Enantioselective Synthesis of (+)-*endo*- and (−)-*exo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane

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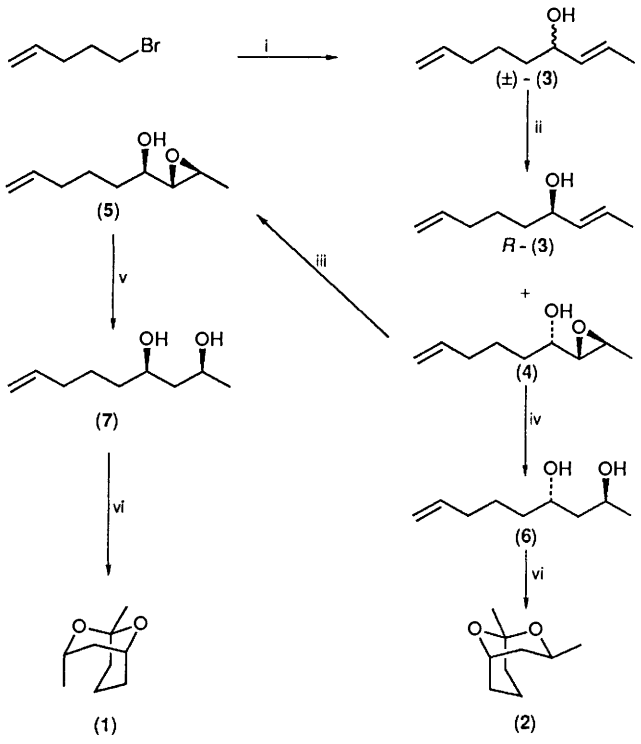
The title compounds, one of which is a host-specific substance isolated from the Norway Spruce *Picea abies* infested by the ambrosia beetle *Trypodendron lineatum*, have been synthesised in an enantioselective and diastereospecific manner using the Sharpless asymmetric epoxidation as the key step and source of optical activity.

In 1976 Heemann and Francke carried out a detailed investigation of the volatile constituents of the bark of the Norway Spruce fir tree *Picea abies* (the common Christmas tree) infested by the ambrosia beetle *Trypodendron lineatum* Oliver.[1] Using capillary gas chromatography (GC) and mass spectrometry (MS) they successfully identified nearly 50 compounds which were mainly terpenes, sesquiterpenes, and their oxidation products. Of these, two were of particular significance: β-pinene oxide was a new naturally occurring compound, as was *endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]-nonane (**1**). The latter compound proved to be present exclusively and permanently in the Norway Spruce under attack by the ambrosia beetle. Further characterisation of this compound from its ^{1}H NMR spectrum was possible after a small sample was obtained by preparative GC of the crude extracts, although the absolute configuration and specific rotation have not been reported.[2]

Compounds isolated in this way, particularly novel compounds present only during infestation of a specific guest, are often found to be pheromonal substances produced by the guest which may be responsible for initial or further infestation of the host tree.[3] The Scolytidae family of coleoptera (of which the ambrosia beetle is a member) account for much of the timber losses in coniferous forests throughout the northern hemisphere.[4] They are therefore serious pests of considerable economic importance. Since the discovery of chiral pheromones in the late 1960's, their synthesis has become an area of considerable interest to organic chemists.[5] The complex stereochemistry–activity relationships which have since emerged make the asymmetric synthesis of such pheromones of great importance for entomological studies.

Although a number of enantioselective syntheses of (**1**) have been published, most suffer from the disadvantages of large numbers of steps, separation of diastereoisomers, and/or low overall yields.[6a] We have devised a six-step enantioselective synthesis involving the Sharpless asymmetric epoxidation as the source of optical activity[7] which gives the product with $[\alpha]_D$ = +36.0° and with an overall yield of 9%; we also report the synthesis of the known (−)-*exo*-1,3-dimethyl-2,9-dioxabicyclo-[3.3.1]nonane (**2**)[6b] in 18% overall yield and just 4 steps (Scheme 1). In addition, as both syntheses involve the kinetic resolution of a secondary allylic alcohol using the Sharpless asymmetric epoxidation, the enantiomeric resolved allylic alcohol is also obtained and could be used to synthesise the antipodes of (**1**) and (**2**).



Scheme 1. *Reagents and conditions:* i, Mg, THF, (*E*)-but-2-enal; ii, 0.10 equiv. $Ti(OPr^i)_4$, 0.12 equiv. L-(+)-DIPT, 0.40 equiv. TBHP, CH_2Cl_2, 20 °C, 3 d; iii, PPh_3, DEAD, 4-nitrobenzoic acid, THF, r.t., 18 h; MeONa, MeOH; iv, 2.0 equiv. Red-Al, THF, 0 °C ⟶ r.t., 12 h; v, 2.0 equiv. Red-Al, 1.0 equiv. MeOH, THF, 0 °C ⟶ r.t., 12 h; vi, $PdCl_2$ (cat.), 1.1 equiv. $CuCl_2 \cdot 2H_2O$, THF, r.t.

