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2-(Penta-1, 3-dienyl)oxazolidines: Synthesis of Hydroxylated Piperidines by a Stereoselective Diels-Alder Reaction

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Abstract: Hexa-2,4-dienal condensed with (-)-ephedrine to give predominantly the oxazolidine **4**, which underwent a stereoselective Diels-Alder reaction with benzyl nitrosoformate to give the cycloadducts **9** and **10** in a *ca* 5:2 ratio. Further transformations of **9** to give the optically active mono- and tri- hydroxypiperidine derivatives **11** and **15** have also been performed.

Introduction

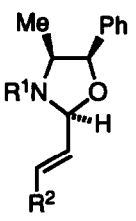
2-(Alk-1-enyl)oxazolidines derived from ephedrine and related homochiral 1,2-aminoalcohols have been demonstrated to participate in stereoselective reactions with reagents as diverse as cuprates and osmium (VIII) oxide.[1] In spite of the commercial availability of some 2,4-dienals and of the recent developments in the general synthesis of compounds of this class,[2] the chemistry of the corresponding dienyloxazolidines has not yet been reported. We decided to investigate the use of some of these dienes in the Diels-Alder reaction, in the expectation that the conversion of a 2,4-dienal into the corresponding oxazolidine might not only be the basis of a chiral auxiliary-mediated asymmetric synthesis, but would also lead to an enhancement of the reactivity of the diene in the normal-demand Diels-Alder reaction. A secondary aim was the formation of crystalline derivatives of the dienals, which might be available as single geometrical isomers: commercially available hexa-2,4-dienal and the derived dimethyl acetal are liquids which both contain 4:1 mixtures of the (2*E*, 4*E*) and (2*E*, 4*Z*) isomers.[3]

Results and Discussion

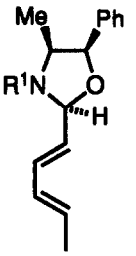
Scolastico[4] has reported that 2-(alk-1-enyl)oxazolidines bearing an electron-withdrawing group at the 3- position (*e.g.* **1** and **2**), which are available by treating the corresponding acetals with the appropriate norephedrine derivative in the presence of pyridinium tosylate, are perfectly stable to water and to chromatography on silica gel, whereas the analogous ephedrine derivatives (R^1=Me) are readily hydrolysed. We were unable to prepare the diene **3** by Scolastico's approach, but we found that hexa-2,4-dienal and *N*-(4-toluenesulfonyl)norephedrine underwent condensation in the presence of methanesulfonic acid and 4Å molecular sieves[5] to give an oily mixture of at least three isomeric oxazolidines, differing in configuration at C-2 of the oxazolidine ring and in the double bond geometry. These products could not be separated by chromatography on silica gel or alumina but instead underwent considerable decomposition. Attempts to prepare other 2-(penta-1,3-dienyl)oxazolidines with an electron-withdrawing substituent on the nitrogen atom, *e.g.* by treating the norephedrine imine

5 with electrophiles such as ethyl chloroformate, acetic anhydride or methanesulfonyl chloride, similarly gave inseparable oily mixtures of isomeric oxazolidines.

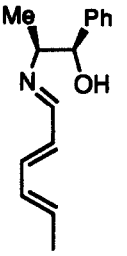
However, condensation of hexa-2,4-dienal with (1*R*, 2*S*)-ephedrine in the presence of 4 Å molecular sieves afforded a low-melting crystalline mass which by ^{1}H nmr spectroscopy was found to be a 12:1 mixture of stereoisomeric oxazolidines in which the existence of a 7% nuclear Overhauser effect (nOe)[6] between the oxazolidine protons at C-2 and C-4 was consistent with the (2*S*, 4*S*, 5*R*) isomer **4** being predominant. In the minor isomer the 2-H of the oxazolidine ring resonated at significantly lower field than for the major isomer; this is consistent with (2*R*, 4*S*, 5*R*) stereochemistry **6** in which the 2-H is deshielded by the phenyl group. This mixture, which was formed almost quantitatively and which contained negligible amounts of (*E*, *Z*)-dienes, was used in Diels-Alder reactions without further purification. The reaction of hexa-2,4-dienal with (1*S*, 2*S*)-pseudoephedrine gave a 4:1 mixture of diastereomers, considered to be the (2*S*, 4*S*, 5*S*) and (2*R*, 4*S*, 5*S*) isomers **7** and **8**, on the basis of the chemical shifts of the protons at 2-C and of literature precedent.[6]



