Isomer Selectivity in Stereocontrolled Payne Rearrangement–epoxide Cleavage of 2,3-Epoxy Alcohols in Aprotic Solvents: Application to an Enantioselective Total Synthesis of (+)-*exo*-Brevicomin

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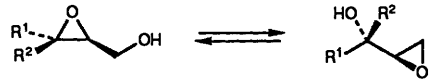
Organo-copper and -cuprate reagents may be used to trap the more reactive epoxy alkoxide isomer in a Lewis acid-catalysed Payne rearrangement process. This methodology has been used as the key step in a five-step enantioselective total synthesis of (+)-*exo*-brevicomin, an aggregation pheromone of the Western Pine beetle *Dendroctonius brevicomis*.

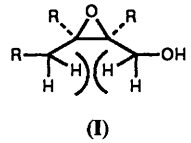
In 1962, Payne published a study of the base-catalysed isomerisation of 2,3-epoxy alcohols.[1] Such a phenomenon had been reported previously in sugar chemistry[2] and was termed epoxide migration. However, in the case of simple 2,3-epoxy alcohols the name 'Payne rearrangement' has been adopted.[3] The reaction involves intramolecular nucleophilic attack by an alkoxide on an adjacent epoxide to form an isomeric alkoxide (Scheme 1).



(1) (2)

Scheme 1.

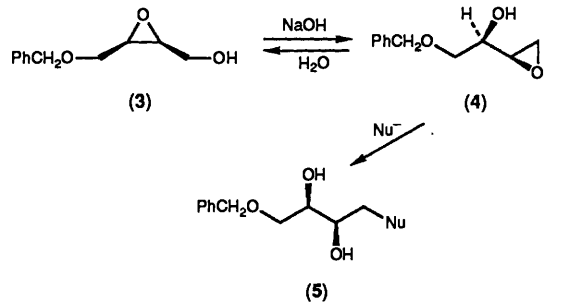
The isomerisation produces an equilibrium mixture of the two epoxides (**1**) and (**2**) controlled by the relative thermodynamic stabilities of the two compounds.[2,4] In the case of acyclic epoxy alcohols, where conformational effects may be small, the relative thermodynamic stabilities of isomeric epoxides have been shown to parallel the acidities of the hydroxy groups in aqueous media.[1] Exceptions to this pattern may be found where one epoxide isomer is particularly disfavoured due to unfavourable steric effects. This appears to be the case for *syn*-epoxy alcohols (**I**) where the rigid structure results in destabilising 1,4-interactions.



(I)

For this reason, *syn*-epoxy alcohols are the substrates of choice when studying the Payne rearrangement and related reactions. In particular, if a large group is present at C-4, then the available relief of strain results in Payne rearrangement with a greater proportion of the terminal *threo*-epoxy alcohol present at equilibrium. The ready availability of *syn*-epoxy alcohol (**3**)[5] made it an ideal substrate for our preliminary investigations.[3]

The Payne rearrangement is not generally a useful preparative method precisely because it produces an equilibrium mixture of epoxy alcohols. However, the different reactivities of the two isomeric epoxides may be utilised in a further reaction to displace the equilibrium and so give essentially one product. This approach forms the basis of the Payne rearrangement–nucleophilic trapping procedure, developed independently by Ganem[7] and Sharpless[3b,8], which involves carrying out the Payne rearrangement in the presence of a nucleophile,[3,6] (Scheme 2) and which has become of considerable importance with the development of the Sharpless asymmetric epoxidation. Under basic conditions the terminal epoxide position of (**4**) is very much more reactive than the internal epoxide positions of (**3**) and (**4**). Thus, with a suitable nucleophile, attack takes place selectively at C-1 of (**4**), displacing the equilibrium to give (**5**) as the sole product of the reaction.



(3) (4) (5)

Scheme 2.

To date the major limitation of this reaction has been the need for protic solvents. If the epoxy alkoxide is generated in aprotic solvents, *e.g.* using sodium hydride, then no rearrangement is observed and the starting material is recovered unchanged.[3b,1] Obviously this imposes serious restrictions on the types of nucleophiles which may be used in the reaction; in particular, carbon nucleophiles in the form of organolithium or organocopper reagents are quite incompatible with the reaction conditions. To overcome this problem a number of alternative multi-step procedures have been developed,[3b,6] however these methods are not without their disadvantages and are not particularly efficient.