Discussion

The racemic secondary allylic alcohol (±)-(**3**) was prepared in 92% yield by the reaction of (*E*)-but-2-enal with the Grignard reagent derived from 1-bromopent-5-ene. The *E*/*Z* isomeric ratio was found to be 96:4 by capillary GC; however as it is known that (*Z*)-allylic alcohols react more slowly than the corresponding *E* isomers in the Sharpless epoxidation, this small impurity was carried through to the next step of the synthesis, the key Sharpless asymmetric epoxidation/kinetic resolution of (±)-(**3**).[8] When (+)-di-isopropyl L-tartrate [L-(+)-DIPT] was used as the chiral auxiliary in this reaction, essentially only the *S* enantiomer of the allylic alcohol reacted to form, stereoselectively, the *anti*-(2*S*,3*S*,4*S*)-epoxy alcohol (**4**).‡

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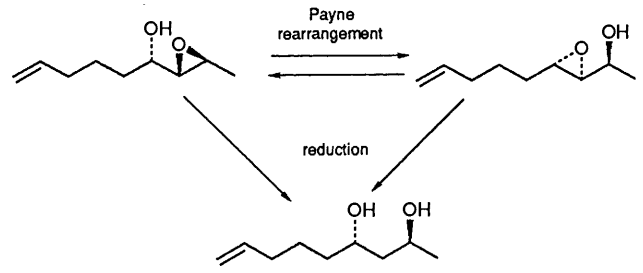
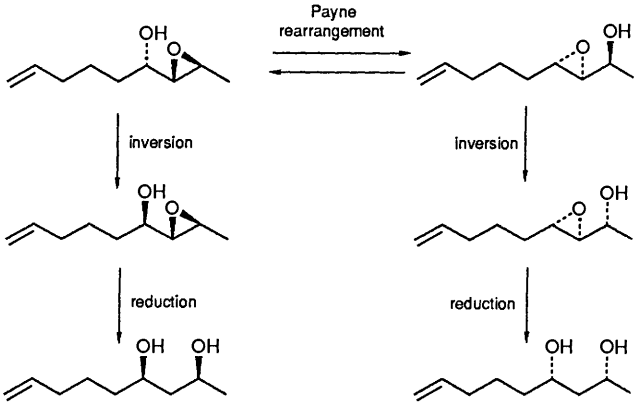
‡ The prefixes *syn* and *anti* are used to indicate the disposition of the hydroxy group relative to the epoxide function.

The reaction was allowed to proceed to 40% completion using a limiting amount (0.40 equiv.) of the oxidant (t-butyl hydroperoxide).

Problems of purification were encountered when using a stoicheiometric quantity of the catalyst system. Usually, aqueous sodium hydroxide hydrolysis of the tartrate ester used in a Sharpless epoxidation can be carried out to give a water-soluble tartaric acid salt which greatly facilitates isolation of the crude epoxy alcohol–resolved allylic alcohol product mixture; however in this case considerable Payne rearrangement was observed during the hydrolysis process (up to 30%).[9] Even using a modified procedure involving a 0.5M solution of sodium hydroxide in brine[10] failed to suppress Payne rearrangement to the degree required in this case (*ca.* 10% still obtained). This is of little consequence for the synthesis of (**2**) where both epoxy alcohol isomers would be expected to give the same reduction product (Scheme 2); however, for the synthesis of (**1**) a serious reduction in optical purity was anticipated (Scheme 3). In



Scheme 2.

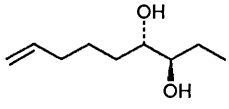


Scheme 3.

addition, only moderate yields of the product mixture were obtained (*ca.* 40%) due to difficulties in extracting the product from the gelatinous orange precipitate formed when using the sodium sulphate work-up procedure. We therefore examined the possible use of a catalytic quantity of catalyst species, a procedure which obviates the need for aqueous basic hydrolysis and which was expected greatly to simplify product purification and work-up.[8] Thus, using 10 mol% of the catalyst, and allowing the epoxidation to proceed to 40% completion, gave after purification (2*S*,3*S*,4*S*)-epoxy alcohol (**4**) (>96% e.e. and >95% diastereoisomeric purity*) in 35% yield together with the resolved allylic alcohol (*R*)-(**3**) in 50% yield.

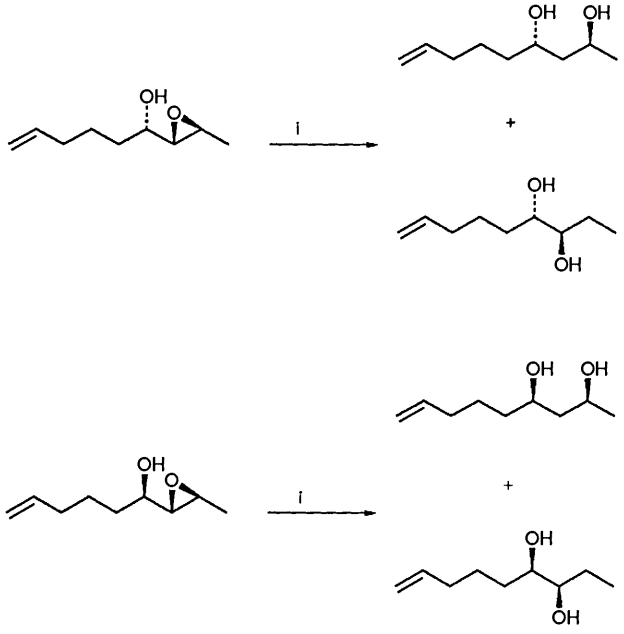
For the synthesis of (**1**) it was necessary to invert the configuration of the C-4 hydroxy group. The Mitsunobu inversion procedure[11] was used; however even after considerable experimentation the overall yield for this reaction to give the epoxy alcohol (**5**) (with >96% e.e. and >93% diastereoisomeric purity*) could not be increased above 55%. It is known that the Mitsunobu reaction is sensitive to steric crowding[12] and this must be presumed to be the reason for the moderate yield obtained in this case. In addition, nucleophilic attack is generally retarded by adjacent electron-withdrawing functionality;[13] this effect may also play a role in reducing the efficiency of the reaction.