1 R^1=CO_2CH_2Ph; R^2= CO_2Me
2 R^1=Ts; R^2=Me



3 R^1= Ts
4 R^1= Me



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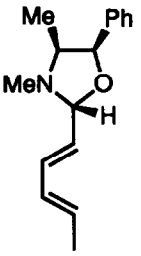

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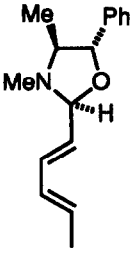

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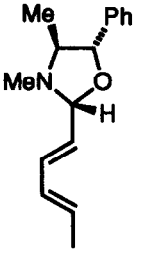

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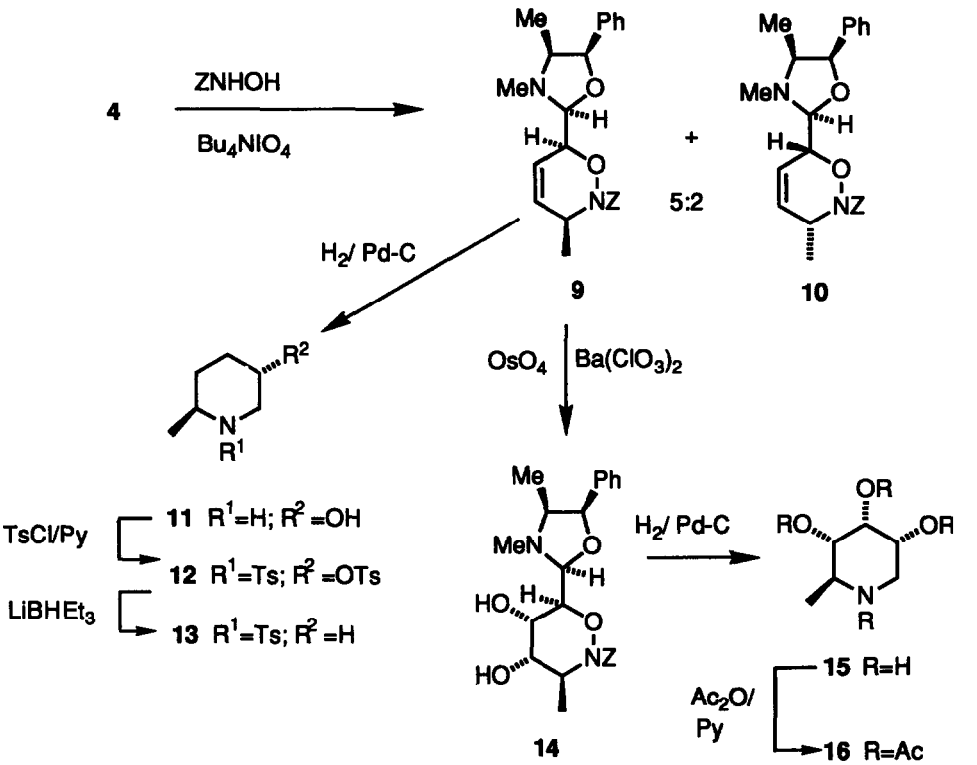
Of all the oxazolidines derived from hexa-2,4-dienal which were investigated, the ephedrine derivative **4** was available in the greatest isomeric purity and was selected as the subject for attempted Diels-Alder reactions. Streith *et al.* [3] have reported the use of the Diels-Alder reaction between the dimethyl acetal of hexa-2,4-dienal and benzyl nitrosoformate, leading to the synthesis of piperidine analogues of sugars in racemic form. In the present work the chiral diene **4** was transformed into

optically active hydroxylated piperidines by a similar approach, thus illustrating a strategy for asymmetric synthesis which complements the reaction of achiral dienes with chiral nitrosoformates.[7]



