1,4-Bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines in Synthesis: Stereoselective Homo- and Hetero-Diels–Alder Reactions

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Abstract: Palladium-catalysed coupling of a vinylstannane or vinyl boronic acids with 5-iodo-1,4-bis(tosyl)-1,2,3,4-tetrahydropyridines yields 1,3-dienes. These participate in homo- and hetero-Diels–Alder reactions with unsaturated carbonyl compounds and with nitroso species generated in situ to give novel bicyclic compounds in a highly stereoselective fashion.

Key words: Diels–Alder reaction, nitroso dienophile, palladium-catalysed coupling, stereoselective synthesis, tetrahydropyridine

Over the past several years we have been investigating the synthesis and chemistry of 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridines (**1**).[1,2] Inspired by Overman's total synthesis of the alkaloid (+)-aloperine, in which the intramolecular Diels–Alder reaction of a substrate possessing an alkenyl-substituted tetrahydropyridine played a key role,[3a] we became interested in evaluating the cycloaddition behaviour of substrates **2** containing a 1,3-diene partially embedded in the tetrahydropyridine core (Figure 1).[4] It occurred to us that the Diels–Alder reactions of **2** with all-carbon dienophiles would offer rapid, stereoselective entries to octahydroquinoline-containing structures, whilst combination of **2** with heterodienophiles possessing N=X groups followed by reductive cleavage would provide structurally complex (aminoalkyl)piperidines and potentially aminoacids. This Letter reports the preliminary results of our investigations.[5]

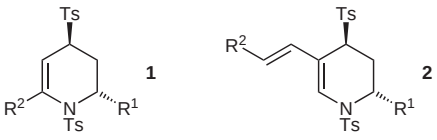
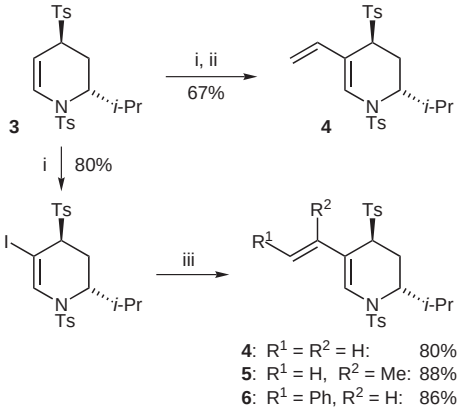


Figure 1

To maximise flexibility in the synthesis of **2**, we elected to assemble the 1,3-diene moiety through Pd(0)-catalysed reactions of a suitably modified tetrahydropyridine nucleus with olefinic coupling partners such as vinylstannanes and vinylboronic acids; Comins[6] and Overman[3a] had both previously demonstrated the viability of this approach. With this in mind, **3** was synthesised from 1-tolylsulfonyl-3,3-dimethoxypropane and (*R*)-1-tolylsulfonyl-2-(1-methylethyl)aziridine[2] using our standard two-step method,[1a] followed by *t*-BuOK-catalysed C-4-epimerisation, providing exclusively the 2*R*,4*S*-isomer in excellent overall yield. This was combined with a slight excess of *N*-iodosuccinimide and a sub-stoichiometric quantity of Koser's reagent[7] in CH_2Cl_2 under reflux to give the iodotetrahydropyridine; subsequent treatment with tri-*n*-butylvinylstannane and Pd_2dba_3-tris(2-furyl)phosphine provided **4** in high overall yield from **3** (Scheme 1). The analogous coupling reactions of tri-*n*-butylvinylstannane with the corresponding bromide derived from **3** were substantially less efficient. We evaluated also alternative Pd(0)-catalysed methods for diene assembly which avoided the use of organostannanes. Substrate **4** was readily prepared using the Suzuki reaction, in which the iodotetrahydropyridine made from **3** previously was coupled with freshly-made, crude ethenylboronic acid in the presence of $[Pd(PPh_3)_4]$ and base. Diene **5** was made in an analogous fashion, again in execellent yield. Finally, diene **6** was prepared in high yield from commercially available *E*-2-phenylethenylboronic acid with the iodotetrahydropyridine (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) *N*-iodosuccinimide (1.05 equiv), PhI(OH)(OTs) (0.1 equiv), CH_2Cl_2, reflux, 16 h; (ii) *n*-$Bu_3SnCH{=}CH_2$ (1.1 equiv), Pd_2dba_3 (0.06 equiv), (2-furyl)$_3$P (0.12 equiv), DMF, 70 °C, 16 h; (iii) $R^1CH{=}C(R^2)B(OH)_2$ (2.5 equiv), $[Pd(PPh_3)_4]$ (0.05 equiv), Na_2CO_3 (10 equiv), dioxane, 80 °C, 16 h