Investigation of the Payne Rearrangement.—The generation of the anion of an epoxy alcohol in an aprotic solvent gives a stable epoxy alkoxide which does not undergo significant Payne rearrangement.[1] This was believed to be due to binding of the alkoxide anion to the sodium cation in a tight ion-pair in such a manner as to prevent intramolecular nucleophilic attack of the epoxide.[1] Under aqueous conditions both the sodium ion and the alkoxide would be solvated by water molecules thus allowing rearrangement.

Our initial experiments were designed to mimic this effect by

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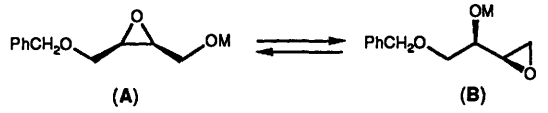
Table 1. Attempted Payne rearrangements under basic conditions.

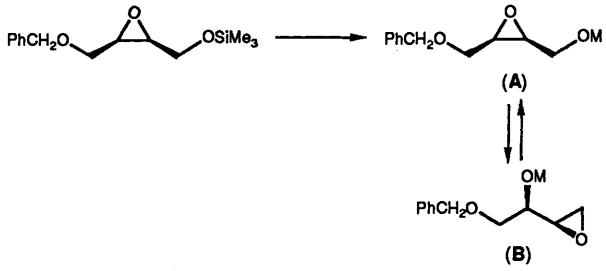


(A) (B)

Entry	conditions[a]	Ratio (A):(B)[b]
a	NaOH, H_2O, 25 °C, 1.5 h	46:54
b	BuLi, THF, 25 °C, 1.5 h	>50:1
c	BuLi, THF, −78 °C, 1.5 h	>50:1
d	BuLi, THF, TMEDA, 25 °C, 15 h	>50:1
e	BuLi, THF, TMEDA, −78 °C, 1.5 h	>50:1
f	BuLi, THF, TMEDA, −30 °C, 20 h	>50:1
g	BuLi, THF, HMPA, 25 °C, 1.5 h	>50:1
h	BuLi, THF, DMSO, 25 °C, 1.5 h	>50:1
i	BuLi (0.14 equiv.), THF, −78 °C, 12 h	>50:1
j	$LiNH_2$, NH_3, −33 °C, 3 h	>50:1
k	NaH, THF, 18-crown-6, 25 °C, 12 h	3:1

[a] 1.0 equiv. BuLi used unless otherwise stated. [b] Determined by capillary gas chromatography.

Table 2. Attempted Payne rearrangements using fluoride anion.



(A) (B)

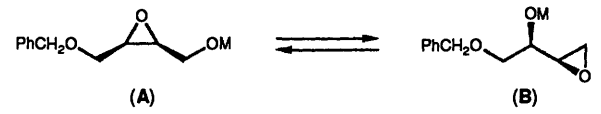
Entry	conditions	Ratio (A):(B)[a]
a	CsF. THF, 25 °C, 48 h	No reaction[b]
b	CsF, DMSO, 25 °C, 5 h	>50:1
c	CsF, DMSO, 25 °C, 20 h	>50:1
d	CsF, MeCN, 25 °C, 5 h	>50:1
e	CsF, MeCN, 25 °C, 20 h	>50:1
f	CsF, CH_2Cl_2, 25 °C, 20 h	>50:1
g	Bu_4NF, DMSO, 25 °C, 5 h	>50:1
h	Bu_4NF, DMSO, 25 °C, 20 h	>50:1
i	Bu_4NF, CH_2Cl_2, 25 °C, 20 h	2:1

[a] Determined by capillary gas chromatography unless otherwise stated. [b] Determined by ^1H NMR spectroscopy.

incorporating metal-complexing agents into the reaction mixture in the hope that they would facilitate the rearrangement process. The results of this study (Table 1) show that in general lithium alkoxides do not undergo Payne rearrangement in aprotic media even in the presence of strongly complexing solvents or additives. It is interesting to note the final entry in which the sodium alkoxide was used in the presence of 18-crown-6. After 12 h a 3:1 mixture of the isomeric alkoxides was formed; however under these conditions the rearrangement was deemed to be too slow for any possible synthetic utility.

We next investigated the effect on the rearrangement of changing the alkoxide counterion. A range of metal alkoxides was accessed *via* the trimethylsilyl ether (**6**), prepared under standard conditions (Scheme 3). Alkoxide formation from (**6**) was carried out under a variety of conditions. Again the results (Table 2) indicated that rearrangement in aprotic media was unfavourable: only in the final case (entry *i*) was any rearrangement observed and again the process was too slow to be of any real preparative value.

