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Carbon-Carbon Bond Formation *via* N-Tosyliminium Ions

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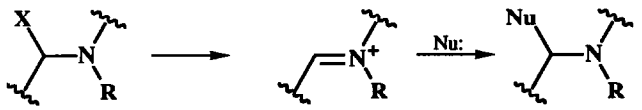
Abstract: Addition of carbon nucleophiles to cyclic N-tosyliminium ions, derived from α-hydroxy and α-methoxy tosylamides (**5a,b** and **6a,b**, respectively) is described. In general, good to excellent yields were obtained when allyltrimethylsilane, 1-^{t}butyldimethylsilyloxy-1-ethoxyethane, and trimethylsilyl cyanide were used as nucleophiles.

The controlled formation of new carbon -carbon bonds is of fundamental importance in organic chemistry and thus constitutes a major area of research activity. In this respect, the generation of N-acyliminium ions (**2a**), from suitable precursors (**1a**), as reactive intermediates toward a number of carbon nucleophiles has become an attractive approach to this problem as documented by the impressive number of natural product syntheses involving such strategy[1] (Scheme 1). The effectiveness of this amidoalkylation is due to: (i) there are a number of ways to generate the N-acyliminium ion **2a**, (ii) such species display versatile reactivity, and (iii) the low tendency of amide **3a**, the product of the reaction, to participate in any Grob-type fragmentation.



1 2 3

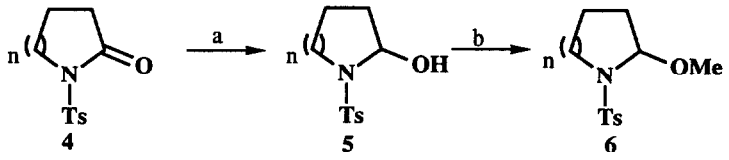
Scheme 1. **a** R=COR′, **b** R=Ts

Considering the widespread use of the above detailed strategy it is somewhat surprising that addition of carbon nucleophiles to the corresponding N-tosyliminium ions **2b** has received much less attention[2,3]. Herein we would like to detail our findings concerning the generation of cyclic N-tosyliminium ions from the corresponding N-tosyl lactams, and their reactions towards some model nucleophiles. Furthermore, the efficiency of the present methodology is demonstrated by the synthesis of the powerful neurotoxic alkaloid (+)-anatoxin-a (**11**)[3] and an enantioselective preparation of (*S,S*)-2,5-bis(methoxymethyl)pyrrolidine (**19**), an efficient chiral auxiliary[4].

The requisite precursors for the generation of the N-tosyliminium ions used in this study were prepared by DIBAL reduction of lactams **4a,b**[5] to afford the α-hydroxytosylamides **5a,b** in good yields (Scheme 2). Compounds **5a,b** proved to be stable towards normal work-up conditions; however, attempted

recrystallisation of these compounds resulted in decomposition of the material. In order to obtain alternative substrates for the subsequent alkylation reaction amides **5a,b** were converted into α-methoxysulfonamides **6a,b**.

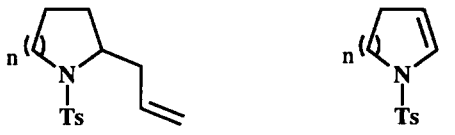
Hydride reduction of N-tosylazetidone and N-tosylcaprolactam yielded complicated mixtures of products and none of the corresponding α-hydroxysulfonamides.



4 **5** **6**

Scheme 2. **a** n=1, **b** n=2. (a) DIBAL, CH_2Cl_2, -78 °C, **a** 94%; **b** 87% (b) PPTS, $HC(OMe)_3$, MeOH, **a** 93%; **b** 98%.