With efficient syntheses of **4**–**6** established, attention was turned to their Diels–Alder reactions. Heating of an equimolar mixture of **4** and maleic anhydride in $CDCl_3$ (ca. 1.3 M) at 65 °C for 2 hours gave in quantitative yield a single cycloadduct, as shown by ^{1}H NMR spectroscopic

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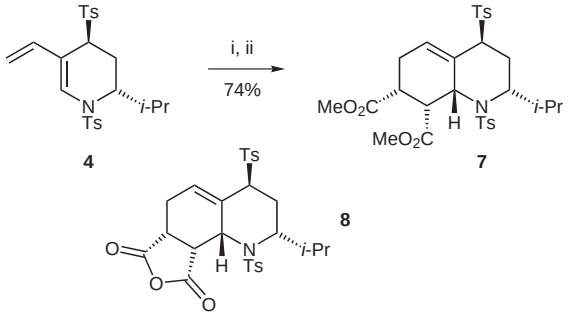
analysis of the crude product. A portion of this material was dissolved in MeOH–CH_2Cl_2 and treated with $TMSCHN_2$ to give the corresponding dimethyl diester **7** in 74% overall yield from **4** (Scheme 2). The structure of **7** was unambiguously assigned by X-ray crystallographic analysis (Figure 2).[8]



Scheme 2 *Reagents and conditions*: (i) maleic anhydride (1 equiv), $CDCl_3$ (ca. 1.3 M), 65 °C, 2 h; (ii) $TMSCHN_2$ (4 equiv), MeOH–CH_2Cl_2 (1.5:1), r.t., 2 h

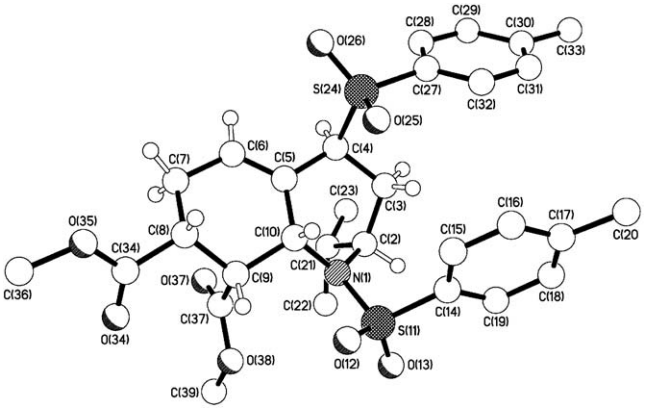
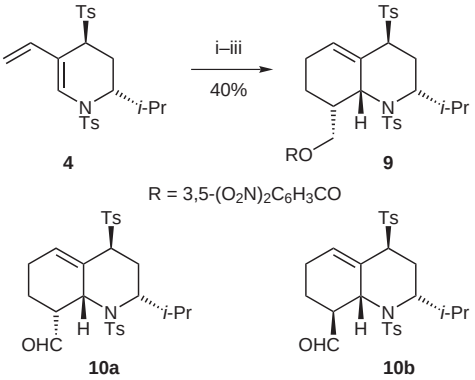


Figure 2 The molecular structure of **7**

The formation of **7** from **4** in the sequence shown in Scheme 2 clearly shows the structure of the maleic anhydride [4+2] cycloadduct to be **8**. Formation of **8** indicates preferred *endo* approach of the dienophile to the α-face of **4**, *syn* to the C-2 isopropyl group. This is in contrast to the results of Comins,[5] who obtained exclusively Diels–Alder products from *N*-carbamoyl-2,3-dihydro-4-pyridones corresponding to dienophile approach *anti* to the C-2 substituent. We attribute this striking reversal in stereoselectivity to the preferred orientation of the *N*-tolylsulfonyl substituent *anti* to the C-2 isopropyl moiety because of mutual steric buttressing. This observation is in accord with the behaviour of **1** (R^1 = *n*-$C_{11}H_{23}$, R^2 = H) in S_N1'[1a] and dihydroxylation[1d] reactions, and that of **1** (R^1 = *n*-$C_{11}H_{23}$, R^2 = Me)[9] in cationic hydrogenation[1b] processes.