The next step for both syntheses was the regioselective reductive cleavage of epoxy alcohols (**4**) and (**5**), possible by using Red-Al.[14] For the synthesis of (**2**), reduction of (**4**) was carried out after hydrolysis of the tartrate in the crude epoxidation product mixture to give a mixture of the resolved allylic alcohol (*R*)-(**3**) and the (*S*,*S*)-1,3-diol (**6**), a procedure which greatly facilitated isolation of the pure components. In general, good regioselectivities in the formation of the 1,3-diol (**6**) in preference to the corresponding 1,2-diol (**8**) were observed



(**8**)

(*ca.* 20:1), however occasionally poor regioselectivity (worst case 4:1 in favour of the 1,3-diol) was encountered for no apparent reason. In addition, reduction of the purified epoxy alcohols (**4**) and (**5**) gave disappointing ratios of 3:1 and 2:1 (1,3-diol:1,2-diol) respectively (Scheme 4). Similar observations



Scheme 4. *Reagents and conditions:* i, 2.0 equiv. Red-Al, THF, 0 °C ⟶ r.t., 12 h.

were published while this work was in progress.[15] We initially believed the presence of the parent allylic alcohol (**3**) in the reaction mixture to be the cause of the improved regioselectivity; however reduction of a 1:1 mixture of authentic purified epoxy alcohol (**4**) and resolved allylic alcohol (*R*)-(**3**) with Red-Al gave a 4:1 mixture of 1,3- and 1,2-diols. The effect on the selectivity of the reduction of the presence of a range of alcohols was therefore investigated (Table).

Although the role of these additives is not understood in full it appears that they reduce the reactivity of the Red-Al reagent, hence increasing its selectivity. The most convenient successful

* Determined by capillary GC analysis and ^{19}F NMR spectroscopy of the Mosher ester derivative.

Table. Ratios of 1,3-diol: 1,2-diol obtained in the Red-Al reduction of epoxy alcohols.

Substrate	Additive	Conditions[a]	Ratio[b]	Yield (%)
(4)	—	4 equiv., 12 h	3:1[c]	84
(4)	1 equiv. (3)	4 equiv., 12 h	4:1[c]	Not determined
(4)	1 equiv. $PhCH_2OH$	4 equiv., 3 d	>20:1[c]	70
(4)	1 equiv. allyl alcohol	3 equiv., 3 d	50:1[d]	93
(4)	0.3 equiv. DIPT	4 equiv., 12 h	30:1[d]	Not determined
(4)	1 equiv. DIPT	4 equiv., 3 d	1,3-diol only[c]	86
(4)	0.3 equiv. $MeOCH_2CH_2OH$	3 equiv., 3 d	No reaction	—
(4)	10 equiv. $MeOCH_2CH_2OH$	10 equiv., 3 d	No reaction	—
(4)	1 equiv. MeOH	3 quiv., 12 h	1,3-diol only[c]	83
(5)	—	3 equiv., 3 d	2:1[c]	80
(5)	1 equiv. MeOH	2 equiv., 12 h	1,3-diol only[c,d]	93

[a] Quantity of Red-Al used, time of reaction. [b] 1,3-Diol: 1,2-diol. [c] Determined by ^1H NMR spectroscopy. [d] Determined by capillary GC.

modification was addition of methanol (1 equiv.), providing minimum 1,2-diol and essentially no other by-products for removal after work-up. Fortunately this modification worked equally efficiently for both of the diastereoisomeric epoxy alcohols (**4**) and (**5**).

The final steps in the syntheses of both (**1**) and (**2**) were palladium-catalysed cyclisation of the olefinic diols (**6**) and (**7**), respectively.[16] Reaction of (**6**) gave a 56% yield of pure (1*R*,3*S*,5*S*)-(−)-(**2**) with optical rotation consistent with the initial stereochemical assignments for the epoxidation {$[\alpha]_D^{24}$ = −4.0 ± 1.0 °C, *c* = 2.5 (pentane); lit.,[12] $[\alpha]_D^{22}$ = −4.4°, *c* = 2.5 (pentane)}. Similar cyclisation of diol (**7**) gave a 52% yield of (1*S*,3*S*,5*R*)-(+)-(**1**), again with consistent optical properties {$[\alpha]_D$ = +36.0°, *c* = 0.77 (pentane); lit.,[12] $[\alpha]_D^{22}$ = +37.5°, *c* = 5.4 (pentane)}.

The overall yields for the syntheses of (−)-(**2**) and (+)-(**1**) are 18% and 9% respectively from 1-bromopent-5-ene. Further recovery of the resolved allylic alcohol (*R*)-(**3**) allows synthesis of the opposite enantiomeric series by the use of D-(−)-DIPT in the epoxidation reaction.

Experimental

General Experimental.—Light petroleum was distilled prior to use. Dichloromethane was dried by distillation from calcium hydride. Diethyl ether (referred to as ether) and tetrahydrofuran (THF) were dried by distillation from the sodium benzophenone ketyl radical.

Commercially available reagents were used as supplied unless otherwise stated. For epoxidation reactions, the tartrate and allylic alcohol were distilled immediately before use. Vanadyl bis(acetoacetonate) and solutions of t-butyl hydroperoxide (TBHP) were prepared according to literature methods.