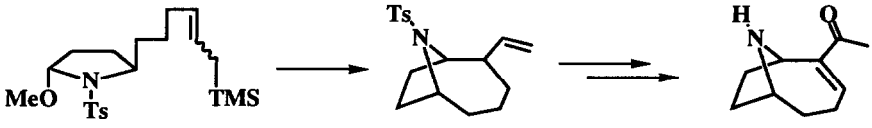
The acid promoted additions of allyltrimethylsilane to compounds **5a,b** and **6a,b** yielding alkenes **7a,b** are summarised in the Table (entries 1-8). In analogy with the corresponding N-acyl derivatives[1], most Lewis acids function as effective promotors for this transformation, the general trend being that compounds **5a,b** and **6a,b** perform equally well in this reaction, affording alkenes **7a,b** in excellent yield. It is noteworthy that while $TiCl_4$ is an effective mediator for this transformation $Ti(O^iPr)_4$ is too weak a Lewis acid while $TiCl_2(O^iPr)_2$ is somewhere in between those two extremes (entries 2-4). The addition of allyltrimethylsilane could also be effected with proton acids such as trifluoroacetic acid, TFA, (entry 7). However, when PPTS was used instead of TFA under otherwise identical conditions none of the expected allylated products could be detected (entry 8). Instead, the corresponding N-tosyl enamines **8a,b** were isolated in high yields.



7 **a** n=1
b n=2

8 **a** n=1
b n=2

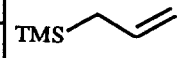
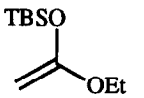
An intramolecular version of the allylation reaction was used as a key step in our synthesis of the bicyclic alkaloid (+)-anatoxin-a (**11**)[3b]. Thus, slow addition of allylsilane **9**, ultimately derived from L-pyroglutamic acid, to a solution of $TiCl_4$ (0.2 eq.) in dichloromethane at -78 °C afforded the bicyclic alkene **10** in 76% yield. Compound **10** was then converted by a series of standard transformations into (+)-Anatoxin-a (**11**).



9 **10** **11**

Next we turned our attention towards the addition of a two carbon chain to substrates **5a,b** and **6a,b** (Table, entries 9-11). As can be seen from the Table (entry 9) the trifluoromethanesulfonate (TMSOTf) catalysed addition of 1-t-butyldimethylsilyloxy-1-ethoxyethane[6] to α-methoxysulfonamides **6a** and **6b**

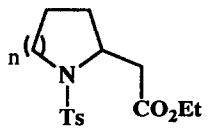
Table. Yields (%) of Products in the Addition Reactions to Substrates **5a,b** and **6a,b**[a].

Entry	Nucleophile	Promoter	5a	5b	6a	6b	Products
1		$SnCl_4$	98	100	100	86	**7a, b**
2		$TiCl_4$	100	92	100	97	
3		$TiCl_2(O^iPr)_2$	71	86	78	56	
4		$Ti(O^iPr)_4$[b]	0	0	0	0	
5		$FeCl_3$	100	73	99	75	
6		$BF_3{\cdot}OEt_2$	88	99	85	100	
7		TFA[c]	92	94	100	100	
8		PPTS	0	0	0	0	
9		TMSOTf	0[e]	0[e]	82[d]	71[d]	**12a, b**
10		$TiCl_4$[d,e]	0	0	0	0	
11		$SnCl_4$[d,e]	0	0	0	0	
12	TMSCN	$SnCl_4$[d]	92	87	90	88	**13a, b**
13		$TiCl_4$[d]	53	61	59	60	
14		$BF_3{\cdot}OEt_2$[d]	49	57	55	62	

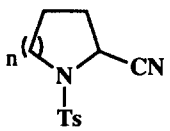
[a]All reactions were performed in CH_2Cl_2 at -78 °C with 1.0 eq. catalyst unless otherwise stated. The yields in the table refer to chromatographically homogeneous material. [b]The starting material was recovered unchanged.[c]4 eq. [d]0.1 eq. [e]No recovery of starting material.

afforded the β-sulfonamidoesters **12a** and **12b**, respectively, in good yields. However, when the corresponding hemiaminals **5a,b** were used as substrates in this reaction using catalytic or stoichiometric amounts of TMSOTf, only complicated product mixtures were obtained. It is interesting to note that Lewis acids such as $TiCl_4$ and $SnCl_4$ did not affect this transformation (entries 10, 11).

Addition of a nitrile group to N-tosyliminium ions would constitute a one carbon homologation. Thus, the Lewis acid catalysed additions of trimethylsilyl cyanide (TMSCN) to substrates **5a,b** and **6a,b** yielding nitriles **13a,b** are summarised in the Table (entries 12-14). In analogy with the addition of TMSCN to N-acyl-2-methoxypiperidine[7], $SnCl_4$ is the most powerful catalyst for this transformation while $TiCl_4$ and $BF_3{\cdot}Et_2O$ are somewhat less efficient.