We next examined the reaction of **4** with acrolein. As anticipated, the cycloaddition was slower than that with maleic anhydride, giving in 79% yield an inseparable mixture of two products in a 82:18 ratio as determined by ^1H NMR analysis of the crude cycloadduct. Subjection of the chromatographically purified product mixture to $LiAlH_4$ reduction followed by 3,5-dinitrobenzoate ester formation enabled separation. X-ray crystallographic analysis of the major isomeric ester allowed unambiguous assignment of structure **9** (Figure 3), and therefore assignment of structure **10a** to the major cycloadduct (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) acrolein (1.2 equiv), $CDCl_3$ (ca. 0.9 M), 53 °C, 24 h; (ii) $LiAlH_4$ (1.35 equiv), THF, r.t., 30 min; (iii) 3,5-$(O_2N)_2C_6H_3COCl$ (1.3 equiv), Et_3N (2 equiv), DMAP (0.05 equiv), CH_2Cl_2, 0 °C, 20 min

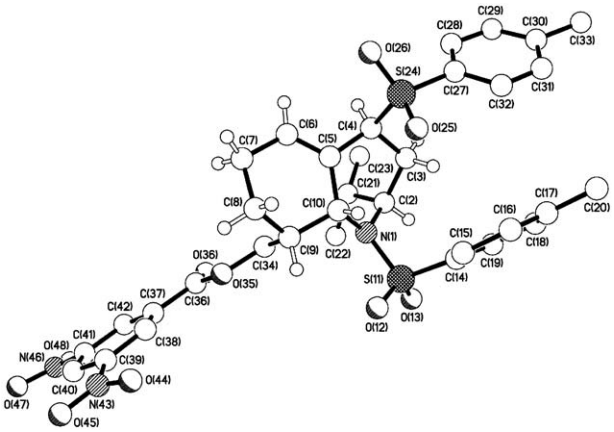
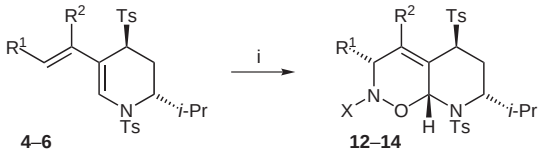


Figure 3 The molecular structure of **9**

The preferred formation of **10a** in the cycloaddition reaction of **4** with acrolein mirrors the *endo*-, *syn*-selectivity observed with maleic anhydride. The erosion of *endo*-selectivity (ratio **10a**:**10b** = ca. 4.5:1) in comparison with the maleic anhydride reaction may be a consequence of the lower reactivity of acrolein as a dienophile, and is in keeping with similar decreases in diastereomer ratios observed for singly-activated dienophiles in Comins' work. Again, the diastereofacial selectivity with respect to the diene is opposite to that observed for the 2,3-dihydro-4-pyridone-derived dienes.[5]

We next looked at the hetero-Diels–Alder reactions of 1,3-dienes **4**–**6**.[10] These were carried out in dichloromethane at ambient temperature with nitroso dienophiles

XN=O (**11a**: X = Boc; **11b**: X = CBz; **11c**: X = Ph) generated in situ in the case of **11a**,**b** by $Bu_4N^+IO_4^-$-mediated oxidation[11] of the corresponding hydroxylamines.[12] All three dienes reacted with the three dienophiles to give single products (Scheme 4, Table 1).



