 6H), 0.85 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 129.9, 129.5, 113.7, 83.1, 73.6, 70.0, 68.0, 55.1, 35.6, 31.7, 28.9, 28.9, 25.1, 22.5, 14.0; IR (NaCl): $\tilde{\nu}=3293$, 2931, 2859, 1613, 1515, 1249 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{24}O_2$ (260.4): C 78.42, H 9.29; found: C 78.29, H 9.63.

(−)-(1*S*)-1-Methoxy-4-(1-vinylheptyloxymethyl)-benzene (19): (−)-(1*S*)-1-(1-Ethynylheptyloxymethyl)-4-methoxybenzene (**18**) (229 mg, 0.879 mmol, 1.0 equiv) and Pd/C 5 wt% on calcium carbonate (209 mg, 0.0982 mmol, 0.11 equiv) were dissolved in ethanol (40 mL). Quinoline (810 mL, 6.84 mmol, 7.8 equiv) was added and the mixture was cooled to −6 °C. One atmosphere of hydrogen was introduced and the mixture was stirred at −6 °C for 1.75 h. The suspension was filtered through Celite and the solvent was removed by evaporation in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:20) on silica gel yielded a pale yellow oil (214 mg, 93%). $[\alpha]_D^{22.0}=-36.08$ (c = 0.203 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, $J=8.7$ Hz, 2H), 6.87 (d, $J=8.7$ Hz, 2H), 5.73 (ddd, $J=17.1$, 10.7, 7.6 Hz, 1H), 5.21 (d, $J=2.4$ Hz, 1H), 5.18 (dd, $J=10.7$, 1.1 Hz, 1H), 4.52 (d, $J=11.6$ Hz, 1H), 4.28 (d, $J=11.6$ Hz, 1H), 3.79 (s, 3H), 3.73–3.66 (m, 1H), 1.69–1.58 (m, 1H), 1.53–1.20 (m, 9H), 0.88 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 139.4, 131.0, 129.2, 116.7, 113.7, 80.2, 69.6, 55.2, 35.5, 31.8, 29.2, 25.3, 22.6, 14.0; IR (NaCl): $\tilde{\nu}=3076$, 2932, 2859, 1615, 1466, 1041, 927 cm^{-1}. HRMS (EI): calcd for $C_{17}H_{26}O_2$: 262.1933; found: 262.1938.

Alkene 22b: DMF and water were degassed for 15 min prior to use by sparging with nitrogen gas. To a solution of (−)-(1*S*)-1-methoxy-4-(1-vinylheptyloxymethyl)-benzene (**19**) (706 mg, 2.69 mmol, 1.3 equiv) in THF (18 mL) was added 9-borabicyclo[3.3.1]nonane dimer (2.07 g, 8.48 mmol, 4.1 equiv) and the mixture was stirred at RT for 1 h. Water (665 μL, 36.8 mmol, 17.7 equiv) was added and the mixture was stirred at RT for 1 h. To a round bottom containing dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct (170 mg, 0.208 mmol, 0.10 equiv), triphenylarsine (66.5 mg, 0.217 mmol, 0.10 equiv), potassium bromide (293 mg, 2.46 mmol, 1.2 equiv), and cesium carbonate (1.37 mg, 4.20 mmol, 2.0 equiv) was added a solution of **12** (1.21 g, 2.08 mmol, 1.0 equiv) in DMF (18 mL).

To this mixture was added the borane solution. The resulting dark red solution was stirred at 60 °C for 14 h. The mixture was cooled to RT and poured into a solution of diethyl ether. The organic layer was washed sequentially with water and a saturated solution of aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (ethyl acetate/hexanes 1:15) afforded a clear oil (1.22 g, 84%). $[\alpha]_D^{20.5}=+100.7$ (c = 0.212 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, $J=8.5$ Hz, 2H), 7.22 (d, $J=8.5$ Hz, 2H), 7.18 (d, $J=7.9$ Hz, 2H), 6.84–6.78 (m, 2H), 5.64–5.56 (m, 2H), 5.53 (dd, $J=10.2$, 1.7 Hz, 1H), 4.42 (dd, $J=18.3$, 11.3 Hz, 2H), 4.11–4.04 (m, 1H), 3.76 (s, 3H), 3.46–3.34 (m, 2H), 2.81 (dd, $J=11.9$, 9.2 Hz, 1H), 2.49–1.96 (m, 6H), 2.36 (s, 3H), 1.91–1.20 (m, 14H), 0.86 (t, $J=6.7$ Hz, 3H), 0.78 (s, 9H), −0.10 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 143.2, 140.0, 137.8, 134.0, 131.4, 129.4, 129.2, 127.7, 122.8, 113.7, 78.8, 70.2, 65.3, 64.2, 55.2, 48.1, 34.0, 33.3, 32.6, 31.9, 29.6, 26.3, 25.7, 25.5, 24.9, 22.7, 21.4, 20.0, 18.1, 14.1, −4.9, −5.0; IR (CCl_4): $\tilde{\nu}=2931$, 2859, 1332, 1162 cm^{-1}; LRMS (CI, ammonia): m/z (%): 696 (8) $[M+H]^+$.