Table 3. Attempted Payne rearrangements in the presence of Lewis acids.

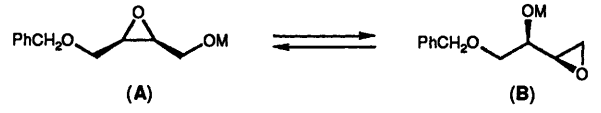


(A) (B)

Entry	conditions[a]	Ratio (A):(B)[b]
a	$ZnCl_2$, THF, 25 °C, 2 h	>50:1
b	$MgCl_2$, THF, 25 °C, 4 h	Starting material destroyed[c]
c	$MgBr_2{\cdot}Et_2O$, THF, −30 °C, 4 h	Starting material destroyed[c]
d	LiBr, THF, 25 °C, 4 h	20:1
e	LiCl, THF, 25 °C, 4 h	2.5:1
f	LiCl, Et_2O, 25 °C, 4 h	>50:1

[a] Alkoxide generated at 0 °C using BuLi (1.0 equiv.); salt (2.0 equiv.) then added and reaction allowed to reach 25 °C. [b] Determined by capillary gas chromatography unless otherwise stated. [c] Determined by ^1H NMR spectroscopy.

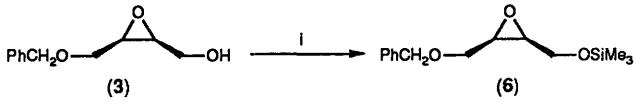
Table 4. Payne rearrangements in the presence of lithium chloride.



(A) (B)

Entry	conditions[a]	Ratio (A):(B)[b]
a	LiCl (2 equiv.), THF, 25 °C, 12 h	1:1.5
b	LiCl (4 equiv.), THF, 25 °C, 4 h	2:1
c	LiCl (8 equiv.), THF, 25 °C, 4 h	1.8:1
d	LiCl (16 equiv.), THF, 25 °C, 3 h	1.7:1
e	LiCl (2 equiv.), THF, heat, 16 h	Starting material destroyed[c]

[a] Reactions carried out using the epoxy alcohol (1.0 mmol) in THF (2 ml); alkoxide generated at 0 °C in the presence of LiCl and reaction allowed to reach 25 °C. [b] Determined by capillary gas chromatography unless otherwise stated. [c] Determined by ^1H NMR spectroscopy.



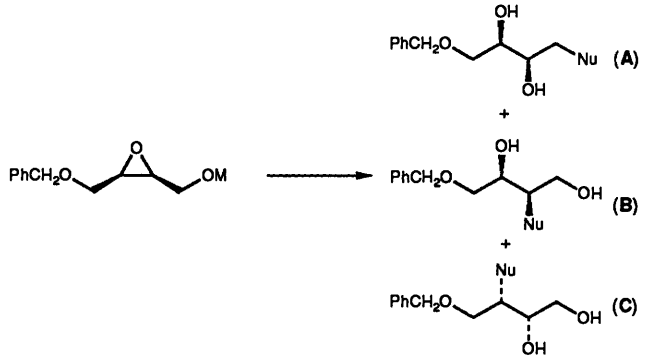
(3) (6)

Scheme 3. *Reagents:* i, Me_3SiCl, Et_3N, THF (82%).

We therefore turned our attention from the reactivity of the alkoxide anion to that of the epoxide. It is well known that Lewis acids promote epoxide cleavage reactions.[2,9] Strong Lewis acids, for example boron trifluoride and titanium tetrachloride, are known to react rapidly with epoxides,[2,9,10], and therefore weaker Lewis acids such as zinc, magnesium, or lithium salts were considered to be more likely candidates for the promotion of efficient clean rearrangement at room temperature. In general the results (Table 3) were not promising, with the one exception of lithium chloride in THF (entry *e*). These conditions were investigated further (Table 4), and to our pleasure suggested that equilibrium had been attained[11] for the Payne rearrangement of the lithium alkoxide of (**3**) in <12 h using a near-saturated solution of lithium chloride in THF.