Scheme 4 *Reagents and conditions*: (i) reactions with **11a**,**b**: add XNHOH (2.2 equiv) to solution of diene and Bu_4NIO_4 (2 equiv) in CH_2Cl_2 (0.12–0.15 M), r.t., 15 min; reactions with **11c**: PhNO (1 equiv), CH_2Cl_2 (0.1 M), r.t., 1–48 h

The structure of cycloadduct **12a** was unequivocally established by X-ray crystallographic analysis (Figure 4), demonstrating that in common with maleic anhydride and acrolein, approach of the hetero-dienophile had occurred exclusively *syn* to the isopropyl group. The assignment of stereochemistry in the other cycloadducts followed from the similarity in the chemical shifts of the O–CH–N methine protons. The yields of the cycloaddition reactions of **5** were consistently lower than for **4** and **6**, perhaps reflecting a less pronounced preference for the reactive *cisoid* over the unreactive *transoid* diene conformation on account of allylic 1,3-strain between the diene methyl group and the sulfonyl-substituted C-4 carbon atom in the piperidine ring (Scheme 5).

In conclusion, we have shown that 5-alkenyl-1,4-bis(4-tolylsulfonyl)-1,2,3,4-tetrahydropyridines are readily available 1,3-dienes which enter into homo- and hetero-Diels–Alder reactions with high stereoselectivity and complete regioselectivity. Application of this chemistry to natural and unnatural products synthesis is ongoing and will be the subject of future reports from this laboratory.

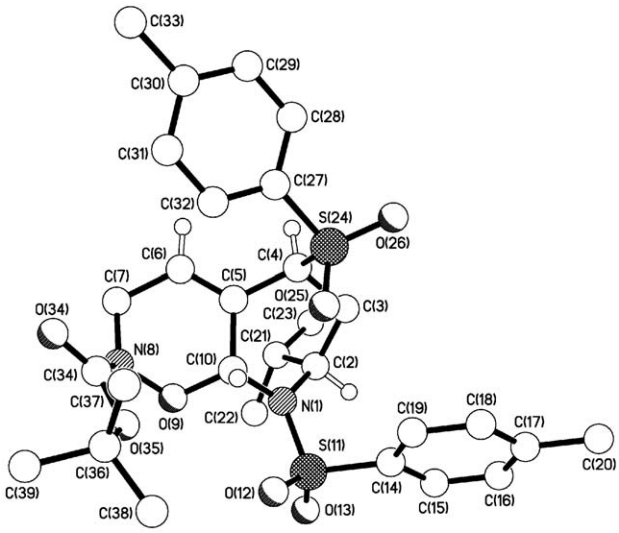
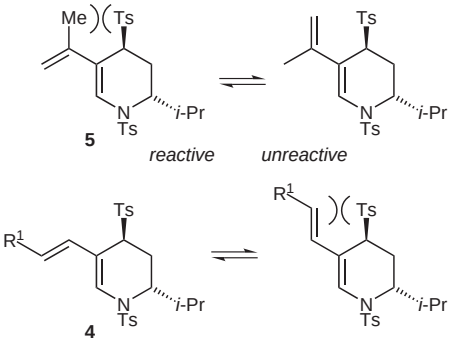


Figure 4 The molecular structure of **12a**



Scheme 5

Table 1 Hetero-Diels–Alder Reactions of **4**–**6**

Entry	Diene	R^1	R^2	X	Product	Yield (%)[a]
1	**4**	H	H	Boc	**12a**	76
2	**4**	H	H	CBz	**12b**	70
3	**4**	H	H	Ph	**12c**	98
4	**5**	H	Me	Boc	**13a**	55
5	**5**	H	Me	CBz	**13b**	50
6	**5**	H	Me	Ph	**13c**	24
7	**6**	Ph	H	Boc	**14a**	73
8	**6**	Ph	H	CBz	**14b**	67
9	**6**	Ph	H	Ph	**14c**	67

[a] Yields are for chromatographically purified products.

A solution of (2*R*,4*S*)-2-(1-methylethyl)-1,4-bis(4-tolylsulfonyl)-5-vinyl-1,2,3,4-tetrahydropyridine (**4**, 0.849 mmol, 390 mg, 1 equiv) and maleic anhydride (0.849 mmol, 84 mg, 1 equiv) in $CDCl_3$ (350 μL) was heated to 65 °C for 2.5 h. The mixture was concentrated under reduced pressure to afford the crude cycloadduct as a light brown solid.