Alkene 23: DMF and water were degassed for 15 min prior to use by sparging with nitrogen gas. To (3*S*)-non-1-en-3-ol (**16**) (11.5 mg, 0.0866 mmol, 1.9 equiv) in THF (0.6 mL) was added 9-borabicyclo[3.3.1]-nonane dimer (62.7 mg, 0.257 mmol, 6.2 equiv) and the mixture was stirred at RT for 1 h. Water (15 μL, 0.830 mmol, 20 equiv) was added via syringe and the mixture was stirred for 1 h. To a round bottom containing dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (6.8 mg, 0.0083 mmol, 0.20 equiv), triphenylarsine (2.5 mg, 0.0082 mmol, 0.20 equiv), potassium bromide (6.4 mg, 0.0538 mmol, 1.3 equiv), and cesium carbonate (28.2 mg, 0.0866 mmol, 2.1 equiv) was added a solution of **12** (1.21 g, 2.08 mmol, 1.0 equiv) in DMF (0.3 mL).

To this mixture was added the borane solution. The resulting dark red solution was stirred at 60 °C for 16 h. The mixture was cooled to RT and poured into a solution of diethyl ether. The organic layer was washed sequentially with water and a saturated solution of aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatog-

raphy (ethyl acetate/hexanes 1:15) afforded a clear oil (10.8 mg, 60%). $[\alpha]_D^{26.5}=+66.9$ (c = 0.187 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.71 (d, $J=8.2$ Hz, 2H), 7.24 (d, $J=7.9$ Hz, 2H), 5.79–5.73 (m, 1H), 5.57–5.50 (m, 3H), 4.09 (dd, $J=9.2$, 5.5 Hz, 1H), 3.82 (dd, $J=12.8$, 5.5 Hz, 1H), 2.93 (dd, $J=12.8$, 9.2 Hz, 1H), 2.39 (s, 3H), 2.21 (ddd, $J=12.8$, 11.9, 3.7 Hz, 1H), 2.12–2.01 (m, 1H), 2.00–1.88 (m, 2H), 1.78–1.68 (m, 1H), 1.67–1.53 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 139.6, 133.7, 130.3, 129.3, 128.8, 128.1, 127.4, 65.1, 60.4, 47.6, 32.6, 25.7, 24.1, 21.4, 19.7, 18.1, −4.8, −4.9; IR (KBr): $\tilde{\nu}=$2931, 2859, 1340, 1163 cm^{-1}; LRMS (CI, ammonia): m/z (%): 434 (49) $[M+H]^+$.

Amine 24: Lithium (12.9 mg, 1.86 mmol, 29 equiv) was washed three times with HPLC grade pentane and dissolved in ammonia (10 mL) at −78°C. A solution of **22b** (44.4 mg, 0.0638 mmol, 1.0 equiv) in THF (3.0 mL) was added. The mixture was stirred for 10 min at −78°C and quenched by the dropwise addition of methanol. A saturated solution of aqueous ammonia chloride was added and the mixture was allowed to warm to RT while open to the atmosphere to allow the ammonia to evaporate. The two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 1:2) on silica gel yielded a clear oil (22.4 mg, 83%). $[\alpha]_D^{19.8}=+72.3$ (c = 0.213 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (d, $J=10.4$ Hz, 1H), 5.60–5.55 (m, 1H), 5.25 (dd, $J=10.4$, 2.1 Hz, 1H), 4.33–4.26 (m, 1H), 3.52–3.42 (m, 1H), 2.99 (ddd, $J=10.7$, 5.8, 1.2 Hz, 1H), 2.66 (dd, $J=10.7$, 9.2 Hz, 1H), 2.14–1.87 (m, 6H), 1.69–1.61 (m, 1H), 1.60–1.49 (m, 1H), 1.47–1.18 (m, 12H), 0.86–0.81 (m, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 134.0, 131.9, 125.3, 67.2, 65.8, 55.9, 46.3, 37.2, 36.6, 31.8, 31.8, 29.5, 26.0, 25.8, 25.4, 25.1, 22.6, 18.9, 18.0, 14.0, −4.6, −4.7; IR (CCl_4): $\tilde{\nu}=$3284, 2930, 2858, 1109 cm^{-1}; LRMS (CI, ammonia): m/z (%): 422 (100) $[M+H]^+$, 421 (8) $[M]^+$.

