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Synthesis of azimic acid using hydroformylation

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Dedicated, on the occasion of his retirement, to Professor Willie Motherwell who introduced the corresponding author to the concept of stereoelectronic control

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ABSTRACT

A synthesis of the alkaloid azimic acid has been achieved using double hydroformylation with a single tandem condensation to form the six membered ring. The oxygen substituent was introduced by diastereoselective dihydroxylation, cis to the existing alkyl substituent. The methyl substituent was introduced via an iminium ion intermediate under stereoelectronic control.

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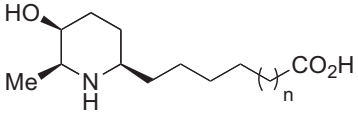
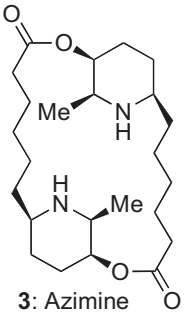
1. Introduction

Azimic acid **1**, a hydrolysis product of the alkaloid azimine **3**, isolated from *azima tetracantha L.*, is a trisubstituted piperidine, with all substituents on the same face of the ring.[1,2] Azimic acid has been the subject of a number of total syntheses. The synthetic challenge is in the installation of the three stereocentres of the piperidine ring cis to each other around the ring.[3] The most common approach has been to install the majority of the stereocentres prior to piperidine ring formation. Brown employed a Henry reaction to form the 1,2-aminoalcohol moiety prior to cyclisation.[4] Hanessian,[5] Datta[6] and Huang[7] employed intramolecular reductive amination reactions. Naito employed a nitrone cycloaddition.[8] In a minority of cases, one or more stereocenters have been installed after ring formation: Ma employed an enaminone cyclisation.[9] Both Padwa[10] and Zhou[11] established the aminoalcohol system using an aza-Achmatowicz reaction. Natsume constructed the molecule from pyridine,[12] while Gerlach started with a substituted pyridine.[13] Carpamic acid **2**, a higher analogue of azimic acid containing an additional carbon atom in the side chain, has also been the subject of several syntheses.[14–18]



1 n = 1: Azimic acid
2 n = 2: Carpamic acid



3: Azimine

2. Results and discussion

It has been shown that dihydroxylation of six membered ring ene-sulfonamides shows good selectivity for the isomer in which the diol is cis to an α′-substituent (Scheme 1).[19] This selectivity, which has been attributed to a combination of lipophilic and electrostatic effects, delivers the correct stereochemistry of the 3 and 6 substituents. We anticipated that replacement of the 2-hydroxy group of the diol **4** with a methyl group via an iminium ion[20] would deliver the desired stereochemistry under stereoelectronic control.[21] The required ene-sulfonamide **5**[22,23] would, in