Scheme 1. (Z = $PhCH_2CO_2$)

Benzyl nitrosoformate was generated by the periodate oxidation of benzyl *N*-hydroxycarbamate in the presence of the diene **4** (-65 °C to 20 °C). ^{1}H nmr spectroscopy on the crude reaction mixture was consistent with the presence of four main oxazolidine derivatives in the ratio 62:24:11:3, the first three of which were considered to be the major cycloadduct **9**, a minor cycloadduct (presumed to be **10**) and unreacted diene **4**. Repeated flash chromatography led to the isolation of the major cycloadduct **9** in 32% yield, but the minor cycloadduct **10** appeared to be less stable to chromatography and could not be isolated in a pure state. The relative configurations of the newly created stereocentres in the adduct **9** were assigned on the basis that 3-H and 6-H of the dihydro-1, 2-oxazine ring must occupy pseudoequatorial positions and therefore have a *cis* relationship, since both participated in 4-bond couplings, with the olefinic protons 5-H and 4-H respectively. The absolute configuration at 3-C of the dihydro-1,2-oxazine ring in compound **9** was established by its transformation into the known (*S*)-(+)-2-methyl-1-(4-toluenesulfonyl)piperidine **13** as follows.

Hydrogenation of the adduct **9** brought about the removal of the *N*-benzyloxycarbonyl group, cleavage of the O-N bond and intramolecular reductive amination of the masked aldehyde, leading to the removal of the ephedrine chiral auxiliary and the formation of (2*S*, 5*S*)-5-hydroxy-2-methylpiperidine **11**, which was freed from ephedrine by solvent extraction followed by ion exchange chromatography and was obtained in 37% yield after sublimation. The optically active product **11** had a similar ^{1}H nmr spectrum, to that reported by Belleau[8] for racemic 5-hydroxy-2-methylpiperidine. Treatment of the amino alcohol **11** with 4-toluenesulfonyl chloride in pyridine then gave the ditosyl derivative **12**, which was not isolated, but was reduced directly by lithium triethylborohydride in refluxing tetrahydrofuran to give (*S*)-(+)-2-methyl-1-(4-toluenesulfonyl)piperidine **13** (42% yield from **11**) with a specific rotation that was within experimental error of the literature value[9] for material derived from (*R*)-(+)-pipecolic acid.

Having established the stereochemistry of the major Diels-Alder adduct **9** we proceeded to transform it into (2*S*, 3*S*, 4*R*, 5*R*)-2-methyl-3,4,5-trihydroxypiperidine **15**, which is diastereoisomeric at 3-C and 4-C with the potent fucosidase and HIV inhibitor deoxyfuconojirimycin.[10] Treatment of the adduct **9** with a catalytic amount of osmium (VIII) oxide in the presence of barium chlorate (V) as reoxidant led to dihydroxylation *anti* to the methyl and oxazolidinyl groups and the formation of the diol **13** in 49% yield. Hydrogenolysis then gave ephedrine (52% recovery as the hydrochloride salt) and the rather hygroscopic triol **15**, for which ^{1}H nmr coupling constants were consistent with a chair conformation in which the 2-Me and 3- and 5-OH groups were equatorial, but the 4-OH was axial. Further characterisation of the triol **15** was perfomed by converting it into its picrate salt and the tetracetyl derivative **16** (40% yield from **14**).

Conclusion

Ephedrine has thus been shown to be a useful chiral auxiliary for enabling asymmetric Diels-Alder reactions to be performed on hexa-2,4-dienal, to yield precursors for the enantioselecive synthesis of piperidine alkaloids and aza-sugars. The extension of this work to other dienophiles and to derivatives of 6-hydroxyhexa-2,4-dienal is in progress.