Reactions requiring rigorously anhydrous conditions were carried out in glassware which had been dried for several hours at 150–200 °C. The apparatus was assembled hot and allowed to cool while a rapid flow of argon was admitted. Reactions were maintained in an atmosphere of argon and reagents and solvents introduced *via* syringe or using cannula techniques, through a septum cap. Solvents were freshly distilled before use.

Silica gel refers to Merck 9385 Kieselgel 60 (230–400 mesh). Alumina refers to Fluka aluminium oxide type 507C (pH 7.0). Preparative TLC was performed on 20 × 20 cm glass plates coated with a 1 mm layer of Merck Kieselgel 60 (PF254).

IR spectra were recorded using a Perkin-Elmer 298 IR spectrophotometer and were calibrated against the 1 602 cm^{-1} absorption of polystyrene. ^1H NMR spectra were recorded using Perkin-Elmer R34 (220 MHz) or Bruker WM250 (250 MHz) spectrometers. ^{13}C NMR spectra were recorded using a Bruker WM250 spectrometer operating at 62.8 MHz or a JEOL FX60Q spectrometer operating at 15.0 MHz. All spectra were recorded using tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded on a Bruker WM250 spectrometer operating at 235.8 MHz. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Micromass 7070E instrument. Capillary GC was performed on a Dani 3800 gas chromatograph. M.p.s were determined on a Kofler block apparatus and are uncorrected. Microanalyses were carried out by the Department of Chemistry microanalytical service. Optical rotations were determined using Optical Activity AA-1000 or AA-100 polarimeters.

(E)-*Nona*-2,8-*dien*-4-*ol* (**3**).—To a suspension of magnesium turnings (0.60 g, 0.106 mol) in THF (2 ml) under an argon atmosphere was added dropwise a solution of 1-bromopent-5-ene (15.75 g, 12.52 ml, 0.105 mol) in THF (20 ml) until reaction commenced. Further THF (50 ml) was added *via* the septum cap using a syringe, and the addition of the 1-bromopent-5-ene solution allowed to continue dropwise over 20 min. The resulting solution was stirred for 30 min at ambient temperature to ensure complete formation of the Grignard reagent. The reaction was cooled to 0 °C and a solution of but-2-enal (7.25 ml, 6.16 g, 87.5 mmol) in THF (10 ml) added dropwise over 15 min. The solution was warmed to ambient temperature and stirred for 1.5 h. Finally, the solution was heated briefly under reflux. After cooling to 0 °C the reaction was quenched by the careful addition of saturated aqueous ammonium chloride (40 ml) and stirred vigorously for 30 min. Ether (50 ml) was added and the organic phase separated. The aqueous phase was extracted with ether (2 × 50 ml) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product was purified by distillation through a fractionating column to yield *compound* (**3**) as a colourless oil (11.44 g, 81.7 mmol, 93%), b.p. 86 °C (20 mmHg); ν_{max}(film) 3 360, 3 080, 3 040, 3 000, 2 980, 2 940, 2 860, 1 675, 1 645, 1 460, 1 450, 1 440, 1 420, 1 380, 1 320, 1 265, 1 185, 1 130, 1 110, 1 065, 1 000, 965, 915, 910, 830, 800, and 740 cm^{-1}; $\delta_H(CDCl_3)$ 1.25–1.60 (4 H, m), 1.65 (3 H, d, *J* 7 Hz), 2.00–2.15 (2 H, m), 2.20 (1 H, br s, removed by D_2O shake), 3.96–4.04 (1 H, m), 4.85–5.05 (2 H, m), and 5.35–5.85 (3 H, m); $\delta_C(CDCl_3)$ 17.67 (q), 24.91 (t), 33.80 (t), 36.84 (t), 72.62 (d), 114.51 (t), 125.93 (d), 134.71 (d), and 138.76 (d); *m/z* (EI) 139 ($M^+ - 1$) (Found: C, 76.95; H, 11.55. $C_9H_{16}O$ requires C, 77.09; H, 11.50%).

(2S,3S,4S)-*Epoxynon*-8-*en*-4-*ol* (**4**).—Dry dichloromethane (150 ml) was cooled to −20 °C under an argon atmosphere. Titanium isopropoxide (2.03 g, 2.13 ml, 7.18 mmol) was added by syringe followed after 5 min by freshly distilled (+)-diisopropyl L-tartrate (2.00 g, 1.80 ml, 8.57 mmol). After a further

15 min (*E*)-nona-2,8-dien-4-ol (**3**) (9.79 g, 69.9 mmol) was added. Finally a solution of t-butyl hydroperoxide in toluene (3.08M; 9.08 ml, 27.9 mmol) was added after an additional 10 min. The solution was placed in a freezer at −20 °C. After 3 days the reaction was removed from the freezer and placed in an ice-bath. Saturated aqueous sodium sulphate solution (8 ml) was added followed by ether (50 ml). Dimethyl sulphide (1 ml) was also added and the resulting solution stirred for 1 h whilst it reached ambient temperature. The gelatinous orange precipitate was filtered off under reduced pressure, washed with ether (2 × 50 ml), and dried under suction to give a fine orange powder. The combined filtrates were evaporated under reduced pressure.

At this stage, the product mixture was either prepared for reduction or for separation by column chromatography.

(*a*) *Preparation for reduction.* The crude product mixture was dissolved in ether (50 ml). Aqueous sodium hydroxide (1M; 15 ml) was added and the two-phase mixture stirred vigorously for 1 h. The ethereal layer was separated and washed with water (2 × 10 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Material recovery at this stage was >90%, comprising 40% epoxy alcohols and 60% partially resolved allylic alcohol (analysed by 220 MHz ^1H NMR spectroscopy).* This mixture was used without further purification in the next step of the synthesis of (**2**).