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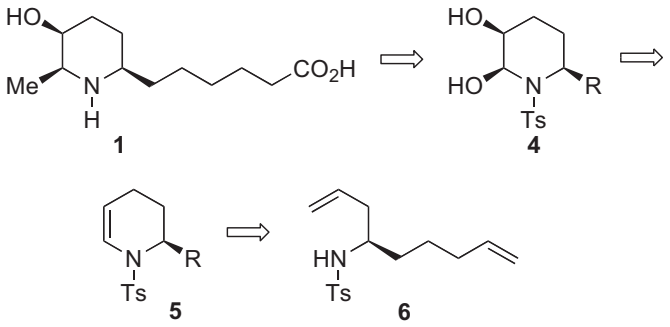
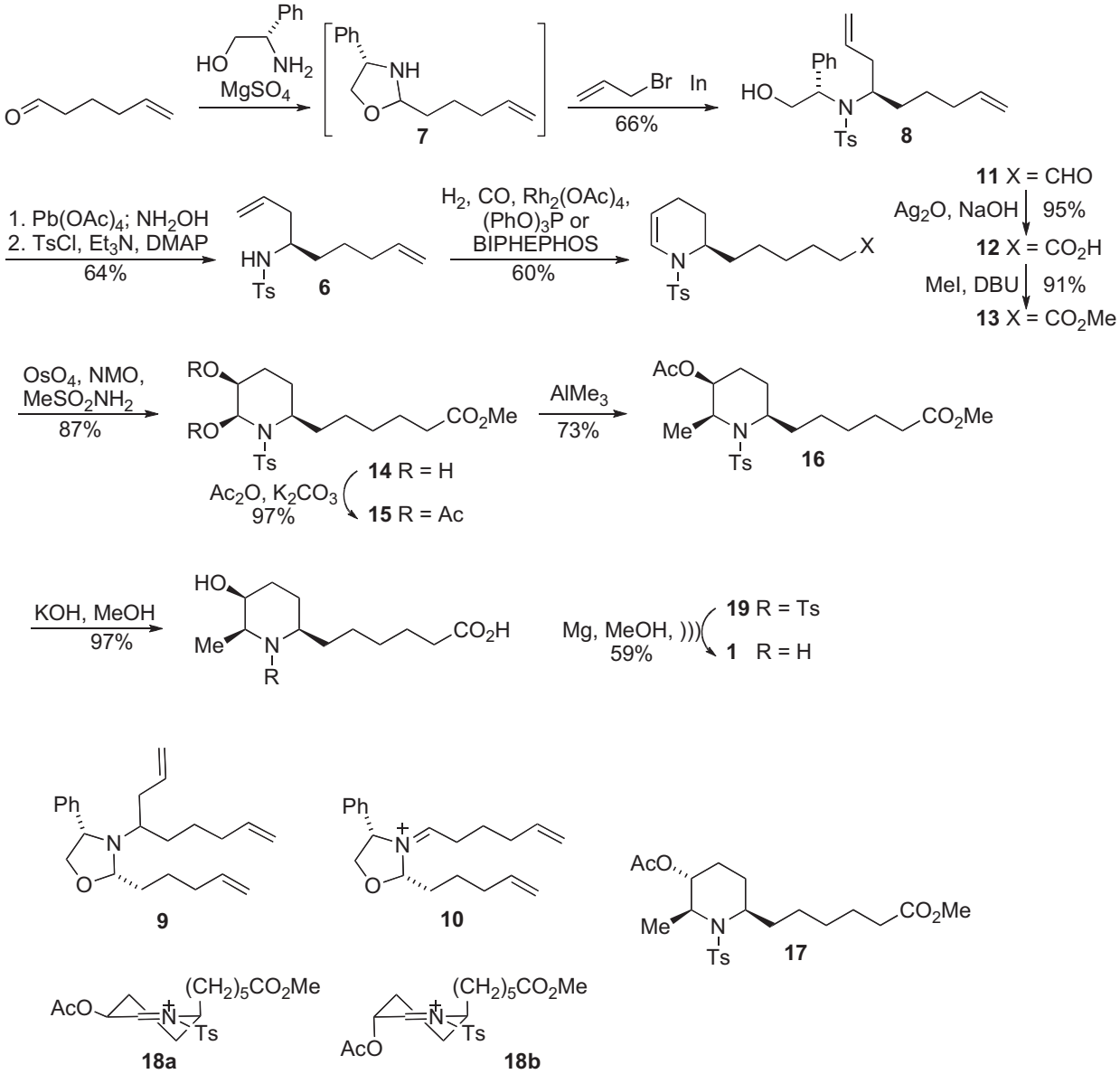


Scheme 1. Azimic acid retrosynthesis.

turn, be available by tandem hydroformylation-condensation,[24–27] as in our recent synthesis of pseudoconhydrine,[19] building on the work of Ojima.[25,28] Given that the long side chain of azimic acid terminates with a carboxylic acid, we planned to employ a double hydroformylation of diene **6**.[29]

The desired diene **6** was prepared using the method of Vilaivan et al. (Scheme 2).[30] Condensation of (*S*)-phenylglycinol with hex-5-enal generated the oxazolidine **7**,[31] which reacted with allyl bromide under Barbier conditions using indium to give the amino-alcohol derivative **6** as a single diastereoisomer after cleavage of the chiral auxiliary, N-sulfonylation and chromatographic purification, in 42% yield (from hex-5-enal) and >98% ee. The diastereoselectivity of the allylation was found to be highly dependent on both the reaction temperature and the rate of addition of the allyl bromide. Hex-5-enal was prepared by IBX oxidation[32] of the commercially available alcohol. It was found to be important to employ a precisely measured quantity of the freshly distilled aldehyde to achieve a satisfactory Barbier allylation. Use of an excess of undistilled aldehyde resulted in the formation of a different allylation product **9** from a 2:1 condensation of the aldehyde with the phenylglycinol. Compound **9** was formed as a single diastereoisomer,[33] and is proposed to arise from Barbier allylation of iminium ion **10**. Double hydroformylation of diene **6** using rhodium acetate and either triphenylphosphite or BIPHEPHOS[34] gave the ene-sulfonamide **11** in 60% and 74% yield, respectively, with the