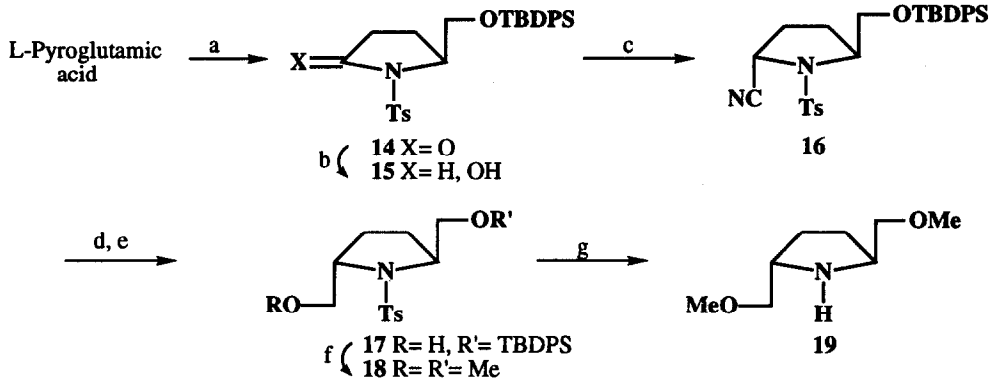
12 **a** n=1
b n=2



13 **a** n=1
b n=2

The addition of TMSCN to N-tosyliminium ions was used in an enatioselective synthesis of (*S*,*S*)-2,5-bis(methoxymethyl)pyrrolidine (**19**), previously prepared by routes involving resolutions[4]. Thus, DIBAL reduction of N-tosyl lactam **14** afforded α-hydroxysulfonamide **15** as a mixture of isomers (3/1), Scheme 3. Treating this mixture with TMSCN and $SnCl_4$ (0.1 eq.) in CH_2Cl_2 at -78 °C yielded the α-nitrile **16** as a

single isomer in 91% yield. DIBAL reduction of compound **16** followed by hydrolysis afforded the corresponding aldehyde (IR: 1728 cm^{-1}) which was immediately reduced (DIBAL) to yield alcohol **17** (72%) as an inseparable mixture of isomers (trans/cis: 9/1). Removal of the silyl protecting group yielded a mixture of diols which was converted into the corresponding readily separable mixture of bis-methyl ethers, thus furnishing pure compound **18**. Finally, removal of the tosyl group (Na-naphthalide, DME) afforded the C_2-symmetric amine **19** in 87% yield.



Scheme 3. Ts=p-toluenesulfonyl; TBDPS=t-Butyldiphenylsilyl. (a) see ref. 3b (b) DIBAL, CH_2Cl_2, -78 °C, 92% (c) TMSCN, $SnCl_4$, CH_2Cl_2, -78 °C, 91% (d) DIBAL, toluene, -20 °C; then 5% aq. H_2SO_4 (e) DIBAL, CH_2Cl_2, -78 °C, 72% (f) i. Bu_4NF, THF, 90% ii. NaH, MeI, THF, 82% (g) Na-naphthalide, DME, -78 °C, 87%.

In conclusion, we have demonstrated that α-hydroxy- and α-methoxysulfonamides, **5a,b** and **6a,b**, respectively, derived from the corresponding N-tosyl lactams, react under mild conditions with some carbon nucleophiles to yield the homologated products. We believe that this methodology should offer an alternative to the existing and widely used techniques relying on the generation and trapping of N-acyliminium ions and we are currently investigating its applicability to the synthesis of some naturally occurring alkaloids.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ ($CHCl_3$ δ 7.26) as solvent. IR spectra were run on a Perkin-Elmer 298 spectrophotometer and only the strongest/structurally most important peaks (ν, cm^{-1}) are listed. Optical rotations, $[\alpha]_D$, were measured on a Perkin Elmer 141 polarimeter at the sodium D line and at ambient temperatures. Flash chromatography employed Grace Amicon silica gel 60 (0.035-0.070 mm). Methylene chloride was distilled from calcium hydride immediately before use; tetrahydrofuran (THF), toluene, and 1,2-dimethoxyethane (DME) were distilled from sodium-benzophenone ketyl. All reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagents being transferred *via* oven dried syringes. N-Tosyl lactams **4 a** and **4 b** were prepared according to the procedure of Thomas[5], and 1-t-butyldimethylsilyloxy-1-ethoxyethane was prepared according to Colvin's procedure[7].