(*b*) *Purification by chromatography.* The crude product mixture was separated by flash column chromatography on silica gel using light petroleum–ether–triethylamine (50:50:1) as eluant to give after distillation (Kügelrohr) compound (**4**) (3.80 g, 2.44 mmol, 35%) as a colourless oil, b.p. 105 °C (0.5 mmHg); ν_{max}(film) 3 450, 3 090, 2 995, 2 940, 2 870, 1 650, 1 465, 1 440, 1 420, 1 385, 1 320, 1 260, 1 200, 1 135, 1 100, 960, 920, 880, 820, and 765 cm^{-1}; $\delta_H(CDCl_3)$ 1.32 (3 H, d, *J* 5.5 Hz), 1.40–1.70 (4 H, m), 2.00–2.20 (2 H, m), 2.20 (1 H, br s, removed by D_2O shake), 2.68 (1 H, dd, *J* 2.5 and 3.5 Hz), 3.09 (1 H, dq, *J* 2.5 and 5.5 Hz), 3.75–3.85 (1 H, m), 4.90–5.10 (2 H, m), and 5.65–5.90 (1 H, m); $\delta_C(CDCl_3)$ 17.20 (q), 24.51 (t), 33.04 (t), 33.67 (t), 51.12 (d), 61.99 (d), 68.71 (d), 114.66 (t), and 138.34 (d); *m/z* (CI, NH_3) 174 ($M^+ + NH_4$), no parent ion observed with EI. (Found: C, 68.9; H, 10.1. $C_9H_{16}O_2$ requires C, 69.19; H, 10.32%). The optical purity was determined using the Mosher ester method by capillary GC and ^{19}F NMR spectroscopy. The diastereoisomeric purity was found to be ⩾95% and enantiomeric excess was ⩾96%. Partially resolved (*R*)-allylic alcohol was also recovered in 50% yield (4.89 g) after Kügelrohr distillation at 100 °C (20 mmHg).

(±)-2,3-*Epoxynon*-8-*en*-4-*ol*.—To a solution of allylic alcohol (**3**) (2.10 g, 15 mmol) in dichloromethane (40 ml) at room temperature was added a few crystals of vanadyl bis(acetoacetonate). The flask was then flushed with argon, sealed with a septum cap, and cooled to 0 °C. t-Butyl hydroperoxide (3.74M solution in toluene; 7 ml, 26 mmol) was added and the solution maintained at 0 °C for 48 h. The solution was then washed with water (2 × 20 ml) and brine (20 ml), dried ($MgSO_4$), filtered, and evaporated. The product was purified by flash column chromatography on silica gel using light petroleum–ethyl acetate (2:1) as eluant to give, after distillation (Kügelrohr), (±)-2,3-epoxynon-8-en-4-ol as a colourless oil (1.91 g, 81%), b.p. 110 °C (0.5 mmHg). ^1H NMR spectroscopy indicated that the product contained *ca.* 70% *anti*-epoxy alcohol and *ca.* 30% of the *syn*-epoxy alcohol.

(2S,3S,4R)-*Epoxynon*-8-*en*-4-*ol* (**5**).—To a solution of compound (**4**) (2.00 g, 12.8 mmol) and triphenylphosphine (4.03 g, 15.4 mmol) in THF (20 ml) was added 4-nitrobenzoic acid (2.57 g, 15.4 mmol). The flask was flushed with argon and placed in a water-bath at ambient temperature. Diethyl azodicarboxylate (DEAD) (2.43 ml, 2.68 g, 15.4 mmol) was added dropwise *via* syringe over 5 min. As the 4-nitrobenzoic acid dissolved, a new precipitate separated from the yellow solution. The reaction was stirred at ambient temperature for 12 h. Ether (40 ml) was added and the reaction mixture washed with saturated aqueous sodium hydrogen carbonate (2 × 50 ml), dilute hydrochloric acid (50 ml), and brine (20 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Ether (50 ml) was added followed by light petroleum (2 ml). After scratching, a white precipitate of triphenylphosphine oxide separated and was filtered off. After removal of the solvent, the residue was passed through a short column of silica gel using light petroleum–ether (1:1) as eluant to give almost pure (2*S*,3*S*,4*R*)-epoxynon-8-en-4-yl nitrobenzoate; ν_{max}(film) 3 140, 3 100, 3 020, 3 000, 2 940, 2 880, 1 735, 1 650, 1 620, 1 540, 1 470, 1 450, 1 420, 1 360, 1 330, 1 310, 1 285, 1 175, 1 130, 1 110, 1 085, 1 020, 1 010, 1 000, 960, 925, 885, 865, 845, 790, 780, 770, 760, 750, 730, 720, 710, and 695 cm^{-1}; $\delta_H(CDCl_3)$ 1.32 (3 H, d, *J* 6.0 Hz), 1.40–1.63 (2 H, m), 1.75–1.92 (2 H, m), 2.05–2.20 (2 H, m), 2.90–3.05 (2 H, m), 4.95–5.10 (3 H, m), 5.65–5.90 (1 H, m), 8.25 (2 H, d, *J* 7 Hz), and 8.30 (2 H, d, *J* 7 Hz); *m/z* (CI, NH_3) 323 ($M + NH_4^+$) and 306 ($M + H^+$), no parent ion observed with EI.