Scheme 2. Azimic acid synthesis.

tandem condensation occurring exclusively at the nearer of the two aldehydes. Oxidation of the remaining aldehyde and esterification then yielded the methyl ester **13** in 86% yield. Dihydroxylation of the alkene following the Upjohn procedure with the addition of methane sulfonamide proceeded in 87% yield and gave an inseparable 5.8:1 mixture of diols **14**. Based upon our previous work[19] and that of Harrity,[35] the major diol was assigned the all-cis stereochemistry. The rather labile diol mixture[36] was acetylated to give the diacetates **15** in 97% yield as a 5.8:1 mixture, still inseparable. Treatment of the diacetates **15** with trimethylaluminium, serving as both a methyl source and as a Lewis acid, gave the all cis methylated product **16** in 73% yield. The minor product of this reaction, isolated in 5% yield and separated by column chromatography, was found by X-ray crystallography to be **17**, with the 2- and 6-substituents cis diaxial.[37] This product arises by methylation of the minor diacetate diastereoisomer. The stereochemistry of both products is consistent with axial attack by a methyl nucleophile on the corresponding iminium ions **18ab** in conformations such that the existing α-side chain is axial.[38] Hydrolysis of the two ester groups of piperidine **16** and reductive detosylation of the known[10] sulfonamide **19** using magnesium in methanol,[39] promoted by ultrasound, yielded the natural product **1**, which was purified by carefully optimised ion exchange chromatography, in 59% yield. The ^{1}H NMR[10] and ^{13}C NMR[10,13] spectroscopic data and the chiroptical data[5–9,11] were in good agreement with those reported for the natural product.

The use of the hydroformylation–dihydroxylation sequence for the stereoselective synthesis of 2,3,6-trisubstituted piperidines has been demonstrated. The synthesis of azimic acid has been achieved in a 10-step sequence from phenylglycinol, employing the less common strategy of installing the majority of the substituents after ring formation. The synthesis further illustrates the utility of hydroformylation as a tool for C–C bond formation in organic synthesis, and the value of ene-sulfonamides as synthetic intermediates.

3. Experimental section

3.1. General

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran was distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane and acetonitrile were dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230–400 mesh.

^{1}H NMR spectra were recorded at 300, 400 or 500 MHz in $CDCl_3$ solutions. ^{13}C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in parts per million and coupling constants are recorded in Hertz. Optical rotations are given with units of 10^{-1} deg cm^2 g^{-1}. Rotations were measured at a wavelength of 589 nm. Enantiomeric excess was determined by chiral HPLC analysis, using a Diacel IC column, eluting with IPA/hexane.

*3.1.1. (4S)-2-(Pent-4-en-1-yl)-4-phenyloxazolidine (**7**).* Hex-5-enal (0.16 g, 1.60 mmol) was added to a mixture of (*S*)-phenylglycinol (0.2 g, 1.46 mmol) and $MgSO_4$ (1.75 g, 14.60 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred overnight, filtered, evaporated to give the crude oxazolidine **7** (0.32 g, quant.) as a mixture of diastereoisomers and as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.20 (m, 5H), 5.88–5.76 (m, 1H), 5.03 (d, *J*=17.4 Hz, 1H), 4.97 (d, *J*=10.1 Hz, 1H), 4.60–4.54 (m, 1H), 4.51 (app. t, *J*=7.0 Hz, 0.5H), 4.38 (app. t, *J*=7.5 Hz, 0.5H), 4.29 (app. t, *J*=7.9 Hz, 0.5H), 4.12 (app. t, *J*=7.7 Hz, 0.5H), 3.68 (app. t, *J*=7.6 Hz, 0.5H), 3.60 (dd, *J*=8.2, 6.6 Hz, 0.5H), 2.21–2.04 (m, 2H), 1.95–1.45 (m, 4H).