EXPERIMENTAL SECTION

General Procedures

Melting points were determined on a Reichert electrothermal melting point apparatus. ^{1}H nmr spectra were recorded at 250 MHz and ^{13}C spectra at 63 MHz, using a Bruker AM250 spectrometer. Ir spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. Mass spectrometry was performed using a Kratos MS50 mass spectrometer. Optical rotations were measured using an Optical Activity AA-1000 digital polarimeter.

Light petroleum refers to petroleum ether of boiling range 40-60 °C. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Organic extracts were dried over anhydrous magnesium sulfate. Evaporation of solvents was performed at reduced pressure, using a Büchi rotary evaporator. All experiments were performed at ambient temperature (*ca* 20 °C) unless stated otherwise.

Experimental

(E, E, 2S, 4S, 5R)-3,4-*Dimethyl*-2-(*penta*-1,3-*dien*-1-*yl*)-5-*phenyloxazolidine* **4**.- Hexa-2,4-dienal (4.61 g, 48.0 mmol), (1*R*, 2*S*)-(-)-ephedrine (7.92 g, 48.0 mmol) and 4 Å powdered molecular sieves (9.2 g) were stirred together in dichloromethane (40 cm^3) for 24 h. Filtration through celite® and evaporation of the solvent gave the title compound **4** (11.04 g, 95 %) as a waxy orange solid, which was shown by ^1H nmr to contain 7% of the isomer **6**, but which was used in subsequent reactions without purification. δ_H ($CDCl_3$) *inter alia* 0.64 (0.2 H, d, *J* 7 Hz, 4-Me of **6**), 0.69 (3 H, d, *J* 7 Hz, 4-Me), 1.78 (3 H, dd, *J* 6 and 1 Hz, 4'-Me), 2.20 (3 H, s, NMe), 2.23 (0.2 H, s, NMe of **6**), 2.80 (1 H, dq, *J* 8 and 7 Hz, 4-H), 4.13 (1 H, d, *J* 7.5 Hz, 2-H), 4.86 (0.06 H, d, *J* 7 Hz, 2-H or 5-H of **6**), 5.03 (1 H, d, *J* 8 Hz, 5-H), 5.32 (0.06 H, d, *J* 7 Hz, 5- or 2-H of **6**), 5.65-5.86 (2 H, m, 1'- and 4'-H), 6.16 (1 H, ddq, *J* 15, 10 and 1 Hz, 3'-H), 6.39 (1 H, dd, *J* 15 and 10 Hz, 2'-H) and 7.22-7.36 (5 H, m, Ph); irradiation of 5-H gave rise to nOe at 2-H (small) and at Ph; irradiation of 2-H gave rise to nOe at NMe, at 4-H (7%), at 5-H (small) and at 2'-H (12%); *m/z* (EI) 243.1622 (M^+, 100%; $C_{16}H_{21}NO$ requires 243.1623).

Reaction of Hexa-2,4-*dienal with* (1S, 2S)-*Pseudoephedrine*.- Hexa-2,4-dienal (0.63 g, 6.55 mmol) and (1*S*, 2*S*)-pseudoephedrine (1.03 g, 6.23 mmol) were kept with 4 Å powdered molecular sieves (2.22 g) in dichloromethane (10 cm^3) for 12 h. The mixture was filtered (celite®) and evaporated to give a pale yellow mobile oil (1.50 g), which was considered on the basis of ^1H nmr to contain a 4:1 mixture of the stereoisomeric oxazolidines **7** and **8**. δ_H ($CDCl_3$) 1.16 (2.4 H, d, *J* 6 Hz, 4-Me of **7**), 1.17 (0.6 H, d, *J* 6 Hz, 4-Me of **7**), 1.78 (2.4 H, dd, *J* 7 and 2 Hz, 4'-Me of **8**), 1.80 (0.6 H, dd, *J* 7 and 2 Hz, 4'-Me of **8**), 2.25 (2.4 H, s, NMe of **7**), 2.28 (0.6 H, s, NMe of **8**), 2.32-2.42 (1 H, m, 4-H), 4.40 (0.8 H, d, *J* 7.5 Hz, 2-H of **7**), 4.47 (0.2 H, d, *J* 7.5 Hz, 2-H of **8**), 4.58 (0.8 H, d, *J* 9 Hz, 5-H of **7**), 4.59 (0.2 H, d, *J* 9 Hz, 5-H of **8**), 5.52-5.86 (2 H, m, 1'- and 4'-H), 6.05-6.18 (1 H, m, 3'-H), 6.35 (0.8 H, dd, *J* 18 and 10 Hz, 2'-H of **7**), 6.72 (0.2 H, dd, *J* 18 and 11 Hz, 2'-H of **8**) and 7.24-7.38 (5H, m, Ph).