To the 4-nitrobenzoate ester was added a solution of sodium methoxide in methanol (0.2M; 8 ml) and the mixture stirred for 45 min at ambient temperature. A cream precipitate began to appear after a few min. The mixture was diluted with methanol (30 ml) and Dowex 50W × 8 acidic ion exchange resin (5 g) added. The mixture was stirred briefly, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using light petroleum–ether–triethylamine (50:50:1) as eluant, and distillation (Kügelrohr) to give compound (**5**) (1.10 g, 55% overall), b.p. 105 °C (0.5 mmHg); ν_{max}(film) 3 450, 3 090, 2 995, 2 940, 2 870, 1 650, 1 465, 1 440, 1 420, 1 385, 1 320, 1 260, 1 200, 1 135, 1 100, 960, 920, 880, 820, and 765 cm^{-1}; $\delta_H(CDCl_3)$ 1.30 (3 H, d, *J* 5.5 Hz), 1.40–1.70 (4 H, m), 2.05–2.20 (2 H, m), 2.48 (1 H, br s, removed by D_2O shake), 2.70 (1 H, dd, *J* 2.2 and 5.0 Hz), 3.00 (1 H, dq, *J* 2.2 and 5.5 Hz), 3.40–3.50 (1 H, m), 4.90–5.10 (2 H, m), and 5.65–5.90 (1 H, m); $\delta_C(CDCl_3)$ 17.20 (q), 24.61 (t), 33.62 (t, two coincident signals), 52.87 (d), 62.81 (d), 71.09 (d), 114.76 (t), and 138.29 (d); *m/z* (CI, NH_3) 174 ($M + NH_4^+$), no parent ion observed with EI. The optical purity was determined using the Mosher ester method and was found to be ⩾96% enantiomeric excess and ⩾93% diastereoisomeric purity using capillary GC and ^{19}F NMR spectroscopy.

(2S,4S)-*Non*-8-*ene*-2,4-*diol* (**6**).—To a solution of crude epoxidation product mixture (*ca.* 5.0 g) from allylic alcohol (**3**) (4.57 g, 32.6 mmol) in THF (50 ml) at 0 °C under argon was added a solution of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in toluene (3.4M; 10 ml, 34.0 mmol). The resulting solution was stirred at 0 °C for 2 h and allowed to reach ambient temperature overnight. Aqueous sodium hydroxide (1M; 10 ml) was added with caution and the reaction mixture stirred for 30 min. Ether (50 ml) was added and the organic phase separated. The aqueous phase was extracted with ether (2 × 40 ml) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced

* The presence of isomeric epoxy alcohols, which could not be isolated, was established by 220 MHz ^1H NMR spectroscopy. In particular, signals at δ 2.90–3.00 (m) and 3.85–3.95 (m) were characteristic of the Payne rearranged product. Typically, rearranged material accounted for *ca.* 30% of the epoxide component. Hydrolysis using 0.5M sodium hydroxide in saturated brine gave *ca.* 10% rearranged material in the epoxide component.

pressure. The product mixture containing 2-methoxyethanol (from the Red-Al reagent), resolved allylic alcohol (**3**), and diol (**6**) was separated by flash column chromatography on deactivated alumina (5 ml H_2O per 1 kg alumina) using light petroleum–ethyl acetate (3:1) as eluant and subsequent distillation (Kügelrohr) gave resolved allylic alcohol *R*-(**3**) (2.52 g, 55%), b.p. 90 °C (20 mmHg) with ^{1}H NMR spectrum identical with that of the racemic material, and the *diol* (**6**) as a colourless oil [1.78 g, 35% from allylic alcohol (**3**)], b.p. 130 °C (0.5 mmHg); ν_{max}(film) 3 380, 3 080, 2 980, 2 960, 2 860, 1 640, 1 450, 1 440, 1 420, 1 380, 1 330, 1 200, 1 140, 1 085, 990, 950, 910, 860, 830, and 805 cm^{-1}; δ_H($CDCl_3$) 1.22 (3 H, d, *J* 6.5 Hz), 1.35–1.64 (6 H, m), 2.00–2.10 (2 H, m), 3.15 (2 H, br s, removed by D_2O shake), 3.90–4.00 (1 H, m), 4.08–4.20 (1 H, m), 4.95–5.10 (2 H, m), and 5.73–5.89 (1 H, m); δ_C($CDCl_3$) 23.54 (q), 25.13 (t), 33.71 (t), 36.92 (t), 44.34 (t), 65.36 (d), 69.07 (d), 114.65 (t), and 138.68 (d); *m/z* (CI, NH_3) 176 (M + NH_4^+) and 159 (M + H^+), no parent ion observed with EI (Found: C, 68.15; H, 11.7. $C_9H_{18}O_2$ requires C, 68.31; H, 11.47%).

Investigation into the Red-Al reduction of (2S,3S,4S)-*Epoxynon-8-en-4-ol* (**4**).—*Reduction in the presence of benzyl alcohol* (1.1 equiv.). To a solution of purified epoxy alcohol (**4**) (100 mg, 0.64 mmol) in THF (20 ml) under an argon atmosphere was added benzyl alcohol (0.07 ml, 0.7 mmol) and the solution cooled to 0 °C. A solution of Red-Al in toluene (3.4M; 0.80 ml, 2.72 mmol) was added, and the solution stirred for 2 h at 0 °C and then allowed to reach room temperature overnight. Wet ether (4 ml) was added followed by aqueous sodium hydroxide (1M; 5 ml) and the mixture stirred for 1 h. Ether (10 ml) was added and the organic phase separated and extracted with ether (20 ml). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. ^{1}H NMR analysis indicated a 20:1 ratio of 1,3-diol to 1,2-diol in the crude reaction mixture (Note: see later) together with benzyl alcohol and methoxyethanol residues. Column chromatography on silica gel using light petroleum–ethyl acetate (1:3) as eluant followed by distillation (Kügelrohr) gave pure 1,3-diol (70 mg, 70%).