*3.1.2. (S)-2-((R)-Nona-1,8-dien-4-ylamino)-2-phenylethanol (**8**).* Allyl bromide (0.53 mL, 6.07 mmol) was added slowly via syringe pump over 3 h to a mixture of indium powder (465 mg, 4.05 mmol) and oxazolidine **7** (440 mg, 2.02 mmol) in methanol (10 mL) at −10 °C and the mixture was stirred for another 6 h. The mixture was diluted with 10% aqueous $NaHCO_3$ (10 mL), extracted with ethyl acetate (15 mL×3), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with 20% ethyl acetate/hexane to give homoallylic amine **8** (350 mg, 66%) as a yellowish oil: FTIR (neat, cm^{-1}): ν_{max} 3326, 1639; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 5.88–5.62 (m, 2H), 5.14–5.03 (m, 2H), 4.98–4.86 (m, 2H), 3.88 (dd, *J*=8.6, 4.6 Hz, 1H), 3.66 (dd, *J*=10.6, 4.5 Hz, 1H), 3.47 (dd, *J*=10.6, 8.7 Hz, 1H), 2.60–2.47 (m, 1H), 2.26–2.12 (m, 2H), 1.96–1.84 (m, 2H), 1.45–1.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 138.7, 135.1, 128.6, 127.6, 127.4, 117.4, 114.6, 66.9, 61.7, 53.6, 37.6, 34.2, 33.7, 25.1; MS (ESI+) *m*/*z* 259 ([M+H]$^+$, 100); HRMS calcd for $C_{17}H_{25}NO$ ([M+H]$^+$) 260.2014, found 260.2025; $[\alpha]_D^{21}$ +82.3 (*c* 1.1, $CHCl_3$).

*3.1.3. (R)-N-Tosylnona-1,8-dienyl-4-amine (**6**).* Lead tetraacetate (1.46 g, 3.29 mmol) was added to a solution of aminoalcohol **8** (711 mg, 2.74 mmol) in dry CH_2Cl_2/MeOH (1:1, 20 mL) at 0 °C and the mixture was stirred until confirmed complete by TLC (30 min). Hydroxylamine hydrochloride (1.90 g, 27.4 mmol) was added to the mixture and it was stirred for another 30 min at 0 °C. The solvents were evaporated under reduced pressure. The residue was washed with hexane (15 mL×3), then suspended in CH_2Cl_2 (20 mL) and filtered. The filtrate was concentrated in vacuo. The residue was taken up in dry CH_2Cl_2 (20 mL), Et_3N (0.76 mL, 5.48 mmol), TsCl (575 mg, 3.02 mmol) and DMAP (33 mg, 0.274 mmol) were added and the mixture was stirred overnight. The reaction mixture was then diluted with satd aq ammonium chloride (20 mL), extracted with ethyl acetate (20 mL×3), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/hexane to give sulfonamide **6** (510 mg, 64% yield) as a colourless oil: FTIR (neat, cm^{-1}): ν_{max} 3279, 1641, 1322, 1156; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=8.1 Hz, 2H), 5.68 (ddt, *J*=16.1, 11.1, 6.7 Hz, 1H), 5.55 (ddt, *J*=17.3, 10.1, 7.3 Hz, 1H), 5.16–4.79 (m, 4H), 4.32 (d, *J*=7.9 Hz, 1H), 3.33–3.24 (m, 1H), 2.43 (s, 3H), 2.10 (app. t, *J*=6.4 Hz, 2H), 1.93 (app. q, *J*=6.9 Hz, 2H), 1.52–1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 138.3, 138.3, 133.4, 129.7, 127.2, 118.9, 114.8, 53.3, 39.2, 34.0, 33.3, 24.7, 21.6; MS (ESI+) *m*/*z* 293 ([M+H]$^+$, 100), 316 ([M$^+$+Na], 71); HRMS Calcd for $C_{16}H_{23}NO_2S$ ([M+H]$^+$) 294.1528, found 294.1537; $[\alpha]_D^{22}$ +3.0 (*c* 1.35, $CHCl_3$).