2-Hydroxy-1-tosylpyrrolidine (5a). To stirred solution of lactam **4a** (1.100 g, 4.603 mmol) in CH_2Cl_2 (20 ml) at -78 °C was added DIBAL (5.06 ml, 5.06 mmol, 1M in hexanes) dropwise. The mixture was stirred at -78 °C for 1 h, then quenched by addition of methanol and poured into aqueous Rochelle salt- methylene

chloride and the phases were separated. The aq. phase was extracted once with methylene chloride, the combined organics were dried ($MgSO_4$) and the solvent was stripped off. Flash-chromatography (heptane/EtOAc 3/2) yielded sulfonamide **5a** as a solid (1.042 g, 94%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (2H, d, J=8.3, tosyl) 7.32 (2H, d, J=8.3, tosyl) 5.42 (1H, m) 3.52 (1H, ddd, J=9.5, 9.5, 2.5) 3.42 (1H, s, -OH) 3.03 (1H, ddd, 9.5, 9.5, 6.5) 2.39 (3H, s, CH_3-tosyl) 2.15-1.96 (1H, m) 1.92-1.80 (1H, m) 1.79-1.63 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4, 135.5, 129.7, 127.4, 89.3, 47.8, 33.7, 23.1, 21.5; IR (KBr) 3440, 2960, 1595, 1335, 1155 cm^{-1}; HRMS $[M]^+$ calcd for $C_{11}H_{15}NO_3S$: 241.0773, found: 241.0779.

2-Hydroxy-1-tosylpiperidine (5b). Prepared as detailed above for compound **5a**. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J=8.4, tosyl) 7.30 (2H, d, J=8.4, tosyl) 5.55 (1H, m) 3.57 (1H, br dd, J=12, 3.0) 3.10 (1H, ddd, J=12, 12, 2.5) 2.52 (1H, s, -OH) 2.42 (3H, s, CH_3-tosyl) 1.87-1.46 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.6, 137.1, 129.7, 127.2, 76.4, 40.1, 31.3, 24.8, 21.5, 17.2; IR (KBr) 3520, 2946, 1595, 1328, 1155 cm^{-1}; HRMS $[M]^+$ calcd for $C_{12}H_{17}NO_3S$: 255.0929, found: 255.0933.

2-Methoxy-1-tosylpyrrolidine (6a). To a solution of compound **5a** (705 mg, 2.925 mmol) in MeOH/$HC(OMe)_3$ (5/2, 7 ml) was added PPTS (cat.) and the resultant mixture stirred at room temperature for 2h. To the reaction mixture was then added solid Na_2CO_3, the solvents were stripped off and the resultant mixture was partitioned between Et_2O-aq. Na_2CO_3 and the phases were separated. The aq. phase was extracted once with Et_2O, the combined organics were dried ($MgSO_4$) and the solventwas stripped off. Flash-chromatography (heptane/EtOAc 3/1) afforded sulfonamide **6a** as an oil (694 mg, 93%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J=8.4) 7.30 (2H, d, J=8.4) 5.10 (1H, d, J=5) 3. 42 (4H, m, $-OCH_3$ and one C_5-H) 3.13 (1H, ddd, J=10.0, 10.0, 2.0) 2.42 (3H, s, CH_3-tosyl) 2.10-1.67 (3H, m) 1.43-1.31 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5, 135.9, 129.7, 127.4, 91.7, 55.3, 47.3, 32.6, 23.1, 21.5; IR (film) 2982, 1598, 1345, 1203 cm^{-1}; HRMS $[M]^+$ calcd for $C_{12}H_{17}NO_3S$: 255.0929, found: 255.0927.

2-Methoxy-1-tosylpiperidine (6b). Prepared as detailed above for compound **6a**. ^1H NMR ($CDCl_3$, 300 MHz) δ 7. 70 (2H, d, J=8.5) 7.28 (2H, d, J=8.5) 5.14 (1H, m) 3.53 (1H, m) 3.36 (3H, s) 3.02 (1H, ddd, J=13.0, 13.0, 2.5) 2.38 (3H, s) 1.90-1.79 (1H, m) 1.72-1.55 (1H, m) 1.52-1.31 (3H, m) 1.29-1.14 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 138.0, 129.5, 127.1, 83.9, 55.0, 40.6, 29.4, 24.1, 21.5, 17.8; IR (film) 2940, 1596, 1334, 1167 cm^{-1}; HRMS $[M]^+$ calcd for $C_{13}H_{19}NO_3S$: 269.1086, found: 269.1099.