Reduction in the presence of allyl alcohol (1.0 equiv.). To a solution of epoxy alcohol (**4**) (1.10 g, 0.64 mmol) in THF (10 ml) was added allyl alcohol (0.037 g, 0.43 ml, 0.64 mmol) and the solution cooled to 0 °C under an argon atmosphere. A solution of Red-Al in toluene (3.4M; 0.5 ml, 1.7 mmol) was added dropwise and the reaction stored at 0 °C for 2 h and allowed to reach room temperature overnight. The reaction mixture was stirred at room temperature for a further 2 days until the starting material was consumed (TLC analysis). Aqueous sodium hydroxide (1M; 5 ml) was cautiously added and the mixture stirred for 30 min. Ether (10 ml) was added and the organic phase separated and extracted with ether (20 ml). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Capillary GC of the crude product mixture indicated a 50:1 ratio of 1,3-diol to 1,2-diol. No 1,2-diol was visible in the ^{1}H NMR spectrum. Methoxyethanol and allyl alcohol residues were removed by distillation (Kügelrohr) to give pure 1,3-diol (0.93 g, 93%).

Reduction in the presence of (+)-*DIPT* (1.0 equiv.). To a solution of epoxy alcohol (**4**) (150 mg, 0.96 mmol) and (+)-DIPT (0.22 g, 0.94 mmol) in THF (20 ml) at 0 °C under an argon atmosphere was added a solution of Red-Al in toluene (3.4M; 1.1 ml, 3.74 mmol). The solution was stirred at 0 °C for 2 h and allowed to reach room temperature overnight. The reaction mixture was then stirred at room temperature for a further 2 days until the starting material was consumed (TLC analysis). Aqueous sodium hydroxide (1M; 5 ml) was added cautiously and the reaction stirred for 2 h. Ether (20 ml) was added and the organic phase separated and extracted with a further portion of ether (20 ml). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. ^{1}H NMR analysis of the crude product mixture indicated the presence of only 1,3-diol and methoxyethanol. The latter was removed by distillation (Kügelrohr) to give 1,3-diol (0.13 g, 86%).

Reduction in the presence of methanol. To a solution of epoxy alcohol (**4**) (0.47 g, 3.0 mmol) and methanol (54 mg, 0.54 ml, 1.68 mmol) in THF (40 ml) at 0 °C under an argon atmosphere was added a solution of Red-Al in toluene (3.4M; 2.65 ml, 9.0 mmol). The resulting solution was stirred at 0 °C for 2 h and allowed to reach room temperature overnight. Aqueous sodium hydroxide (1M; 5 ml) was added cautiously and the solution stirred for 30 min. Ether (20 ml) was added and the organic phase separated. The aqueous layer was extracted with ether (20 ml), and the combined extracts were washed with brine (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. ^{1}H NMR analysis of the crude product mixture indicated the presence of only 1,3-diol and methoxyethanol. The product was purified by flash column chromatography on deactivated alumina using light petroleum–ethyl acetate (1:1) followed by methanol as eluant. Concentration under reduced pressure followed by distillation (Kügelrohr) gave 1,3-diol (0.39 g, 83%).

Reduction of (2S,3S,4R)-*epoxynon-8-en-4-ol* (**5**) *in the presence of methanol.* To a solution of epoxy alcohol (**5**) (0.75 g, 4.8 mmol) and methanol (86 mg, 0.86 mol, 2.69 mmol) in THF (150 ml) at 0 °C under an argon atmosphere was added a solution of Red-Al in toluene (3.4M; 2.8 ml, 9.6 mmol). The resulting solution was stirred at 0 °C for 2 h and allowed to reach room temperature overnight. Aqueous sodium hydroxide (1M; 5 ml) was added and the solution stirred for 30 min. Ether (50 ml) was added and the organic phase separated. The aqueous phase was extracted with ether (20 ml) and the combined extracts were washed with brine (5 ml), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. ^{1}H NMR analysis of the crude product mixture indicated the presence of only 1,3-diol and methoxyethanol. The product was purified by flash column chromatography on deactivated alumina using light petroleum–ethyl acetate (1:1) followed by methanol as eluant. Concentration under reduced pressure followed by distillation (Kügelrohr) gave 1,3-diol (**7**) as a colourless oil (0.70 g, 93%); ν_{max}(film) 3 340, 3 080, 2 975, 2 920, 1 680, 1 460, 1 440, 1 410, 1 370, 1 320, 1 200, 1 140, 1 090, 1 060, 995, 935, 910, 860, 830, and 805 cm^{-1}; δ_H($CDCl_3$) 1.23 (3 H, d, *J* 6 Hz), 1.30–1.70 (6 H, m), 2.00–2.20 (2 H, m), 3.85–3.95 (1 H, m), 4.05–4.15 (1 H, m), 4.30–4.50 (2 H, br s, removed by D_2O shake), 4.95–5.10 (2 H, m), and 5.73–5.95 (1 H, m); *m/z* (CI, NH_3) 176 (M + NH_4^+) and 159 (M + H^+).