Tricyclic amine 25: To a cold (0°C) solution **24** (129 mg, 0.306 mmol, 1.0 equiv) and triphenylphosphine (160 mg, 0.612 mmol, 2.0 equiv) in dichloromethane (6.0 mL) was added carbon tetrabromide (203 mg, 0.612 mmol, 2.0 equiv) followed by the addition of triethylamine (85 μL, 0.610 mmol, 2.0 equiv). The pale yellow solution turned red as it was allowed to warm to RT and stirred for 0.5 h. The solvent was removed by evaporation in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 1:11) on silica gel afforded a pale yellow oil (113 mg, 92%). $[\alpha]_D^{21.7}=+120.2$ (c = 0.205 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dd, $J=10.4$, 1.5 Hz, 1H), 5.68 (d, $J=$ 10.4 Hz, 1H), 5.43–5.39 (m, 1H), 4.40–4.32 (m, 1H), 3.18 (ddd, $J=14.4$, 6.2, 1.0 Hz, 1H), 3.10 (dd, $J=14.4$, 9.9 Hz, 1H), 2.74–2.66 (m, 1H), 2.38–2.30 (m, 1H), 2.06–1.88 (m, 4H), 1.77–1.58 (m, 5H), 1.54–1.08 (m, 10H), 0.90–0.84 (m, 12H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.2, 16.5, 129.6, 122.1, 60.7, 57.9, 55.5, 47.7, 39.9, 34.3, 32.4, 32.1, 31.8, 29.9, 26.0, 25.3, 25.2, 22.6, 20.2, 18.3, 14.1, −4.5, −4.6; IR (CCl_4): $\tilde{\nu}=$3084, 2931, 2859, 1519, 1250 cm^{-1}; LRMS (CI, ammonia): m/z (%): 404 (100) $[M+H]^+$, 403 (5) $[M]^+$.

Alcohol 29: Alkene **24** (143.9 mg, 0.341 mmol, 1.0 equiv) and Rh/C 5 wt% on carbon (141 mg, 0.0684 mmol, 0.20 equiv) were dissolved in ethanol (17 mL). The mixture was stirred under 1 atm H_2 at RT for 24 h. The mixture was filtered through Celite and the solvent was removed by evaporation in vacuo. Purification by gradient column chromatography (ethyl acetate/hexanes 1:2 → ethyl acetate) on silica gel afforded (−)-(3*S*)-1-[(3*S*,6*R*,7*S*)-3-(*tert*-butyldimethylsilyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3-ol (**30**) as a clear oil (9.6 mg, 6.6%) and (+)-(3*S*)-1-[(3*S*,6*R*,7*R*)-3-(*tert*-butyldimethylsilyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3-ol (**29**) as a clear oil (99.7 mg, 69%).

Compound **29**: $[\alpha]_D^{20.7}=+31.60$ (c = 0.201 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59–3.44 (m, 2H), 2.80 (ddd, $J=11.6$, 5.5, 4.9 Hz, 1H), 2.69 (dd, $J=11.6$, 10.1 Hz, 1H), 2.28–2.19 (m, 1H), 1.78–1.51 (m, 6H), 1.48–0.82 (m, 32H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.3, 69.9, 53.3, 48.0, 46.1, 37.6, 35.9, 32.6, 31.8, 29.8, 29.4, 28.3, 25.8, 25.3, 25.1, 24.6, 22.6, 18.1, 14.1, −4.6; IR (CCl_4): $\tilde{\nu}=$ 3255, 3148, 2929, 2857, 1456, 1361, 1110 cm^{-1}; HRMS (EI): m/z: calcd for $C_{25}H_{51}NO_2Si$: 425.3689; found: 425.3691.

Compound **30**: $[\alpha]_D^{20.4}=-22.37$ (c = 0.152 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.57–3.47 (m, 2H), 2.77 (ddd, $J=12.2$, 4.6, 1.2 Hz, 1H), 2.55 (dd, $J=12.2$, 8.9 Hz, 1H), 2.09–1.99 (m, 1H), 1.82–1.65 (m, 3H), 1.63–1.15 (m, 20H), 1.06–0.96 (m, 3H), 0.87–0.83 (m, 12H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.6, 69.3, 52.6, 47.6, 44.3, 37.5, 36.8, 32.5, 31.8, 30.6, 29.7, 29.4, 26.8, 25.9, 25.6, 24.3, 22.6, 21.2, 18.1, 14.1, −4.6; IR (CCl_4): $\tilde{\nu}=$3628, 3368, 2859 cm^{-1}; HRMS (EI): m/z: calcd for $C_{25}H_{51}NO_2Si$: 425.3689; found: 425.3697.