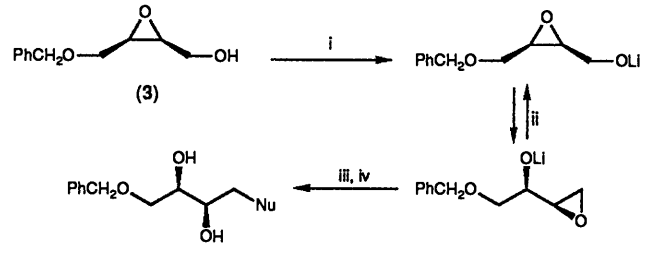
The crucial problem remaining to be solved was that of inducing the more reactive epoxide isomer to undergo selective reaction with a carbon nucleophile in the equilibrium mixture (Scheme 4). We observed a delicate balance between the reactivity of the organometallic reagent studied and the regioselect-

Table 5. Nucleophilic trapping in lithium chloride-assisted Payne rearrangements.



Entry	nucleophile[a]	Ratio (A):(B):(C)[b]	Yield (%)
a	MeCu	50:1:1	94
b	MeCuCNLi	50:1:1	95
c	Me_2CuLi	1:3:2	95
d	BuCu	incomplete reaction	
e	BuCuCNLi	50:1:1	90
f	Bu_2CuLi	0:2:1	93
g	PhCu·DMS	50:1:1	92
h	Ph_2CuLi	2:2:1	91
i	$CH_2{=}C(CH_3)CuCNLi$	no reaction	0
j	$[CH_2{=}C(CH_3)]_2CuCNLi_2$	20:1:1	86
k	$CH_2{=}C(CH_3)Li$	substrate destroyed	0

[a] Alkoxide generated at −78 °C using BuLi (1.0 equiv.) in the presence of LiCl; reaction then warmed to 0 °C and nucleophile added and allowed to reach 25 °C. [b] Determined by capillary gas chromatography or ^1H NMR spectroscopy.



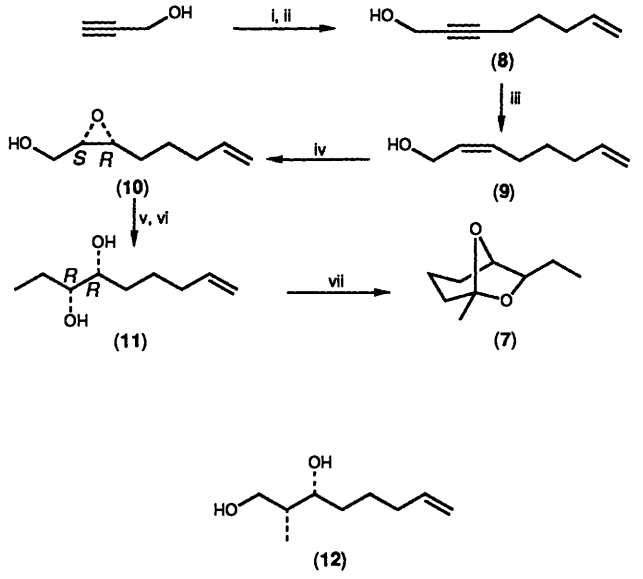
Scheme 4. *Reagents and conditions:* i, BuLi, THF, −78 °C, LiCl; ii, LiCl, THF, 25 °C; iii, Nu^-, LiCl, THF, 0–25 °C, 16 h; iv, H_3O^+.

ivity of attack at epoxy alkoxides. However, after considerable experimentation we were gratified to observe good to excellent selectivity for a range of organocopper nucleophiles (Table 5).

For the introduction of a methyl group, methylcopper or the corresponding cyanocuprate reagent was especially successful, giving excellent selectivities and yields. Use of the more reactive higher-order cuprate reagents, as expected, gave mainly products resulting from nucleophilic ring opening of the unrearranged epoxide (**3**) and little of the desired product. In contrast, for the introduction of a butyl group, butylcopper was unsuccessful due to its low thermal stability.[12] However, use of the cyanocopper reagent lithium cyano(butyl)cuprate provided a more thermally stable nucleophile which again reacted with excellent selectivity and in good yield. For the introduction of the phenyl group, phenylcopper was the reagent of choice, the use of the corresponding higher-order cuprate giving substantial amounts of undesired products. For the introduction of a propenyl group, the lower-order propenylcopper (entry *i*) was too unreactive to give the desired product and propenyl-lithium (entry *k*) destroyed the starting material. However the higher order cyanocuprate reagent (entry *j*) gave good selectivity and yield of the desired product.