Notes: Ratios derived from NMR analysis were calculated by comparison of the relative peak areas of the C-1 methyl groups of 1,2-diol [δ 0.94 (3 H, t, *J* 7 Hz)] and 1,3-diol [δ 1.20 (3 H, d, *J* 6 Hz)]. An authentic sample of 1,2-diol was obtained in low yield by chromatography on silica gel of a 3:1 mixture of 1,3- and 1,2–diols; δ_H($CDCl_3$) 0.97 (3 H, t, *J* 7.0 Hz), 1.35–1.70 (6 H, m), 2.00–2.20 (2 H, m), 2.82 (2 H, br s, peak removed by D_2O shake), 3.30–3.50 (2 H, m), 4.95–5.10 (2 H, m), and 5.70–5.95 (1 H, m). Further evidence of structure was obtained by treating a mixture of 1,2- and 1,3-diols with $NaIO_4$. This resulted in the removal of the signals due to 1,2-diol, whereas those of the 1,3-diol were unaffected.

exo-(1R,3S,5S)-1,3-*Dimethyl*-2,9-*dioxabicyclo*[3.3.1]*nonane* (**2**).—A suspension of $CuCl_2$·$2H_2O$ (0.495 g, 2.92 mmol) and $PdCl_2$ (75 mg) in THF (2 ml) was stirred for 1.5 h at room temperature. A solution of 1,3-diol (**7**) (0.40 g, 2.56 mmol) in THF (5 ml) was added and the reaction stirred for 12 h. Water (5 ml) was added, the mixture was extracted with ether (3 × 25 ml), and the combined extracts were allowed to stand overnight. The aqueous residue was acidified (1M HCl; 2 ml),

stirred overnight, and extracted with ether (2 × 25 ml). The combined organic extracts were washed with aqueous sodium hydroxide (1M; 20 ml) and brine (10 ml), dried ($MgSO_4$), and filtered. Most of the solvent was removed through a fractionation column and the residue distilled (Kügelrohr) to give (**2**) as a colourless liquid with the characteristic odour of a damp pine forest (0.23 g, 1.49 mmol, 56%), b.p. 90 °C (70 mmHg); ν_{max}(film) 2 970, 2 920, 2 875, 2 845, 1 470, 1 440, 1 385, 1 350, 1 340, 1 325, 1 300, 1 260, 1 245, 1 230, 1 200, 1 155, 1 125, 1 105, 1 060, 1 040, 1 025, 1 010, 990, 970, 940, 930, 905, 885, 860, 845, 820, 795, 785, 760, 745, 720, and 700 cm^{-1}; $\delta_H(CDCl_3)$ 1.09 (3 H, d, *J* 6.0 Hz), 1.22 (3 H, s), 1.45–2.25 (8 H, m), 4.13 (1 H, t, *J* 5.3 Hz), and 4.50–4.60 (1 H, m); $\delta_C(CDCl_3)$ 19.78 (t), 24.02 (q), 27.78 (q), 30.16 (t), 33.72 (t), 36.74 (t), 66.08 (d), 67.29 (d), and 95.17 (s); *m/z* (EI) 157 ($M^+ + 1$). Capillary GC indicated a diastereoisomeric purity of >95%; $[\alpha]_D^{24} = -4.0° \pm 1.0°$, *c* = 2.5 (pentane) [lit.,[12] $[\alpha]_D^{22} = -4.4°$, *c* = 2.5 (pentane)].

endo-(1S,3S,5R)-1,3-*Dimethyl*-2,9-*dioxabicyclo*[3.3.1]*nonane* (**1**).—A suspension of $CuCl_2 \cdot 2H_2O$ (0.495 g, 2.92 mmol) and $PdCl_2$ (75 mg) in THF (5 ml) was stirred for 1.5 h at room temperature. A solution of 1,3-diol (**6**) (0.46 g, 2.91 mmol) in THF (5 ml) was added and the reaction mixture stirred for 12 h. Water (5 ml) was added, the mixture extracted with ether (2 × 20 ml), and the combined extracts were allowed to stand overnight. The aqueous residue was acidified (1M HCl; 3 ml), stirred overnight, and extracted with ether (2 × 20 ml). The combined extracts were washed with aqueous sodium hydroxide (1M; 20 ml) and brine (10 ml), dried ($MgSO_4$), and filtered. Most of the solvent was removed through a fractionation column and the residue distilled (Kügelrohr) to give (**1**) as a colourless liquid with the characteristic odour of a damp pine forest (0.232 g, 1.49 mmol, 52%); ν_{max}(film) 2 970, 2 930, 2 880, 1 465, 1 445, 1 380, 1 355, 1 290, 1 270, 1 240, 1 225, 1 200, 1 165, 1 155, 1 135, 1 120, 1 080, 1 070, 1 035, 1 025, 1 000, 970, 945, 875, 855, 830, 800, 770, and 725 cm^{-1}; $\delta_H(CDCl_3)$ 1.19 (3 H, d, *J* 6.1 Hz), 1.26 (3 H, s), 1.31–1.83 (6 H, m), 2.01–2.17 (2 H, m), 3.90–4.00 (1 H, m), and 4.22–4.30 (1 H, m); $\delta_C(CDCl_3)$ 14.19 (t), 20.78 (q), 27.26 (q), 29.57 (t), 34.68 (t), 36.79 (t), 61.34 (d), 66.71 (d), and 97.29 (s); *m/z* (EI), 156 (M^+). Capillary GC indicated a diastereoisomeric purity of *ca.* 95%; $[\alpha]_D^{28} = +36.0°$, *c* = 0.77 (pentane) [lit.,[12] $[\alpha]_D^{22} = +37.5°$, *c* = 5.4 (pentane)].

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