Reaction of (E, E, 2S, 4S, 5R)-3,4-*Dimethyl*-2-(*penta*-1,3-*dienyl*)-5-*phenyloxazolidine* **4** *with Benzyl nitrosoformate*.- A solution of (*E*, *E*, 2*S*, 4*S*, 5*R*)-3,4-Dimethyl-2-(penta-1,3-dienyl)-5-phenyloxazolidine **4** (6.01 g, 24.7 mmol) and tetrabutylammonium periodate (5.35 g, 12.4 mmol) in dichloromethane (240 cm^3) was cooled to -65 °C and treated with a solution of benzyl *N*-hydroxycarbamate (6.19 g, 37.1 mmol) in dichloromethane (60 cm^3), dropwise over 45 min. The mixture was allowed to warm up to room temperature over 2h, then was washed with 10% aqueous Na_2SO_3 (2 x 200 cm^3) and saturated aqueous $NaHCO_3$ (200 cm^3). The organic layer was dried and concentrated to give a brown oil (17.3 g). The ^1H nmr spectrum of this crude product in $CDCl_3$ was consistent with the presence of at least four different oxazolidine derivatives, considered to be the major cycloadduct **9**, minor cycloadduct **10**, the diene **4** and an unidentified substance, in the molar ratio 62:24:11:3, as determined by integration of the singlets arising from the oxazolidine NMe groups (δ 2.45, 2.35, 2.20 and 2.50 respectively) and from the doublets corresponding to the oxazolidine 2'-H (centred on δ 3.93, 4.07, 4.14 and 4.21). The crude product was subjected to repeated flash chromatography, eluting with light petroleum-diethyl ether (6:1), to yield the *major cycloadduct* **9** (3.23 g, 32%) as a pale yellow waxy solid, m.p. 47-49 °C (from Et_2O-light petroleum) (Found: C, 70.4; H, 6.8; N, 6.8. $C_{24}H_{28}N_2O_4$ requires C, 70.6; H, 6.9; N, 6.9%); $[\alpha]_D$ +48° (*c* 1.0 in CH_2Cl_2); $\nu_{max.}$

(film)/cm^{-1} 1704 (urethane C=O); δ_H ($CDCl_3$) 0.66 (3 H, d, *J* 6.5 Hz, 4'-Me), 1.36 (3 H, d, *J* 7 Hz, 3-Me), 2.45 (3 H, s, NMe), 2.84-2.94 (1 H, m, 4'-H), 3.93 (1 H, d, *J* 5 Hz, 2'-H), 4.48-4.60 (1 H, m, 3-H), 4.77-4.81 (1 H, m, 6-H), 5.02 (1 H, d, *J* 8 Hz, 5'-H), 5.17 and 5.28 (each 1 H, d, *J* 12 Hz, together PhC*H*$_2$), 5.91 (1 H, ddd, *J* 10,4, and 2 Hz, 4-H), 6.10 (1 H, dt, *J* 10 and 2 Hz, 5-H) and 7.23-7.44 (10 H, m, 2x Ph); irradiation of 3-H caused the signal due to 3-Me to collapse to a singlet, the signal due to 4-H to collapse to a dd (*J* 10 and 2 Hz) and the signal due to 5-H to collapse to a dd (*J* 10 and 2 Hz); irradiation of 6-H caused the signal due to 2'-H to collapse to a singlet, the signal due to 4-H to collapse to a dd (*J* 10 and 4 Hz) and the signal due to 5-H to collapse to a dd (*J* 10 and 2 Hz); assignments were further supported by a ^1H COSY spectrum; δ_C ($CDCl_3$) 15.8 (q), 19.4 (q), 38.0 (q), 51.6 (d), 65.6 (d), 68.6 (t), 81.2 (d), 83.2 (d), 96.8 (d), 125.6 (d), 128-131 (m), 137.3 (s), 140.5 (s), and 156.0 (s); *m/z* (EI) 390.1920 (M^+-H_2O, 2%; $C_{24}H_{26}N_2O_3$ requires 390.1943) and 176.1078 (100%; $C_{11}H_{14}NO^+$ requires 176.1075).