Amine 31: To a cold (0°C) solution of (+)-(3*S*)-1-[(3*S*,6*R*,7*R*)-3-(*tert*-butyldimethylsilyloxy)-1-azaspiro[5.5]undec-7-yl]-nonan-3-ol (**29**) (36.7 mg, 0.0862 mmol, 1.0 equiv) and triphenylphosphine (74.6 mg, 0.284 mmol, 3.3 equiv) in dichloromethane (2.5 mL) was added carbon tetrabromide (94.3 mg, 0.284 mmol, 3.3 equiv) followed by the addition of triethylamine (40 μL, 0.287 mmol, 3.3 equiv). The pale yellow solution was allowed to warm to RT and stirred for 5 h. The solvent was removed by evaporation in vacuo. Purification by column chromatography (diethyl ether/petroleum ether 1:4; 2% ammonium hydroxide) on silica gel afforded a clear oil (29.6 mg, 84%). $[\alpha]_D^{20.8}=+4.51$ (c = 0.265 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$3.95–3.86 (m, 1H), 2.97–2.82 (m, 3H), 2.63 (d, $J=13.1$ Hz, 1H), 1.84–1.47 (m, 1H), 1.40–1.10 (m, 17H), 1.03–0.93 (m, 1H), 0.86 (s, 12H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$62.5, 56.6, 53.5, 47.3, 45.9, 34.5, 34.2, 32.6, 31.8, 30.0, 29.9, 29.8, 27.2, 26.2, 25.9, 25.4, 22.8, 22.6, 18.2, 17.5, 14.1, −4.6; IR (CCl_4): $\tilde{\nu}=$2929, 2860, 1464, 1092 cm^{-1}; HRMS (EI): m/z: calcd for $C_{25}H_{49}NOSi$: 407.3583; found: 407.3579.

Alcohol 32: A solution of silyl ether **31** (40.0 mg, 0.0981 mmol, 1.0 equiv) in THF (5.0 mL) was added to a round bottom containing powdered activated 4 Å molecular sieves (500 mg). Tetrabutylammonium fluoride, pretreated with 4 Å molecular sieves, (300 μL, 0.300 mmol, 3.1 equiv) was added and the mixture was stirred at RT for 0.5 h. The reaction was filtered and the solvent removed by evaporation in vacuo. Purification by gradient column chromatography (diethyl ether→diethyl ether/methanol 19:1; 2% ammonium hydroxide) afforded a white solid (23.7 mg, 82%). M.p. 69–71°C (ethyl acetate/hexanes); $[\alpha]_D^{20.3}=+4.2$ (c = 0.259 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$):δ = 3.99–3.87 (m, 1H), 3.07 (ddd, $J=14.4$, 4.6, 1.8 Hz, 1H), 2.90–2.80 (m, 2H), 2.57 (d, $J=13.1$ Hz, 1H), 1.95–1.47 (m, 8H), 1.41–0.96 (m, 18H), 0.85 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 61.8, 56.7, 53.5, 47.1, 45.8, 34.5, 34.0, 32.5, 31.9, 29.9, 29.7, 27.1, 26.1, 25.5, 22.7, 22.6, 17.4, 14.1; IR (CCl_4): $\tilde{\nu}=$3084, 2925, 2860, 1469, 1083 cm^{-1}.

Alcohol 33: A solution of alcohol **32** (22.9 mg, 0.0780 mmol, 1.0 equiv) in dichloromethane (2.5 mL) was added to a round bottom containing powdered activated 4 Å molecular sieves (83 mg). Tetrapropylammonium perruthenate (3.1 mg, 0.0088 mmol, 0.11 equiv) was added in one portion. The mixture was cooled to 0°C and 4-methylmorpholine *N*-oxide (12.9 mg, 0.110 mmol, 1.4 equiv) was added in one portion. The mixture was warmed to RT, stirred for 2 h, filtered through Celite, and the solvent was removed by evaporation in vacuo. Purification by column chromatography (diethyl ether/hexanes 1:1) on silica gel afforded a clear oil (18.0 mg, 79%). $[\alpha]_D^{21.2}=+102.6$ (c = 0.178 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$3.95–3.86 (m, 1H), 2.97–2.82 (m, 3H), 2.63 (d, $J=$ 13.1 Hz, 1H), 1.84–1.47 (m, 1H), 1.40–1.10 (m, 17H), 1.03–0.93 (m, 1H), 0.86 (s, 12H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$213.3, 56.5, 54.8, 53.6, 45.1, 35.8, 34.1, 33.8, 32.2, 31.8, 29.7, 26.8, 25.9, 24.7, 23.2, 22.6, 20.1, 14.0; IR (CCl_4): $\tilde{\nu}=$2931, 2861, 1719 cm^{-1}.