*3.1.4. 6-((R)-1,2,3,4-Tetrahydro-1-tosylpyridin-2-yl)hexanal (**11**).* Sulfonamide **6** (440 mg, 1.50 mmol), $Rh_2(OAc)_4$ (7 mg, 15.0×10^{-3} mmol) and $P(OPh)_3$ (98 μL, 0.375 mmol) were dissolved in THF (15 mL) in a Fisher–Porter tube. The Fisher–Porter tube was purged (three times) with H_2/CO (1:1) and finally charged with H_2 (30 psi)/CO (30 psi). The reaction mixture was stirred vigorously at 65 °C for 18 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with 2% ethyl acetate/hexane to give ene-sulfonamide **11** (300 mg, 60% yield) as a colourless oil: FTIR (neat, cm^{-1}): ν_{max} 1721, 1645, 1339, 1164; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J*=1.6 Hz, 1H), 7.66 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=8.1 Hz, 4H), 6.57 (d, *J*=8.3 Hz, 1H), 5.09–4.97 (m, 1H), 3.89 (br s, 1H), 2.48–2.38 (m, 2H), 2.41 (s, 3H), 2.01–1.07 (m, 10H), 1.02–0.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 143.4, 136.1, 129.7, 127.0, 123.5, 109.7, 52.8, 43.8, 31.3, 28.9, 25.6, 23.0, 22.0, 21.6, 17.3; MS (ESI+) *m*/*z* 336 ([M+H]$^+$, 100); HRMS

calcd for $C_{18}H_{25}NO_3S$ ($[M+H]^+$) 336.1633, found 336.1634; $[\alpha]_D^{22}$ −265.8 (*c* 1.0, $CHCl_3$).

*3.1.5. 6-((R)-1,2,3,4-Tetrahydro-1-tosylpyridin-2-yl)hexanoic acid (**12**).* NaOH (137 mg, 3.43 mmol) was added to a suspension of Ag_2O (175 mg, 0.754 mmol) in H_2O (5 mL). Aldehyde **11** (230 mg, 0.686 mmol) dissolved in diethyl ether (3 mL) was added and the mixture was stirred overnight. The reaction mixture was acidified with 2 M HCl (15 mL), extracted with Et_2O (20 mL×3), washed with water (20 mL) and brine (20 mL), and dried ($MgSO_4$), filtered and evaporated to give carboxylic acid **12** (228 mg, 95% yield) as a pale yellowish oil: FTIR (neat, cm^{-1}): ν_{max} 2930, 1705, 1646, 1339, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=8.1 Hz, 2H), 6.58 (d, *J*=8.2 Hz, 1H), 5.08–4.98 (m, 1H), 3.89 (br s, 1H), 2.41 (s, 3H), 2.36 (t, *J*=7.4 Hz, 2H), 1.99–1.16 (m, 11H), 0.97–0.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 143.4, 136.1, 129.7, 127.0, 123.6, 109.7, 52.9, 34.1, 31.3, 28.9, 25.5, 24.6, 23.0, 21.6, 17.3; MS (ESI+) *m/z* 352 ($[M+H]^+$, 100); HRMS calcd for $C_{18}H_{25}NO_4S$ ($[M+H]^+$) 352.1583, found 352.1583; $[\alpha]_D^{23}$ −260.2 (*c* 0.25, $CHCl_3$).

*3.1.6. Methyl 6-((R)-1,2,3,4-tetrahydro-1-tosylpyridin-2-yl)-hexanoate (**13**).* Methyl iodide (78 μL, 1.25 mmol) dissolved in toluene (10 mL) was added to a solution of carboxylic acid **12** (200 mg, 0.569 mmol) and DBU (0.10 mL, 0.683 mmol) in toluene. The mixture was heated at reflux with vigorous stirring for 3 h. The mixture was filtered, washing with Et_2O (20 mL). The organic layer was washed with water (10 mL), 2 M HCl (10 mL), satd aq $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), and dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 20% ethyl acetate/hexane to give ene-sulfonamide **13** (189 mg, 91% yield) as a colourless oil: FTIR (neat, cm^{-1}): ν_{max} 1734, 1645, 1340, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.3 Hz, 2H), 7.28 (d, *J*=8.3 Hz, 2H), 6.57 (dd, *J*=8.2, 0.8 Hz, 1H), 5.06–4.98 (m, 1H), 3.89 (br s, 1H), 3.67 (s, 3H), 2.41 (s, 3H), 2.31 (t, *J*=7.5 Hz, 2H), 1.98–1.21 (m, 11H), 0.96–0.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.4, 136.3, 129.8, 127.1, 123.7, 109.7, 53.0, 51.6, 34.2, 31.4, 29.1, 25.6, 25.0, 23.1, 21.7, 17.4; MS (ESI+) *m/z* 366 ($[M+H]^+$, 100), 388 ($[M+Na]^+$, 15); HRMS calcd for $C_{18}H_{25}NO_4S$ ($[M+H]^+$) 366.1739, found 366.1735; $[\alpha]_D^{23}$ −173.4 (*c* 0.4, $CHCl_3$).