By elution of the chromatographic column with light petroleum-Et_2O (3:1) it was possible to obtain a small quantity of the minor cycloadduct **10** in a slightly impure state, δ_H ($CDCl_3$) *inter alia* 0.68 (3 H, d, *J* 7 Hz, 4'-Me), 1.38 (3 H, d, *J* 6 Hz, 3-Me), 2.35 (3 H, s, NMe), 2.88 (3 H, quintet, *J* 7 Hz, 4'-H), 4.08 (1 H, d, *J* 3 Hz, 2'-H), 4.54-4.66 (1 H, m, 3-H), 4.82-4.85 (1 H, m, 6-H), 5.01 (1 H, d, *J* 7.5 Hz, 5'-H) 5.16 and 5.30 (each 1 H, d, *J* 12.5 Hz, together PhC*H*$_2$O), 5.95-5.98 (2 H, m, 4- and 5-H) and 7.23-7.42 (10 H, m, 2 x Ph).

(2S, 5S)-5-*Hydroxy*-2-*methylpiperidine* **11**.- A solution of the major cycloadduct **9** (0.183 g, 0.45 mmol) in ethanol (10 cm^3) was shaken with 5% Pd-on-C (0.15 g) under a hydrogen atmosphere (2 bar) for 3 d. The catalyst was filtered off and the filtrate was evaporated. The residue was partitioned between water (10 cm^3) and ether (4x 5 cm^3), then the aqueous extract was concentrated and chromatographed on Dowex® 50X2-100 (H^+ form), eluting with water followed by 0.1 M aqueous ammonia. Fractions were investigated by tlc (butan-1-ol-acetic acid-water 1:1:1) and those containing the lower R_f ninhydrin-positive component were pooled, evaporated and resublimed in a Büchi kugelrohr apparatus at 200 °C (bath temp.) and 15 mmHg to give (2S, 5S)-5-*hydroxy*-2-*methylpiperidine* **11** (18.9 mg, 37%) as large colourless prisms m.p. 116-119 °C (subl.)(lit.[8] m.p for racemate 96 °C)(Found: C, 62.8; H, 11.5; N, 12.2. $C_6H_{13}NO$ requires C, 62.6; H, 11.4; N, 12.2%); $[\alpha]_D$ +24° (*c* 0.35, pyridine); ν_{max}/cm^{-1} (KBr) 3274 and 3123 (O-H and N-H); δ_H(D_2O) 1.03 (3 H, d, *J* 6 Hz, Me), 1.07-1.24 (1 H, m, 3-H_{ax}). 1.26-1.42 (1-H, m, 4-H_{ax}), 1.76 (1 H, ddd, *J* 13, 6 and 3 Hz, 3-H_{eq}) 1.95-2.06 (1 H, m, 4-H_{eq}), 2.38 (1 H, t, *J* 11 Hz, 6-H_{ax}), 2.57 (1 H, dqd, *J* 8, 6 and 3 Hz, 2-H), 3.08 (1 H, ddd, *J* 11.5, 5 and 2 Hz, 6-H_{eq}), and 3.63 (1 H, tt, *J* 11 and 4.5 Hz, 5-H); decoupling of 5-H caused changes in the appearances of the signals from 4-H_2 and 6-H_2; decoupling of 6-H_{eq} caused changes in the appearances of the signals from 6-H_{ax} and 5-H; *m/z* (EI) 115.1001 (M^+, 25%; $C_6H_{13}NO$ requires 115.0097) and 100.0773 (M^+-Me, 100%; $C_5H_{10}NO$ requires 100.0762).