To a cold (−78°C) solution of (+)-(1*R*,7*R*,10*R*)-7-hexyl-6-azatricyclo[8.4.0.01,6]tetradecan-4-one (11.2 mg, 0.0384 mmol, 1.0 equiv) in THF (1.9 mL) was added L-Selectride (25 μL, 0.0250 mmol, 1.7 equiv) and the mixture was stirred at −78°C for 1 h. 3N Sodium hydroxide (0.48 mL) was added followed by the addition of 30% hydrogen peroxide (0.42 mL). The mixture was warmed to RT and poured into a saturated solution of aqueous potassium sodium tartrate. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by gradient column chromatography (diethyl ether/methanol 19:1→ diethyl ether/methanol 9:1; 1% ammonium hydroxide) on silica gel yielded a clear oil (7.5 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$3.77 (s, 1H), 3.43–3.33 (m, 1H),

3.19 (d, $J=16.2$ Hz, 1H), 3.09 (dd, $J=16.2$, 2.4 Hz, 1H), 2.39 (d, $J=11.9$ Hz, 1H), 2.05 (dt, $J=13.7$, 3.9 Hz, 1H), 1.87 (tt, $J=14.0$, 3.9 Hz, 1H), 1.82–1.54 (m, 5H), 1.45–0.93 (m, 19H), 0.85 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=67.4$, 57.0, 55.5, 46.6, 45.1, 34.9, 33.8, 32.7, 31.9, 30.3, 30.0, 29.4, 27.7, 27.2, 26.2, 25.2, 22.7, 14.1, 13.0.

Mesylate 34: Triethylamine (10 μL, 0.0717 mmol, 2.1 equiv), 4-dimethylaminopyridine (2.7 mg, 0.022 mmol, 0.64 equiv) were added in one portion and methanesulfonyl chloride (5.0 μL, 0.065 mmol, 1.9 equiv) to a cold (0 °C) solution of alcohol **33** (10.2 mg, 0.0348 mmol, 1.0 equiv) in dichloromethane (1.0 mL). The mixture was stirred at 0 °C for 3.5 h and then poured into a saturated solution of aqueous sodium bicarbonate. The two layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated in vacuo. Purification by column chromatography (ethyl acetate/methanol 9:1) on silica gel gave a pale yellow oil (10.8 mg, 84 %). $[\alpha]_D^{19.4}=-13.0$ ($c=0.108$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.70$ (s, 1H), 3.40 (d, $J=17.1$ Hz, 1H), 3.23 (dd, $J=16.8$, 2.3 Hz, 1H), 3.20–3.12 (m, 1H), 2.97 (s, 3H), 2.32 (d, $J=12.5$ Hz, 1H), 2.10–1.93 (m, 3H), 1.80–1.55 (m, 4H), 1.48–0.95 (m, 19H), 0.85 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=78.4$, 56.6, 54.8, 46.4, 43.7, 38.4, 34.2, 33.7, 32.3, 32.0, 30.0, 29.2, 27.0, 26.1, 25.6, 24.9, 22.7, 14.1, 13.1; IR (CCl_4): $\tilde{\nu}=2931$, 2861, 1462, 1342 cm^{-1}.

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[1] A. D. Patil, A. J. Freyer, R. Reichwein, B. Carte, L. B. Killmer, L. Faucette, R. K. Johnson, D. J. Faulkner, *Tetrahedron Lett.* **1997**, *38*, 363–364.

[2] W. K. Eng, L. Faucette, R. K. Johnson, R. Sternglanz, *Mol. Pharmacol.* **1988**, *34*, 755–760.

[3] a) Lepadiformine: J. F. Biard, S. Goyut, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber, K. Boukef, *Tetrahedron Lett.* **1994**, *35*, 2691–2694; b) M. Juge, N. Grimaud, J. F. Biard, M. P. Sauviat, M. Nabil, J. F. Verbist, J. Y. Petit, *Toxicon* **2001**, *39*, 1231–1237; c) cylindricines A and B: A. J. Blackman, C. Li, D. C. R. Hockless, B. W. Skelton, A. H. White, *Tetrahedron* **1993**, *49*, 8645–8656; d) cylindricines C–G: C. Li, A. J. Blackman, *Aust. J. Chem.* **1994**, *47*, 1355–1361; e) cylindricines H–K: C. Li, A. J. Blackman, *Aust. J. Chem.* **1995**, *48*, 955–965.

[4] Total and formal syntheses of **1**, see: a) H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2000**, *122*, 4583–4592; b) J.-H. Maeng, R. L. Funk, *Org. Lett.* **2002**, *4*, 331–333; c) M. D. B. Fenster, G. R. Dake, *Org. Lett.* **2003**, *5*, 4313–4316.

[5] For other synthetic approaches to **1**, see: a) D. J. Wardrop, W. M. Zhang, C. L. Landrie, *Tetrahedron Lett.* **2004**, *45*, 4229–4231; b) D. J. Wardrop, M. S. Burge, W. Zhang, J. A. Ortiz, *Tetrahedron Lett.* **2003**, *44*, 2587–2591.

[6] For synthetic work on the cylindricines, see: a) J. F. Liu, C. H. Heathcock, *J. Org. Chem.* **1999**, *64*, 8263–8266; b) G. A. Molander, M. Rönn, *J. Org. Chem.* **1999**, *64*, 5183–5187; c) B. B. Snider, T. Liu, *J. Org. Chem.* **1997**, *62*, 5630–5633; d) B. M. Trost, M. T. Rudd, *Org. Lett.* **2003**, *5*, 4599–4602; e) W. Oppolzer, C. G. Bochet, *Tetrahedron: Asymmetry* **2000**, *11*, 4761–4770; f) S. Canesi, D. Bouchu, M. A. Ciufolini, *Angew. Chem.* **2004**, *116*, 4436–4438; S. Canesi, D. Bouchu, M. A. Ciufolini, *Angew. Chem.* **2004**, *116*, 4436–4438; *Angew. Chem. Int. Ed.* **2004**, *43*, 4336–4338.