Enantioselective Synthesis of (+)-exo-*Brevicomin.*—(+)-*exo*-Brevicomin (**7**) is produced by three species of Dendroctonius beetles as part of their pheromone complex.[13] Of these, D. brevicomis[13b,c] (Western Pine beetle) and D. ponderosae[13d,e] (Mountain Pine beetle) are of major economic importance in western North America. It is known that the latter insect produces (+)-*exo*-brevicomin with >98% e.e., and hence enantioselective syntheses are of considerable importance.[14,15]

We have devised a five-step enantioselective synthesis of (+)-*exo*-brevicomin involving the Sharpless asymmetric epoxidation as the source of optical activity[16] and utilising the stereoselectivity of our Payne rearrangement-nucleophilic trapping procedure to synthesise the pure *exo* diastereoisomer in an almost enantiomerically pure form. The synthetic route is shown in Scheme 5.[17]

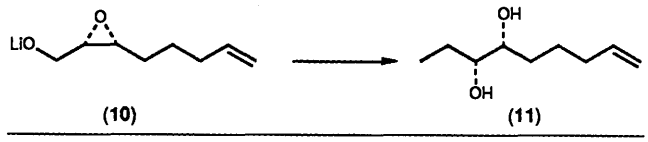


Scheme 5. *Reagents and conditions:* i, $LiNH_2$, NH_3; ii, $Br(CH_2)_3CH{=}CH_2$, THF; iii, H_2, Lindlar, MeOH; iv, $Ti(OPr^i)_4$ (1.0 equiv.), (+)-diethyl tartrate (1.2 equiv.), ^tBuOOH (2.0 equiv.), 4 Å molecular sieve, −20 °C, 6 days; v, BuLi (1.0 equiv.), THF, LiCl, −78 °C; vi, MeCuCNLi (3.0 equiv.), LiCl, THF, 0–25 °C, 4 days; vii, $PdCl_2$ (catalyst), $CuCl_2{\cdot}2H_2O$, THF, 25 °C, 12 h.

Thus, alkylation of the lithio dianion of prop-2-yn-1-ol with 5-bromopent-1-ene in liquid ammonia solution gave the disubstituted acetylene (**8**) in 80% yield. Catalytic hydrogenation of (**8**) produced the *Z*-allylic alcohol (**9**) in 93% yield and >95% *cis* by capillary gas chromatography. This was epoxidised using the Sharpless procedure with (+)-diethyl tartrate as the chiral auxiliary resulting in the formation of the 2(*S*),3(*R*)-epoxy alcohol (**10**) from the known selectivity of the reaction in 78% yield. The enantiomeric excess of this compound was determined to be >94% by ^1H NMR chiral lanthanide shift studies using $Eu(hfc)_3$ and the acetate derivative of compound (**10**).

The next step of the synthesis was the Payne rearrangement–nucleophilic trapping procedure. The nucleophile chosen in this case was lithium methyl(cyano)cuprate due to its relatively high thermal stability[12] and the excellent selectivity and yield previously attained on the model system. Unfortunately, Payne rearrangement of epoxy alcohol (**10**) is slower in this case due to

Table 6. Payne rearrangement– nucleophilic trapping of (12).



(10) (11)

Entry	Conditions[a]	Ratio (10):(11)[b]
a	MeCuCNLi (2 equiv.), 25 °C. 16 h	1:1.5
b	MeCuCNLi (2 equiv.), 25 °C. 36 h	1:1[c]
c	MeCuCNLi (2 equiv.), 25 °C. 48 h	1:2.3
d	MeCuCNLi (3 equiv.), 25 °C. 4 days	1:4
e	MeCuCNLi (6 equiv.), 25 °C. 4 days	1:4
f	MeCuCNLi (3 equiv.), 10 °C. 4 days	1:4
g	MeCuCNLi (6 equiv.), 25 °C. 6 days	1:4

[a] Alkoxide generated at −78 °C using base (1.0 equiv.) in a saturated solution of LiCl in THF. Reaction allowed to reach 0 °C before addition of a solution of MeCuCNLi. [b] Determined by ^{1}H NMR spectroscopy. [c] Alkoxide solution allowed to stir at 25 °C before addition of MeCuCNLi.