General procedure for the additions of nucleophiles to α-hydroxysulfonamides 5a,b and α-methoxysulfonamides 6a,b. To a solution of the substrate (1.0 mmol) and the nucleophile (2.0 mmol) in CH_2Cl_2 at -78 °C was added the catalyst (1.0 eq. or as indicated in the Table). The resultant mixture was stirred at -78 °C until the reaction was complete, then aq. saturated Na_2CO_3 was added, the phases were separated, the aq. phase was extracted with CH_2Cl_2 and the combined organics were dried ($MgSO_4$). Removal of the solvents and flash-chromatography (heptane/EtOAc) gave the corresponding products as indicated in the Table.

2-(2-propenyl)-1-tosylpyrrolidine (7a). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J=8.3) 7.30 (2H, d, J=8.3) 5.79 (1H, m) 5.08 (2H, m) 3.66 (1H, m) 3.39 (1H, m) 3.15 (1H, dt, J=10.0, 7.1) 2.59 (1H, m) 2.42 (3H, s) 2.30 (1H, m) 1.85-1.40 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.3, 134.9, 134.6, 129.6, 127.5, 117.5, 59.7, 49.2, 40.8, 30.1, 24.0, 31.5; IR (film) 3085, 2980, 1640, 1597, 1347, 1160 cm^{-1}; HRMS $[M]^+$ calcd for $C_{14}H_{19}NO_2S$: 265.1137, found: 265.1097.

2-(2-propenyl)-1-tosylpiperidine (7b). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J=8.3) 7.28 (2H, d, J=8.3) 5.69 (1H, m) 5.03 (2H, m) 4.10, (1H, m) 3.76 (1H, br dd, J=14.0, 5.1) 2.87 (1H, dt, J=14.0, 2.5) 2.42 (3H, s) 2.29 (2H, br t, J=8.0) 1.56-1-08 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.8, 138.8, 134.9, 129.6,

127.0, 117.1, 52.4, 40.7, 34.0, 26.6, 24.6, 21.5, 18.2; IR (film) 3090, 2940, 1690, 1597, 1335, 1165 cm^{-1}; HRMS $[M]^+$ calcd for $C_{15}H_{21}NO_2S$: 279.1293, found: 279.1299.

1-Tosyl-2,3-dihydropyrrole (8a). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (2H, d, J=8.4) 7.32 (2H, d, J=8.4) 6.37 (1H, td, J=4.0, 2.5) 5.11 (1H, td, J=4.0, 2.1) 3.47 (2H, t, J=8.5) 2.44 (3H, s) 2.51-2.37 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 134.8, 130.7, 129.7, 127.7, 111.2, 47.2, 29.6, 21.5; IR (film) 3100, 2940, 1615, 1595, 1340, 1165 cm^{-1}.

1-Tosyl-1,2,3,4-tetrahydropyridine (8b). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (2H, d, J=8.3) 7.31 (2H, d, J=8.3) 6.64 (1H, td, J=8.5, 1.0) 4.97 (1H, td, J=8.5, 4.0) 3.36 (2H, t, J=5.0) 2.42 (3H, s) 1.96-1.85 (2H, m) 1.69-1.58 (2H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.5, 135.2, 129.7, 127.1, 125.1, 108.2, 77.2, 43.8, 21.5, 20.9; IR (film) 2929, 1645, 1598, 1345, 1165 cm^{-1}.

2-[(Ethoxycarbonyl)methyl]-1-tosylpyrrolidine (12a). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (2H, d, J=8.2) 7.31 (2H, d, J=8.2) 4.15 (2H, m) 3.94 (1H, m) 3.43 (1H, m) 3.11 (1H, m) 3.09 (1H, dd, J=16.0, 4.0) 2.46 (1H, dd, J=16.0, 10.0) 2.42 (3H, s) 1.88-1.45 (4H, m) 1.59 (3H, t, J=7.0); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3, 143.5, 134.2, 129.7, 127.6, 60.5, 56.6, 49.2, 41.4, 31.7, 23.8, 21.5, 14.2; IR (film) 2980, 1723, 1595, 1345, 1153 cm^{-1}; HRMS $[M+H]^+$ calcd for $C_{15}H_{22}NO_4S$: 312.1270, found: 312.1274.