[7] a) The synthetic work on lepadiformine has been nicely summarized: S. M. Weinreb, *Acc. Chem. Res.* **2003**, *36*, 59–65; see also: b) H. Abe, S. Aoyagi, C. Kibayashi, *Angew. Chem.* **2002**, *114*, 3143–3146; H. Abe, S. Aoyagi, C. Kibayashi, *Angew. Chem.* **2002**, *114*, 3143–3146; *Angew. Chem. Int. Ed.* **2002**, *41*, 3017–3020; c) P. Sun, C. Sun, S. M. Weinreb, *J. Org. Chem.* **2002**, *67*, 4337–4345; d) P. Sun, C. Sun, S. M. Weinreb, *Org. Lett.* **2001**, *3*, 3507–3510; e) T. J. Greshock, R. L. Funk, *Org. Lett.* **2001**, *3*, 3511–3514; f) H. Abe, S. Aoyogi, C. Kibayashi, *Tetrahedron Lett.* **2000**, *41*, 1205–1208; g) K. M. Werner, J. M. De los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 4865–4873; h) W. H. Pearson, Y. Ren, *J. Org. Chem.* **1999**, *64*, 688–689; i) K. M. Werner, J. M. De los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 686–687; j) W. H. Pearson, N. S. Barta, J. W. Kampf, *Tetrahedron Lett.* **1997**, *38*, 3369–3372; k) R. Hunter, P. Richards, *Synlett* **2003**, 271–273; l) S. Canesi, P. Belmont, D. Bouchu, L. Rousset, M. A. Ciufolini, *Tetrahedron Lett.* **2002**, *43*, 5193–5195.

[8] For examples, see: a) T. Saito, T. Suzuki, M. Morimoto, C. Akiyama, T. Ochiai, K. Takeuchi, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1998**, *120*, 11633–11644; b) J. Li, S. Jeong, L. Esser, P. G. Harran, *Angew. Chem.* **2001**, *113*, 4901–4906; J. Li, S. Jeong, L. Esser, P. G. Harran, *Angew. Chem.* **2001**, *113*, 4901–4906; *Angew. Chem. Int. Ed.* **2001**, *40*, 4765–4769; c) K. D. Eom, J. V. Raman, H. Kim, J. K. Cha, *J. Am. Chem. Soc.* **2003**, *125*, 5415–5421; d) Y. Kita, S. Kitagaki, Y. Yoshida, S. Mihara, D.-F. Fang, M. Kondo, S. Okamoto, R. Imai, S. Akai, H. Fujioka, *J. Org. Chem.* **1997**, *62*, 4991–4997.

[9] a) G. R. Dake, M. D. B. Fenster, P. B. Hurley, B. O. Patrick, *J. Org. Chem.* **2004**, *69*, 5668–5675; b) G. R. Dake, M. D. B. Fenster, M. Fleury, B. O. Patrick, *J. Org. Chem.* **2004**, *69*, 5676–5683.

[10] C. Herdeis, *Synthesis* **1986**, 232–233.

[11] a) K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, G.-i. Tsuchihashi, *J. Am. Chem. Soc.* **1986**, *108*, 3827–3829; b) K. Suzuki, M. Shimazaki, G.-i. Tsuchihashi, *Tetrahedron Lett.* **1986**, *27*, 6237–6240; c) K. Suzuki, T. Matsumoto, K. Tomooka, K. Matsumoto, G.-i. Tsuchihashi, *Chem. Lett.* **1987**, 113–116; d) K. Suzuki, M. Miyazawa, G.-i. Tsuchihashi, *Tetrahedron Lett.* **1987**, *28*, 3515–3518; e) M. Shimazaki, H. Hara, K. Suzuki, G.-i. Tsuchihashi, *Tetrahedron Lett.* **1987**, *28*, 5891–5894; f) K. Suzuki, M. Miyazawa, M. Shimasaki, G.-i. Tsuchihashi, *Tetrahedron* **1988**, *44*, 4061–4072; g) M. Shimazaki, H. Hara, K. Suzuki, *Tetrahedron Lett.* **1989**, *30*, 5443–5446; h) M. Shimazaki, M. Morimoto, K. Suzuki, *Tetrahedron Lett.* **1990**, *31*, 3335–3338; i) T. Nagasawa, K. Taya, M. Kitamura, K. Suzuki, *J. Am. Chem. Soc.* **1996**, *118*, 8949–8950; see also: j) C. J. Cheer, C. R. Johnson, *J. Am. Chem. Soc.* **1968**, *90*, 178–183.