*3.1.7. Methyl 6-((2R,5S,6S)-5,6-dihydroxy-1-tosylpiperidin-2-yl)-hexanoate (**14**).* Methanesulfonamide (62 mg, 0.657 mmol) was added to a solution of ene-sulfonamide **13** (240 mg, 0.657 mmol) in THF (4.50 mL), and the mixture was stirred until it was completely dissolved. NMO (50% w/w) (0.40 mL, 1.97 mmol), H_2O (0.50 mL) and K_2OsO_4 (24 mg, 65.7×10^{-3} mmol) were added to the solution, and the mixture was stirred overnight. The mixture was quenched with satd aq $Na_2S_2O_3$ (10 mL), washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and evaporated to give diols **14** (228 mg, 87% yield) as a yellowish oil and as an inseparable mixture of diastereoisomers: FTIR (neat, cm^{-1}): ν_{max} 3475, 1734, 1327, 1159; ^1H NMR (400 MHz, $CDCl_3$, major diastereoisomer) δ 7.69 (d, *J*=8.2 Hz, 2H), 7.29 (d, *J*=8.2 Hz, 2H), 5.40 (app. t, *J*=3.1 Hz, 1H), 3.92–3.77 (m, 1H), 3.67 (s, 3H), 3.51 (d, *J*=2.8 Hz, 1H), 3.34–3.21 (m, 1H), 2.42 (s, 3H), 2.31 (t, *J*=7.5 Hz, 2H), 1.97–1.19 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer) δ 174.5, 143.6, 138.3, 129.9, 126.9, 78.4, 69.3, 52.5, 51.7, 34.1, 34.1, 29.0, 27.0, 26.6, 24.9, 22.5, 21.6; MS (ESI+) *m/z* 382 ($[M^+-OH]$, 100), 422 ($[M+Na]^+$, 40); HRMS calcd for $C_{19}H_{29}NO_6S$ ($[M+H]^+$) 400.1794 found 400.1803.

*3.1.8. Methyl 6-((2R,5S,6S)-5,6-diacetoxy-1-tosylpiperidin-2-yl)-hexanoate (**15**).* Acetic anhydride (0.25 mL, 2.64 mmol), triethylamine (0.42 mL, 3.00 mmol) and DMAP (7 mg, 6.01×10^{-2} mmol) were added to a solution of diols **14** (240 mg, 0.601 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 3 h. The reaction mixture was diluted with satd aq NH_4Cl (20 mL), extracted with CH_2Cl_2 (15 mL×3), washed with water (20 mL) dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with 25% ethyl acetate/hexane to give diacetates **15** (280 mg, 97% yield) as a colourless oil and as an inseparable mixture of diastereoisomers: FTIR (neat, cm^{-1}): ν_{max} 1738, 1346, 1240, 1162; ^1H NMR (400 MHz, $CDCl_3$, major diastereoisomer) δ 7.71 (d, *J*=8.3 Hz, 1H), 7.29 (d, *J*=8.3 Hz, 1H), 6.78 (d, *J*=3.8 Hz, 1H), 4.59 (dt, *J*=12.1, 4.2 Hz, 1H), 3.96–3.87 (m, 1H), 3.66 (s, 3H), 2.41 (s, 3H), 2.29 (t, *J*=7.5 Hz, 2H), 2.02 (s, 3H), 1.96 (s, 3H), 1.80–1.13 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer) δ 174.2, 170.0, 169.2, 143.9, 137.8, 129.9, 127.2, 76.0, 69.7, 52.6, 51.6, 34.1, 33.2, 29.1, 26.9, 26.4, 24.9, 21.7, 21.1, 20.9, 19.3. MS (ESI+) *m/z* 424 ($[M^+-Oac]$, 100), 506 ($[M+Na]^+$, 54); HRMS calcd for $C_{23}H_{33}NO_8S$ ($[M+Na]^+$) 506.1825 found 506.1824.