2-[(Ethoxycarbonyl)methyl]-1-tosylpiperidine (12b). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (2H, d, J=8.42) 7.26 (2H, d, J=8.42) 4.51 (1H, m) 4.08 (2H, m) 3.77 (1H, br dd, J=8.9, 3.0) 2.92 (1H, dt, J=12.5, 2.2) 2.60 (1H, dd, J=14.5, 9.0) 2.45 (1H, dd, J=14.5, 5.7) 2.39 (3H, s) 1.59-1.42 (5H, m) 1.30 (1H, m) 1.21 (3H, t, J=7.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 143.1, 138.2, 129.7, 127.0, 60.7, 49.7, 40.9, 35.1, 27.7, 24.6, 21.5, 18.3, 14.1; IR (film) 2935, 1725, 1595, 1339, 1155 cm^{-1}; HRMS $[M+H]^+$ calcd for $C_{16}H_{24}NO_4S$: 326.1246, found: 326.1421.

2-Cyano-1-tosylpyrrolidine (13a). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79 (2H, d, J=8.1) 7.35 (2H, d, J=8.1) 4.59 (1H, dd, J=7.1, 2.5) 3.38 (2H, m) 2.43 (3H, s) 2.28-1.91 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.4, 134.4, 129.9, 127.6, 118.0, 48.6, 47.5, 31.9, 24.6, 21.6; IR (KBr) 2990, 2241, 1590, 1345, 1155 cm^{-1}; HRMS $[M]^+$ calcd for $C_{12}H_{14}N_2O_2S$: 250.0776, found: 250.0784.

2-Cyano-1-tosylpiperidine (13b). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (2H, d, J=8.2) 7.47 (2H, d, J=8.2) 4.98 (1H, m) 3.84 (1H, m) 2.67 (1H, dt, J=11.9, 2.8) 2.43 (3H, s) 2.02-1.48 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 133.4, 129.9, 127.9, 115.2, 45.8, 43.1, 29.4, 24.5, 21.6, 19.7; IR (KBr) 2940, 2880, 2239, 1590, 1347, 1160 cm^{-1}; HRMS $[M]^+$ calcd for $C_{13}H_{16}N_2O_2S$: 264.0933, found: 264.0929.

Nitrile 16. To a stirred solution of N-tosyl hemiaminal **15** (1.00g, 1.965 mmol) and trimethylsilyl cyanide (524 µl, 3.929 mmol) in CH_2Cl_2 (25 ml) at -78 °C was added $SnCl_4$ (22 µl, 0.2 mmol) and the resultant mixture stirred at -78 °C for 5h then warmed to -20 °C and stirred for an additional 3 h. The reaction was terminated by addition of sat. Na_2CO_3, the phases were separated and the aq. phase was extracted once with CH_2Cl_2. The combined organics were dried ($MgSO_4$), and the solvents stripped off. Flash-chromatography (heptane/EtOAc 3/1) afforded nitrile **16** as an oil (928 mg, 91%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77-7.61 (6H, m) 7.52-7.37 (6H, m) 7.29 (2H, d, J=8.1) 4.66 1H, d, J=7.7) 3.97 (1H, dd, J=9.9, 2.9) 3.67 (2H, m) 2.42 (3H, s) 2.34-2.21 (2H, m) 2.17-2.04 (2H, m) 1.08 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1, 135.9, 135.0, 133.3, 133.1, 130.0, 129.7, 127.9, 127.6, 117.2, 64.9, 59.9, 50.1, 29.8, 28.0, 27.1, 21.8, 19.2; IR (film) 3065, 2957, 2251, 1595, 1351, 1161 cm^{-1}; $[\alpha]_D$=-84.2° (c 1.51, $CHCl_3$); HRMS $[M+H]^+$ calcd for $C_{29}H_{35}N_2O_3SSi$: 519.2138, found: 519.2148.