^{1}H NMR (270 MHz): δ = 7.73 (2 H, d, *J* = 8.5 Hz, *ortho*-Ts), 7.41–7.18 (6 H, m, *ortho*-Ts and *meta*-Ts), 6.24 (1 H, br s, –CH=), 4.66 (1 H, br d, *J* = 7.0 Hz, H-8a), 4.35 (1 H, t, *J* = 8.5 Hz, H-8), 3.77 (1 H, br t, *J* = 9.0 Hz, H-4), 3.44 (1 H, ddd, *J* = 11.0, 7.5, 4.5 Hz, H-7), 3.27–3.23 (1 H, m, H-2), 2.66–2.28 (2 H, m, CH_2–CH=), 2.46 (3 H, s, CH_3 of Ts), 2.28 (3 H, s, CH_3 of Ts), 1.45–1.11 [2 H, m, CH(CH_3)$_2$ and H-3], 0.96 [3 H, d, *J* = 6.5 Hz, CH(CH_3)$_2$], 0.96–0.71 (1 H, m, H-3), 0.59 [3 H, d, *J* = 6.5 Hz, CH(CH_3)$_2$]. ^{13}C NMR (67.5 MHz): δ = 172.6 (–COOCH$_3$), 168.2 (*C*OOCH$_3$), 145.4 (*ipso*-Ts), 144.2 (*ipso*-Ts), 135.0 (–CH=), 133.2 (*para*-Ts), 132.6 (*para*-Ts), [130.0, 129.9, 128.8, 128.3 (*ortho* and *meta*)], 123.6 (CH=*C*–), 60.0 (C-4), 59.1 (C-2), 49.9 (C-6), 47.2 (C-8), 39.0 (C-7), 30.5 [*C*H(CH$_3$)$_2$], 23.6 (*C*H$_2$CH=), 23.1 (C-3), 21.7 (CH$_3$ of Ts), 21.7 (CH$_3$ of Ts), 21.0 [CH(*C*H$_3$)$_2$], 19.8 [CH(*C*H$_3$)$_2$]. MS (CI): *m/z* = 575 [M + NH$_4$]$^+$, 558 [M + H]$^+$, 402, 248, 174.

Part of the crude mixture (0.141 mmol, 77 mg, 1 equiv) in solution in MeOH–CH_2Cl_2 (1.5:1, 2 mL) was treated at r.t. with trimethylsilyldiazomethane (0.55 mL of a 1 M solution in hexanes, 4 equiv). The reaction mixture was stirred for 2 h. Concentration under reduced pressure and chromatography (40% EtOAc–PE) yielded (2*R*,4*S*,7*R*,8*R*,8a*R*)-2-(1-methylethyl)-1,4-bis-(4-tolylsulfonyl)-1,2,3,4,6,7,8,8a-octahydroquinoline-7,8-dicarboxylic acid dimethyl ester (**7**, 60 mg, 74% over 2 steps) as a colourless solid, mp 140 °C (dec.); $[\alpha]_D^{25}$ –16 (*c* 3.4, CH_2Cl_2).