*3.1.9. Methyl 6-((2R,5S,6S)-5-acetoxy-6-methyl-1-tosylpiperidin-2-yl)hexanoate (**16**).* Trimethylaluminium (0.22 mL of a 2 M solution in toluene, 0.447 mmol) was added dropwise to a solution of diacetates **15** (180 mg, 0.372 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with water (10 mL), extracted with CH_2Cl_2 (15 mL×3), washed with water (20 mL), dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 15% ethyl acetate/hexane to give acetate **16** (120 mg, 73% yield) as a pale yellowish oil: FTIR (neat, cm^{-1}): ν_{max} 1736, 1337, 1238, 1164; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=8.2 Hz, 2H), 4.44–4.24 (m, 2H), 3.91 (app. q, *J*=6.8 Hz, 1H), 3.66 (s, 3H), 2.40 (s, 3H), 2.31 (t, *J*=7.5 Hz, 2H), 2.00 (s, 3H), 1.81–1.30 (m, 12H), 1.25 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 170.2, 143.2, 138.7, 129.9, 126.8, 70.8, 52.1, 51.6, 49.6, 35.1, 34.1, 29.1, 27.0, 26.9, 24.9, 21.7, 21.2, 19.6, 15.8; MS (ESI+) *m/z* 440 ($[M^+$+H], 100), 462 ($[M^+$+Na], 13); HRMS calcd for $C_{18}H_{25}NO_4S$ ($[M+H]^+$) 440.2107, found 440.2109; $[\alpha]_D^{23}$ +16.7 (*c* 0.3, $CHCl_3$).

*3.1.10. Methyl 6-((2R,5R,6S)-5-acetoxy-6-methyl-1-tosylpiperidin-2-yl)hexanoate (**17**).* Colourless crystalline solid: FTIR (neat, cm^{-1}): ν_{max} 1733, 1329, 1243, 1159; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J*=7.8 Hz, 2H), 7.26 (d, *J*=7.8 Hz, 2H), 4.63 (s, 1H), 4.13–3.88 (m, 2H), 3.67 (s, 3H), 2.39 (s, 3H), 2.31 (t, *J*=7.7 Hz, 2H), 1.98–1.12 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 170.2, 142.7, 139.1, 129.5, 127.2, 70.5, 52.6, 51.9, 51.6, 35.6, 34.1, 29.1, 27.1, 24.9, 21.5, 21.3, 21.0, 20.9, 18.7; MS (ESI+) *m/z* 440 ($[M+H]^+$, 100), 462 ($[M+Na]^+$, 13); HRMS Calcd for $C_{18}H_{25}NO_4S$ ($[M+H]^+$) 440.2107, found 440.2101; mp 96–99 °C; $[\alpha]_D^{24}$ +7.4 (*c* 0.79, $CHCl_3$).

*3.1.11. 6-((2R,5S,6S)-5-Hydroxy-6-methyl-1-tosylpiperidin-2-yl)-hexanoic acid (**19**).*[10] Potassium hydroxide (3 mL of a 2 M aqueous solution, 6 mmol) solution was added to a solution of acetate **16** (0.1 g, 0.227 mmol) in MeOH (1 mL). The mixture was stirred at room temperature for 24 h. The volatiles were evaporated. The remaining aqueous layer was washed with CH_2Cl_2 (10 mL), acidified with 2 M HCl (10 mL) and extracted with CH_2Cl_2 (15 mL×3). The combined organic layers were washed with brine (20 mL), and dried ($MgSO_4$), filtered and evaporated to give carboxylic acid **19** (84 mg, 97% yield) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.2 Hz, 2H), 7.26 (d, *J*=8.2 Hz, 2H), 4.17 (app. quin., *J*=6.9 Hz, 1H), 3.98–3.88 (m, 1H), 3.36 (ddd, *J*=11.7, 6.9, 4.4 Hz, 1H), 2.41 (s, 3H), 2.35 (t, *J*=7.3 Hz, 2H), 1.75–1.30 (m, 12H), 1.24 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.6, 22.9, 24.7, 27.1, 27.3, 29.0, 34.0, 34.9, 51.9, 52.3, 69.0, 126.8, 129.8, 138.8, 143.1, 179.5. MS (ESI+) *m/z* 384 ($[M+H]^+$, 100); HRMS calcd for