[12] a) K. Maruoka, T. Ooi, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 6431–6432; b) K. Maruoka, S. Nagahara, T. Ooi, H. Yamamoto, *Tetrahedron Lett.* **1989**, *30*, 5607–5610; c) K. Maruoka, R. Bureau, H. Yamamoto, *Synlett* **1991**, 363–364; d) K. Maruoka, T. Ooi, S. Nagahara, H. Yamamoto, *Tetrahedron* **1991**, *47*, 6983–6998; e) K. Maruoka, J. Sato, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 5449–5450; f) K. Maruoka, T. Ooi, H. Yamamoto, *Tetrahedron* **1992**, *48*, 3303–3312; g) K. Maruoka, J. Sato, H. Yamamoto, *Tetrahedron* **1992**, *48*, 3749–3762; h) T. Ooi, K. Maruoka, H. Yamamoto, *Org. Synth.* **1995**, *72*, 95–103; i) H. Nemoto, H. Ishibashi, M. Nagamochi, K. Fukumoto, *J. Org. Chem.* **1992**, *57*, 1707–1712; j) H. Nemoto, M. Nagamochi, H. Ishibashi, K. Fukumoto, *J. Org. Chem.* **1994**, *59*, 74–79.

[13] a) M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1993**, *115*, 12208–12209; b) M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1995**, *117*, 7379–7388; c) M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1997**, *119*, 12150–12158; d) M. E. Jung, R. Marquez, *Org. Lett.* **2000**, *2*, 1669–1672; e) M. E. Jung, W. S. Lee, D. Sun, *Org. Lett.* **1999**, *1*, 307–310; f) M. E. Jung, B. Hoffmann, B. Rausch, J.-M. Contreras, *Org. Lett.* **2003**, *5*, 3159–3161; g) M. E. Jung, A. van den Heuvel, *Org. Lett.* **2003**, *5*, 4705–4707; h) M. E. Jung, A. van den Heuvel, A. G. Leach, K. N. Houk, *Org. Lett.* **2003**, *5*, 3375–3378.

[14] a) C. M. Marson, A. J. Walker, J. Pickering, A. D. Hobson, R. Wrigglesworth, S. J. Edge, *J. Org. Chem.* **1993**, *58*, 5944–5951; b) C. M. Marson, S. Harper, A. J. Walker, J. Pickering, J. Campbell, R. Wrigglesworth, S. J. Edge, *Tetrahedron* **1993**, *49*, 10339–10354; c) Y. Q. Tu, L. D. Sun, P. Z. Wang, *J. Org. Chem.* **1999**, *64*, 629–633; d) C.-A. Fan, B.-M. Wang, Y. Q. Tu, Z.-L. Song, *Angew. Chem.* **2001**, *113*,

3995–3998; C.-A. Fan, B.-M. Wang, Y. Q. Tu, Z.-L. Song, *Angew. Chem.* **2001**, *113*, 3995–3998; *Angew. Chem. Int. Ed.* **2001**, *40*, 3877–3880; e) S. W. Baldwin, P. Chen, N. Nikolic, D. C. Westheimer, *Org. Lett.* **2000**, *2*, 1193–1196; f) Y. Q. Tu, C. A. Fan, S. K. Ren, A. S. C. Chan, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3791–3794; g) L. Pettersson, T. Frejd, *J. Chem. Soc. Perkin Trans. 1* **2001**, 789–800; h) J. F. Bickley, B. Hauer, P. C. A. Pena, S. M. Roberts, J. Skidmore, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1253–1255; i) F. Wang, Y. Q. Tu, C. A. Fan, S. H. Wang, F. M. Zhang, *Tetrahedron: Asymmetry* **2002**, *13*, 395–398; j) C. M. Marson, A. Khan, R. A. Porter, A. J. A. Cobb, *Tetrahedron Lett.* **2002**, *43*, 6637–6640; k) B. Hauer, J. F. Bickley, J. Massue, P. C. A. Pena, S. M. Roberts, J. Skidmore, *Can. J. Chem.* **2002**, *80*, 546–550; l) C. M. Marson, C. A. Oare, J. McGregor, T. Walsgrove, T. J. Grinter, H. Adams, *Tetrahedron Lett.* **2003**, *44*, 141–143; m) C. A. Fan, X. D. Hu, Y. Q. Tu, B. M. Wang, Z. L. Song, *Chem. Eur. J.* **2003**, *9*, 4301–4310; n) X. D. Hu, C. A. Fan, F. M. Zhang, Y. Q. Tu, *Angew. Chem.* **2004**, *116*, 1734–1737; X. D. Hu, C. A. Fan, F. M. Zhang, Y. Q. Tu, *Angew. Chem.* **2004**, *116*, 1734–1737; *Angew. Chem. Int. Ed.* **2004**, *43*, 1702–1705; for reviews of α-hydroxy epoxide reactions, see: o) G. Magnusson, *Org. Prep. Proced.* **1990**, *22*, 547–574; p) B. Rickborn, in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 733–775.