IR (CH_2Cl_2): 2953, 2869, 1730, 1593, 1303, 1185, 1161, 1146, 911, 742 cm^{-1}. ^{1}H NMR (270 MHz): δ = 7.77 (2 H, d, *J* = 8.5 Hz, *ortho*-Ts), 7.42–7.34 (4 H, m, *meta*-Ts), 7.25 (2 H, d, *J* = 8.5 Hz, *ortho*-Ts), 5.86–5.84 (1 H, m, –CH=), 4.52 (1 H, br s, H-8a), 4.21 (1 H, dd, *J* = 6.5, 3 Hz, H-2), 3.76–3.65 (1 H, m, H-4), 3.69 (3 H, s, OCH$_3$), 3.65 (3 H, s, OCH$_3$), 3.11 (1 H, dt, *J* = 11.0, 3.0 Hz, H-8), 3.11 (1 H, ddd, *J* = 11.5, 4.5, 3.5 Hz, H-7), 2.83–2.71 (1 H, m, CH_2–CH=), 2.47 (3 H, s, CH_3 of Ts), 2.41 (3 H, s, CH_3 of Ts), 2.25–2.18 (1 H, m, CH_2–CH=), 1.64 [1 H, doublet of septets, *J* = 11.0, 6.5 Hz, CH(CH$_3$)$_2$], 1.54 (1 H, ddd, *J* = 15.0, 9.0, 2.5 Hz, H-3), 1.32 (1 H, ddd, *J* = 15.5, 11.5, 4.0 Hz, H-3), 0.69 [3 H, s, *J* = 6.5 Hz, CH(CH$_3$)$_2$], 0.63 [3 H, s, *J* = 6.5 Hz, CH(CH$_3$)$_2$]. ^{13}C NMR (67.5 MHz): δ = 172.7 (*C*OOCH$_3$), 171.2 (*C*OOCH$_3$), 145.1 (*ipso*-Ts), 144.0 (*ipso*-Ts), 135.9 (–CH=), 135.2 (*para*-Ts), 133.5 (*para*-Ts), [129.9, 129.7, 129.1, 128.5 (*ortho* and *meta*)], 120.5 (CH=*C*–), 61.4 (C-4), 59.4 (C-2), 54.4 (C-6), 52.2 (CH$_3$O), 51.7 (CH$_3$O), 46.0 (C-8), 40.4 (C-7), 29.7 (*C*H(CH$_3$)$_2$), 25.3 (*C*H$_2$CH=), 22.7 (C-3), 21.7 (CH$_3$ of Ts), 21.6 (CH$_3$ of Ts), 20.9 [CH(*C*H$_3$)$_2$], 19.8 [CH(*C*H$_3$)$_2$]. MS (CI): *m/z* = 621 [M + NH$_4$]$^+$, 604 [M + H]$^+$. Anal. Calcd for $C_{30}H_{37}NO_8S_2$: C, 59.68; H, 6.18; N, 2.32%. Found: C, 59.76; H, 6.24; N, 2.24.

To a solution of (2*R*,4*S*)-2-(1-methylethyl)-1,4-bis(4-tolylsulfonyl)-5-vinyl-1,2,3,4-tetrahydropyridine (**4**, 0.246 mmol, 113 mg, 1 equiv) in $CDCl_3$ (250 μL) was added freshly distilled acrolein (0.295 mmol, 30 μL, 1.2 equiv). The reaction mixture was heated at 53 °C for 24 h and the solvent evaporated under reduced pressure. ^{1}H NMR Analysis of the crude product indicated a diastereoisomeric ratio of 82:18. Chromatography (25% EtOAc–PE) yielded an inseparable mixture of (2*R*,4*S*,8*R*,8a*R*)-2-(1-methylethyl)-1,4-bis-(4-tolylsulfonyl)-1,2,3,4,6,7,8,8a-octahydroquinoline-8-carbaldehyde (**10a**) and (2*R*,4*S*,8*S*,8a*R*)-2-(1-methylethyl)-1,4-bis(4-tolylsulfonyl)-1,2,3,4,6,7,8,8a-octahydroquinoline-8-carbaldehyde (**10b**, 108 mg, 79%) as a colourless solid; data for **10a** taken from the mixture.

^{1}H NMR (270 MHz): δ = 10.0 (1 H, s, CHO), 7.72 (2 H, d, *J* = 8.5 Hz, *ortho*-Ts), 7.40 (2 H, 8.0, *ortho*-Ts), 7.36 (2 H, d, *J* = 8.0 Hz, *meta*-Ts), 7.23 (2 H, d, *J* = 8.0 Hz, *meta*-Ts), 5.80 (1 H, br s, –CH=), 4.47 (1 H, br s, H-8a), 3.73–3.63 (2 H, m, H-4 and H-2), 3.38–3.31 (1 H, m, C*H*CHO), 2.48 (3 H, s, CH_3 of Ts), 2.41 (3 H, s, CH_3 of Ts), 2.30–1.85 (3 H, m, H-3, CH_2–CH=), 1.76–1.61 (2 H, m, H-7), 1.58 [1 H, doublet of septets, *J* = 10.5, 6.5 Hz, CH(CH$_3$)$_2$], 1.38 (1 H, ddd, *J* = 15.5, 11.5, 4.0 Hz, H-3), 0.87 [3 H, s, *J* = 6.5 Hz, CH(CH$_3$)$_2$], 0.72 [3 H, s, *J* = 6.5 Hz, CH(CH$_3$)$_2$]. ^{13}C NMR (67.5 MHz): δ = 205.5 (CH0), 145.1 (*ipso*-Ts), 144.2 (*ipso*-Ts), 138.2 (–CH=), 134.8 (*para*-Ts), 133.4 (*para*-Ts), [130.0, 129.7, 129.2, 128.2 (*ortho* and *meta*)], 122.6 (CH=C–), 61.7 (C-4), 60.2 (C-2), 53.4 (C-6), 49.4 (CHCHO), 30.6 [CH(CH$_3$)$_2$], 22.8 (CH$_2$CH=), 22.3 (C-3), 22.0 (C-8), 21.7 (CH$_3$ of Ts), 21.7 (CH$_3$ of Ts), 20.6 [CH(CH$_3$)$_2$], 20.0 [CH(CH$_3$)$_2$].