(S)-(+)-2-*methyl*-1-(4-*toluenesulfonyl)piperidine* **13**.- A solution of (2*S*, 5*S*)-5-Hydroxy-2-methylpiperidine **11** (15.0 mg, 0.13 mmol) in pyridine (0.5 cm^3) was treated with 4-(dimethylamino)pyridine (4.0 mg, 0.03 mmol) and 4-toluenesulfonyl chloride (0.30 g, 1.56 mmol) for 24 h. The pyridine was then evaporated and the residue was taken up in CH_2Cl_2 (10 cm^3) , which was

washed with 1M citric acid (3 x 10 cm^3), dried and evaporated. The residue was refluxed under N_2 with a 1M solution of $LiBHEt_3$ in THF (4 cm^3, 4 mmol) for 2 h. The mixture was then cooled, treated with aqueous $NaHCO_3$, concentrated *in vacuo* and partitioned between aqueous $NaHCO_3$ (10 cm^3) and $CHCl_3$ (10 cm^3). The organic extract was dried, evaporated and subjected to flash chromatography (1:1 CH_2Cl_2-light petroleum) to give (*S*)-(+)-2-methyl-1-(4-toluenesulfonyl)piperidine **13** (13.7 mg, 42%) as a colourless oil, identical by ^1H nmr spectroscopy (250 MHz; $CDCl_3$) to racemic material prepared by treatment of (±)-2-methylpiperidine (Aldrich) with 4-toluenesulfonyl chloride in pyridine; $[\alpha]_D$ + 39° (*c* 0.69, EtOH), [lit.[9] +41° (*c* 0.98, EtOH) for (*S*)-(+)-**13** prepared from (*R*)-(+)-pipecolic acid].

(3S, 4S, 5S, 6S, 2'S, 4'S, 5'R)-2-*Benzyloxycarbonyl*-4,5-*dihydroxy*-6-(3,4-*dimethyl*-5-*phenyloxazolidin*-2-*yl*)-3-methyl-3,4,5,6-*tetrahydro*-1,2-*oxazine* **14**.- The major Diels-Alder adduct **9** (1.01 g, 2.47 mmol) was dissolved in THF (25 cm^3) and treated with a solution of barium chlorate monohydrate (0.79 g, 2.47 mmol) in water (15 cm^3) followed by osmium (VIII) oxide (0.030 g, 0.012 mmol) in *tert*-butanol (1.5 cm^3). The mixture was stirred at 20 °C for 28 h, then treated with 10% aqueous Na_2SO_3 (180 cm^3) and extracted with chloroform (180 cm^3). The chloroform extract was washed with saturated aqueous $NaHCO_3$ solution (2x180 cm^3), dried and evaporated. Flash chromatography [dichloromethane-ethyl acetate (6:1) to dichloromethane-ethyl acetate (4:1); gradient elution] afforded the *title compound* **14** (0.54 g, 49 %) as an off-white foam, m.p. *ca* 70-80 °C (Found: C, 65.2; H, 7.1; N, 6.2. $C_{24}H_{30}N_2O_6$ requires C, 65.1; H, 6.8; N, 6.3 %); $[\alpha]_D$ -9° (*c* 2.1, CH_2Cl_2); ν_{max}/cm^{-1} (KBr) 3488 (O-H) and 1718 (urethane C=O); *m/z* (EI) 279 (10%), 176 (16%) and 91 (100%).

(2S, 3S, 4R, 5R)-2-*Methyl*-3,4,5-*trihydroxypiperidine* **15**.- A solution of the above diol **14** (0.263 g, 0.595 mmol) in ethanol (10 cm^3) was shaken with 5 % palladium on carbon (0.15 g) under an atmosphere of hydrogen (2 bar) for 25 h. The mixture was then filtered through celite and the solvent was evaporated. The residue was dissolved in water (20 cm^3), and extracted with chloroform (5x 10 cm^3).