[15] M. D. B. Fenster, B. O. Patrick, G. R. Dake, *Org. Lett.* **2001**, *3*, 2109–2112.

[16] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585; b) M. J. Robins, J. S. Wilson, F. Hansske, *J. Am. Chem. Soc.* **1983**, *105*, 4059–4065; c) D. H. R. Barton, J. C. Jaszberenyi, *Tetrahedron Lett.* **1989**, *30*, 2619–2622.

[17] a) T. N. Birkinshaw, A. B. Holmes, *Tetrahedron Lett.* **1987**, *28*, 813–816; b) F. Chavez, A. D. Sherry, *J. Org. Chem.* **1989**, *54*, 2990–2992.

[18] a) A. Abad, D. Mellier, J. P. Pète, C. Portella, *Tetrahedron Lett.* **1971**, *12*, 4555–4558; b) W. Yuan, K. Fearson, M. H. Gelb, *J. Org. Chem.* **1989**, *54*, 906–910.

[19] C. H. Heathcock, K. M. Smith, T. A. Blumenkopf, *J. Am. Chem. Soc.* **1986**, *108*, 5022–5024.

[20] a) D. Boyall, F. López, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233–4236; b) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373–381; c) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; d) N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688; e) H. Sasaki, D. Boyall, E. M. Carreira, *Helv. Chim. Acta* **2001**, *84*, 964–971; f) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605–2606.

[21] a) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–288; b) K. Matsumura, S. Hashigushi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739; for the preparation of the catalyst, see: c) M. A. Bennett, T.-N. Huang, T. W. Matheson, A. K. Smith, *Inorg. Synth.* **1982**, *21*, 74–78; d) T. Oda, R. Irie, T. Katsuki, H. Okawa, *Synlett* **1992**, 641–643; e) R. ter Halle, A. Bréhéret, E. Schulz, C. Pinel, M. Lemaire, *Tetrahedron: Asymmetry* **1997**, *8*, 2101–2108; f) L. F. Tietze, Y. Zhou, E. Töpken, *Eur. J. Org. Chem.* **2000**, 2247–2252.

[22] N. Nakajima, K. Horita, R. Abe, O. Yonemitsu, *Tetrahedron Lett.* **1988**, *29*, 4139–4142.

[23] a) A. G. Brook, *J. Am. Chem. Soc.* **1958**, *80*, 1886–1889; b) A. G. Brook, C. M. Warner, M. E. McGriskin, *J. Am. Chem. Soc.* **1959**, *81*, 981–983; c) A. G. Brook, *Acc. Chem. Res.* **1974**, *7*, 77–84.

[24] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

[25] C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424; for a recent review: b) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740–2767; P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740–2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.

[26] a) N. Miyaura, T. Ishiyama, M. Ishikawa, A. Suzuki, *Tetrahedron Lett.* **1986**, *27*, 6369–6372; b) M. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314–321; c) T. Oh-e, N. Miyaura, A. Suzuki, *J. Org. Chem.* **1993**, *58*, 2201–2208; d) M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett.* **1989**, 1405–1408; For a recent review, see: e) S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568.

[27] a) K. Kondo, M. Sodeoka, M. Shibasaki, *Tetrahedron: Asymmetry* **1995**, *6*, 2453–2464; b) K. Kondo, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 4322–4323.

[28] C. R. Johnson, M. P. Braun, *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015.

[29] a) Y. Shishido, C. Kibayashi, *J. Org. Chem.* **1992**, *57*, 2876–2883; b) D. F. Taber, P. B. Deker, L. J. Silverberg, *J. Org. Chem.* **1992**, *57*, 5990–5994.

[30] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.

[31] H. C. Kolb, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735–2762.

[32] C. Ahn, R. Correia, P. DeShong, *J. Org. Chem.* **2002**, *67*, 1751–1753.

[33] a) W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627; b) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666

[34] a) A. W. Erian, S. M. Sherif, *Tetrahedron* **1999**, *55*, 7957–8024; b) L. A. Spurlock, G. W. Cox, *J. Am. Chem. Soc.* **1971**, *93*, 146–151; c) Y. Tamura, T. Kawasaki, M. Adachi, M. Tanio, Y. Kita, *Tetrahedron Lett.* **1977**, *18*, 4417–4420; d) J. Burski, J. Kieszkowski, J. Michalski, M. Pakulski, A. Skowronska, *Tetrahedron* **1983**, *39*, 4175–4181; e) H.-R. Sliwka, S. Liaaen-Jensen, *Tetrahedron: Asymmetry* **1993**, *4*, 361–368.

[35] Personal communication with Drs. Patil and Freyer.

[36] W. G. Kofron, L. M Baclawski, *J. Org. Chem.* **1976**, *41*, 1879–1880.

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