Alcohol 17. The nitrile **16** (1.340 g, 2.587 mmol) was dissolved in toluene (10 ml), cooled to -20 °C and DIBAL (3.6 ml, 3.6 mmol, 1 M in hexanes) was added dropwise. After stirring for 1 h at -20 °C, 5% H_2SO_4 (20 ml) was added and the resultant mixture warmed to room temperature and stirred vigorously until the layers separated. The phases were separated, the aq. phase was extracted once with Et_2O, the combined organics were dried ($MgSO_4$) and the solvents stripped off to afford the corresponding aldehyde as a slightly yellow oil (1.256 g, crude). This matematerial was taken on to the next step without any further purification. IR (film) 1728 cm^{-1}.

The aldehyde from above (1.256 g) was dissolved in CH_2Cl_2, cooled to -78 °C and DIBAL (3 ml, 3 mmol, 1M in hexanes) was added dropwise. The resultant mixture was stirred at -78 °C for 1 h and then quenched by careful addition of methanol. Rochelle salt work-up as detailed above for compound **5a** gave a yellow oil which was flash-chromatographed (heptane/EtOAc 3/1) to afford alcohol **17** as an inseparable mixture of isomers (976 mg, 72%; trans/cis 9/1).

Bis-methyl ether 18. To a solution of alcohols **17** (1.301 g, 2.487 mmol; trans/cis 9/1) in THF (20 ml) was added Bu4NF (3.23 ml, 3.23 mmol, 1M in THF). After stirring for 2 h the mixture was poured into Et_2O-water, the phases were separated and the aq. phase was extracted twice with Et_2O. The combined organics were dried ($MgSO_4$) and the solvents stripped off. Flash-chromatography (heptane/EtOAc 3/7→0/1) gave the corresponding diols as an inseparable mixture (637 mg, 90%; trans/cis 9/1).

The diols from above (637 mg, 2.237 mmol) were dissolved in THF (10 ml), cooled to 0 °C and NaH (430 mg, 8.948 mmol, 50% in oil) was added slowly. The resultant mixture was warmed to room temperature and stirred for 1 h, re-cooled to 0 °C and then MeI (835 µl, 13.42 mmol) was added. The mixture was allowed to warm to room temperature over night and then quenched by careful addition of water. The phases were separated, the aq. phase was extracted twice with Et_2O, dried ($MgSO_4$) and the solvent stripped off. Flash-chromatography (heptane/EtOAc 9/1→4/1) afforded pure compound **18** (700 mg, 82%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (2H, d, J=8.1) 7.27 (2H, d, J=8.1) 3.97 (2H, m) 3.57 (2H, dd, J=9.1, 3.0) 3.33 (2H, dd, J=9.1, 7.2) 3.19 (6H, s) 2.42 (3H, s) 2.11-1.87 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.5, 139.0, 129.6, 126.4, 73.1, 60.2, 58.4, 27.1, 21.6; IR (film) 2920, 1597, 1339, 1155, 1115 cm^{-1}; $[\alpha]_D$=-59.0° (c 1.73, $CHCl_3$); HRMS $[M]^+$ calcd for $C_{15}H_{24}NO_4S$: 314.1426, found: 314.1417.

(S,S)-2,5-Bis(methoxymethyl)pyrrolidine (19). Recrystallized naphthalene (3.73 g, 29.14 mmol) was dissolved with stirring in DME (10 ml) and sodium metal (670 mg) was added. The mixture was stirred for 1 h at room temperature and the resultant blue-green solution of sodium naphthalide was cooled to -78 °C before addition of **18** (1.520 g, 4.856 mmol) in DME (1 ml). The reaction was stirred for 1 h at -78 °C and then water was added dropwise until the colour of the anion was discharged. The resultant colourless mixture was then partitioned between water and $CHCl_3$, the phases were separated and the aqueous layer was extracted with three portions of $CHCl_3$. The combined organics were dried ($MgSO_4$)and the solvents stripped off to afford a yellow oil which was purified by flash-chromatography (EtOAc/MeOH 9/1→4/1, 2% NH_4OH). The slightly yellow oily product (671 mg, 87%) was dissolved in Et_2O (10 ml) and the resultant solution was saturated with HCl (g). Removal of the solvents afforded **19·HCl** (805 mg) as crystals (m.p. 108 °C [lit[4a]. m. p. 108.5 °C]). The spectroscopic data (^1H and ^{13}C NMR, and IR) for this material were in agreement with those published. $[\alpha]_D$=-6.40° (c 1.00, $CHCl_3$) [lit[4a]. $[\alpha]_D$=-6.5° (c 1.10, $CHCl_3$)].

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