The combined organic layers were dried and evaporated and taken up in ether (5 cm^3) which was then saturated with hydrogen chloride, whereupon (1*R*, 2*S*)-ephedrine hydrochloride (0.062 g, 52%) separated as crystals, m.p 219-220 °C (lit.[11] 218-220 °C), $[\alpha]_D$ -34° (*c* 0.5, H_2O) [lit.[11] -34° (*c* 4, H_2O).

The aqueous phase from the solvent extraction was evaporated to leave a pale straw-coloured syrup, which was dissolved in methanol and divided into two equal portions.

The first aliquot of the aqueous extract was applied to a column of Dowex 50X2-100 ion exchange resin (H^+ form), which was eluted with water followed by 0.2 M aqueous ammonia. Evaporation of appropriate fractions followed by lyophilisation and desiccation over NaOH and P_2O_5 gave (2*S*, 3*S*, 4*R*, 5*R*)-2-Methyl-3,4,5-trihydroxypiperidine **15** (0.028 g, 64%) as a hygroscopic colourless solid, δ_H (D_2O) 1.25 (3 H, d, *J* 6 Hz, 2-Me), 2.82 (1 H, t, *J* 12 and 11 Hz, 6-H_{ax}), 2.85-2.94 (1 H, m, 2-H), 2.95 (1 H, dd, *J* 12 and 5 Hz, 6-H_{eq}), 3.35 (1 H, dd, *J* 10 and 3 Hz, 3-H), 3.84 (1 H, ddd, *J* 11, 5 and 3 Hz, 5-H) and 4.19 (1 H, t, *J* 3 Hz, 4-H).

Treatment of the base **15** with picric acid gave the crystalline *picrate*, m.p. 148-150°C (from EtOH-Et_2O) (Found: C, 38.3; H, 4.4; N, 14.5. $C_{12}H_{16}N_4O_{10}$ requires C, 38.3; H, 4.3; N, 14.9 %); $[\alpha]_D$ -17° (*c* 0.5, EtOH).

The second aliquot of the aqueous extract was evaporated, dissolved in pyridine (4 cm^3) and treated with acetic anhydride (1.5 cm^3). The mixture was kept at 20°C for 21h, then treated with methanol (2 cm^3) and evaporated after a further 1.5 h. The residue was re-evaporated from toluene and subjected to flash chromatography [gradient elution; ethyl acetate-dichloromethane (1:4) to ethyl acetate] followed by recrystallisation from ether-light petroleum to give (2S, 3S, 4R, 5R)-1-*acetyl*-2-*methyl*-3,4,5-*triacetoxypiperidine* (**16**) (0.038 g, 40%) as white crystals, m.p. 119-120 °C (Found: C, 52.4; H, 6.8; N, 4.4. $C_{14}H_{21}NO_7.1/3H_2O$ requires C, 52.3; H, 6.8; N, 4.4); $[\alpha]_D$ -4° (*c* 0.23, $CHCl_3$); ν_{max}/cm^{-1} 1732 (ester C=O) and 1654 (amide C=O); δ_H (250 MHz; $(CDCl_2)_2$; temp. = 93°C) 1.35 (3 H, d, *J* 7 Hz, 2-Me), 2.05 (3 H, s, NAc), 2.107, 2.109 and 2.114 (each 3 H, s, together 3 x OAc), 3.28 (1 H, bd, *J* 15 Hz, 6-H), 4.40 (1 H, bd, *J* 15 Hz, 6-H), 4.70-4.80 (1 H, m, 5-H) and [5.08-5.12 (1 H, m) and 5.19-5.23 (2H, m) (together 2-, 3- and 4-H)]; *m/z* (EI) 316.1420 (MH^+, 2%; $C_{14}H_{22}NO_7$ requires 316.1396), 255(22), 180(100) and 138(76).

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