To a solution of (2*R*,4*S*,8*RS*,8a*R*)-2-(1-methylethyl)-1,4-bis-(4-tolylsulfonyl)-1,2,3,4,6,7,8,8a-octahydro-quinoline-8-carbaldehyde (**10a**,**b**, 108 mg, 0.20 mmol) in THF (2 mL) at r.t. was added $LiAlH_4$ (265 μL of a 1 M solution in hexanes, 1.35 equiv) causing the colourless solution to turn yellow. After 30 min the reaction was quenched with EtOAc followed by the addition of sat. aq Rochelle salt. The mixture was stirred for 16 h and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the corresponding primary alcohols. To a solution of the crude product (75 mg) in CH_2Cl_2 (1 mL) was added Et_3N (30 μL, 0.21 mmol, 2 equiv), DMAP (0.05 equiv) and 3,5-dinitrobenzoyl chloride (33 mg, 0.141 mmol, 1.3 equiv) at 0 °C. After 20 min the reaction was quenched with sat. aq NH_4Cl, extracted with EtOAc, and washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography (25% EtOAc–PE) yielded (2*R*,4*S*,8*R*,8a*R*)-2-(1-methylethyl)-1,4-bis-(4-tolylsulfonyl)-1,2,3,4,6,7,8,8a-octahydroquinolin-8-ylmethyl 3,5-dinitrobenzoate (**9**) as a colourless solid (52 mg, 51% over two steps based on **10a** present in starting material, 42% based on 82:18 **10a**:**10b** mixture), mp 124–125 °C (dec.); $[\alpha]_D^{25}$ –43 (*c* 1.1, CH_2Cl_2).

IR (CH_2Cl_2): 2963, 2926, 1730, 1711, 1546, 1343, 1164, 1142, 1086, 977, 814 cm^{-1}. ^{1}H NMR (270 MHz): δ = 9.21 (3 H, s, Ar-H of dinitrophenyl), 7.73 (2 H, d, *J* = 8.0 Hz, *ortho*-Ts), 7.41–7.36 (4 H, m, *meta*-Ts), 7.25 (2 H, d, *J* = 8.0 Hz, *ortho*-Ts), 5.82 (1 H, br s, –CH=), 4.71 (1 H, dd, *J* = 11.0, 5.5 Hz, CH$_2$OCO), 4.53–4.46 (2 H, m, H-4 and H-8a), 3.66 (1 H, t, *J* 11.5, 5.5 Hz, CH$_2$OCO), 3.60 (1 H, t, *J* = 10.0 Hz, H-4), 3.46 (1 H, br s, C*H*CH$_2$OCO), 3.38 (1 H, br d, *J* = 10.5 Hz, H-2), 2.51 (3 H, s, CH_3 of Ts), 2.43 (3 H, s, CH_3 of Ts), 2.20–1.87 (2 H, m, CH_2–CH=), 1.87–1.54 (3 H, m, H-7 and H-3), 1.25–1.20 [2 H, m, H-3 and CH(CH$_3$)$_2$], 1.08 [3 H, s, *J* = 6.5 Hz, CH(CH_3)$_2$], 0.74 [3 H, d, *J* = 6.5 Hz, CH(CH_3)$_2$]. ^{13}C NMR (67.5 MHz): δ = 162.8 (C=O), 148.7, (Ar-C of dinitrophenyl), 145.0 (*ipso*-Ts), 144.0 (*ipso*-Ts), 137.4 (–CH=), 135.0 (*para*-Ts), 134.0 (Ar–C of dinitrophenyl), 133.4 (*para*-Ts), [130.0, 129.9, 129.6, 129.1, 128.0 (*ortho* and *meta*) and Ar–C of dinitrophenyl], 122.7 (Ar–C of dinitrophenyl), 122.3 (CH=C–), 65.1 [CH$_2$–O(C=O)], 61.9 (C-4), 59.4 (C-2), 54.6 (C-6), 36.3 (CHCH$_2$OCO), 31.1 [CH(CH$_3$)$_2$], 23.1 (CH$_2$CH=), 22.7 (C-3), 21.7 (CH$_3$ of Ts), 21.7 (CH$_3$ of Ts), 21.2 (C-8), 20.5 [CH(CH$_3$)$_2$], 20.4 [CH(CH$_3$)$_2$]. Anal. Calcd for $C_{34}H_{37}N_3O_{10}S_2$: C, 57.37; H, 5.24; N, 5.90%. Found: C, 57.39; H, 5.22; N, 5.83.