$C_{19}H_{29}NO_5S$ ($[M+H]^+$) 384.1845, found 384.1836; $[\alpha]_D^{23}$ −5.13 (*c* 0.23, EtOAc).

*3.1.12. Azimic acid (**1**).* Mg turnings (13 mg, 0.52 mmol) were added to a solution of tosylpiperidinol **19** (20 mg, 0.052 mmol) in MeOH (3 mL) as the reaction mixture was sonicated (ultrasonic cleaning bath). The addition of Mg turnings was repeated till complete consumption of the starting material as judged by TLC. The reaction mixture was quenched with water (10 mL), evaporated to remove methanol, taken up in water (10 mL) again and filtered to remove the insoluble magnesium salts. The resulting aqueous layer was acidified with 2 M HCl washed with CH_2Cl_2 (10 mL×3), evaporated till dryness. The crude product was taken up in water and loaded onto a column of water washed amberlite® CG-50—type 1 ion exchange resin (4 g) suspended in water, and further washed with water (100 mL). The resin column was eluted with 0.5% aq NH_4OH collecting the fractions containing azimic acid as identified by LCMS, to give azimic acid **1** (7 mg, 59% yield) as a yellowish solid: ^{1}H NMR (400 MHz, MeOD) δ 3.83 (br s, 1H), 3.23 (br q, *J*=6.9 Hz, 1H), 3.10–3.00 (m, 1H), 2.17 (t, *J*=7.2 Hz, 1H), 2.00–1.90 (m, 1H), 1.85–1.34 (m, 11H), 1.33 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 15.9, 23.7, 25.8, 27.0, 30.0, 31.0, 34.5, 38.6, 57.4, 58.5, 65.9, 182.5; MS (ESI+) *m*/*z* 230 ($[M+H]^+$, 100); HRMS calcd for $C_{12}H_{23}NO_3$ ($[M+H]^+$) 230.1756, found 230.1758; mp 216–219 °C [lit. 214–215 °C,[5] 210–214 °C,[11] 217 °C,[8] 209–211 °C,[6] 212–214 °C[7]]; $[\alpha]_D^{23}$ +7.7 (*c* 0.37, MeOH) [lit.+8 (MeOH),[5] +7.6 (*c* 1.1, MeOH),[9] +7.9 (*c* 1, MeOH),[6,11] +7.4 (*c* 0.52, MeOH),[8] +7.7 (*c* 0.5, MeOH)[7]].

*3.1.13. (4S)-3-(Nona-1,8-dien-4-yl)-2-(pent-4-en-1-yl)-4-phenyloxazolidine (**9**).* Pale yellow oil: FTIR (neat, cm^{-1}): ν_{max} 2920, 2851, 1639, 908; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H), 5.91–5.61 (m, 3H), 5.28 (t, *J*=7.2 Hz, 1H), 5.13–4.83 (m, 6H), 3.77 (dd, *J*=6.8, 4.7 Hz, 1H), 3.69 (dd, *J*=10.5, 4.6 Hz, 1H), 3.49 (dd, *J*=10.5, 6.9 Hz, 1H), 3.08 (t, *J*=6.4 Hz, 1H), 2.25 (t, *J*=6.5 Hz, 2H), 2.14–1.77 (m, 10H), 1.50–1.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 139.9, 138.9, 138.7, 135.8, 128.6, 127.8, 127.6, 127.3, 117.0, 114.7, 114.6, 65.7, 61.5, 61.4, 38.9, 33.7, 33.6, 29.2, 28.0, 27.2; MS (ESI+) *m*/*z* 340 ($[M+H]^+$, 100).

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **6**, **8**, **9**, **11**–**17** and **19**. ORTEP structure for compound **17**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.060.

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