To a stirred solution of (2*R*,4*S*)-2-isopropyl-1,4-bis-(toluene-4-sulfonyl)-5-vinyl-1,2,3,4-tetrahydropyridine (**4**, 13 mg, 0.03 mmol, 1 equiv) in $CDCl_3$ (0.5 mL) was added nitrosobenzene (3 mg, 0.03 mmol, 1 equiv). After 40 min at r.t. the reaction was complete as evidenced by ^{1}H NMR analysis. The reaction mixture concentrated under reduced pressure. Flash chromatography (50% Et_2O–PE) gave (5*S*,7*R*,8a*R*)-7-(1-methylethyl)-2-phenyl-5,8-bis(4-tolylsulfonyl)-3,5,6,7,8,8a-hexahydro-2*H*-pyrido[3,2-*e*][1,2]oxazine (**12c**, 15.8 mg, 0.03 mmol, 98%); R_f 0.19 (50% Et_2O–PE). ^{1}H NMR (500 MHz): δ = 7.85 (2 H, d, *J* = 8.5 Hz, *ortho* PhSO$_2$), 7.60 (2 H, d, *J* = 8.0 Hz, *ortho* PhSO$_2$), 7.26–7.35 (6 H, m, 4 × Ph and *meta* PhSO$_2$),

7.18 (2 H, d, J = 7.5 Hz, *meta* $PhSO_2$), 7.01 (1 H, t, J = 7.5 Hz, Ph), 6.15 (1 H, s, OCHN), 5.75 (1 H, dd, J = 16.5, 8.0 Hz, CC*H*CH_2), 3.91–3.96 (2 H, m, 1 × CCHCH_2 and NTsCH), 3.73 (1 H, d, J = 16.5 Hz, 1 × CCHCH_2), 3.41–3.50 [1 H, m, C*H*$CH(CH_3)_2$], 2.47 (3 H, s, $ArCH_3$), 2.46 (3 H, s, $ArCH_3$), 2.00 (1 H, m, 1 × CHTsCH_2), 1.68–1.78 [2 H, 1 × CHTsCH_2 and C*H*$(CH_3)_2$], 0.85 [3 H, d, J = 6.5 Hz, $CH(CH_3)_A(CH_3)_B$], 0.79 [3 H, d, J = 6.5 Hz, $CH(CH_3)_A(CH_3)_B$]. ^{13}C NMR (67.5 MHz): δ = 132.3, 129.7, 129.4, 128.8, 128.1, 122.3, 115.5, 84.8, 82.0, 65.8, 61.5, 59.6, 51.4, 31.0, 29.4, 24.3, 21.7, 21.6, 20.4, 20.2. MS (CI): *m/z* = 577, 567 $[M + H]^+$, 477, 411, 304, 174, 150, 109, 94. HRMS: *m/z* $[MH]^+$ calcd for $C_{30}H_{34}N_2O_5S_2$: 567.1987; found: 567.1985.

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