the lack of substituents at C-4 (*cf.* (I)], resulting in a much longer reaction time being needed for acceptable yields of the products. The results of a selection of nucleophilic trapping experiments are shown in Table 6. These results indicate that a maximum of only 80% reaction is possible even after prolonged reaction times with a large excess of nucleophile, perhaps due to decomposition of the organocopper reagent under the reaction conditions; although if this were the case the use of lower temperatures (entry *f*) and/or larger amounts of cuprate reagent might be expected to give better results. In addition to this problem, it proved impossible to separate the unchanged epoxy alcohol (**10**) and diol (**11**) by chromatography on a number of absorbents or by fractional distillation. For this reason, the crude product mixture was subjected to the next step of the synthesis without purification. It was however possible to prepare a pure sample of diol (**11**) using a higher-order organocopper reagent of unknown composition but with the general formula $(MeLi)_{1.2}CuCN$. This gave a 2:1 mixture of the regioisomeric diols (**11**) and (**12**) in 91% yield. An authentic sample of (**16**) was prepared selectively by treating epoxy alcohol (**10**) with an excess of methyl-lithium.

The final step of the synthesis was the intramolecular Heck reaction.[18] Thus treatment of the crude product mixture from the Payne rearrangement–nucleophilic trapping procedure (entry *d*) with $PdCl_2/CuCl_2$ in THF followed by chromatography on silica gel (pentane eluant) gave a 31% overall yield of (+)-*exo*-brevicomin (**7**) (>98% purity by capillary GC) from epoxy alcohol (**10**). This compound was identical to that previously reported[19] by ^{1}H and ^{13}C, NMR, IR and high resolution mass spectrometry; however this compound gave an apparently anomalous optical rotation, $[\alpha]_D^{18} = 67.5°$, $c = 1.05$ in ether (lit.,[19] $[\alpha]_D^{26} = 84.1°$, $c = 2.2$ in ether). Further examination of values reported in the literature show a considerable discrepancy in this value. However, of particular importance must be that of Oeschlager ($[\alpha]_D^{27} = 59.0°, c = 2.5$ in chloroform, *cf.* our value $[\alpha]_D^{28} = 65.1°$, $c = 0.76$ in chloroform) whose sample displayed an optical purity verified as >95% e.e. by chiral complexation gas chromatography.[14]

Conclusions

In conclusion, conditions for a Payne rearrangement–nucleophilic trapping procedure using organocopper nucleophiles in aprotic conditions have been established to give selectively the desired regioisomeric product in good to excellent yield. This new methodology has been exploited in an efficient five-step enantioselective synthesis of (+)-*exo*-brevicomin. Although a number of syntheses of this compound are reported in the literature, ours ably demonstrates the synthetic utility of the new process.

Experimental

General Procedure.—Light petroleum (b.p. 40–60 °C and b.p. 60–80 °C) was distilled prior to use. Dichloromethane was dried by distillation from calcium hydride. Diethyl ether was dried by distillation from lithium aluminium hydride. Tetrahydrofuran (THF) was dried by distillation from the sodium benzophenone ketyl radical. Acetonitrile was dried by distillation from phosphorus pentoxide and stored over 3 Å molecular sieve. Chloroform was dried by distillation from phosphorus pentoxide as required. Dimethylformamide (DMF) was dried by azeotropic removal of water with benzene followed by distillation, and stored over 3 Å molecular sieve. Pyridine was dried by storage over potassium hydroxide pellets and distilled before use. Tetramethylethylenediamine (TMEDA) was dried by distillation from the sodium benzophenone ketyl radical. Hexamethylphosphoramide (HMPA) was dried by distillation from calcium hydride and stored over 4 Å molecular sieves.

Commercially available reagents were used as supplied unless otherwise stated. Copper(I) iodide was purified by washing with THF (2 × 10 ml) and dried at 0.5 mm Hg. Copper(I) cyanide was used without purification. For epoxidation reactions, the tartrate and allylic alcohol were distilled immediately before use. Solutions of t-butyl hydroperoxide (TBHP) were prepared according to literature methods.

Commercial solutions of butyl-lithium were fitted with septum caps and stored at −20 °C. The reagent was dispensed by syringe under argon and standardised by the method of Gilman. Vanadyl bis(acetoacetonate) was prepared according to the standard literature procedure.

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 using a 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. ^{1}H NMR spectra were recorded using Perkin Elmer R 34 (220 MHz) or Bruker WM 250 (250 MHz) spectrometers. ^{13}C NMR spectra were recorded using a Bruker WM 250 spectrometer operating at 62.8 MHz or a JEOL FX 60 Q spectrometer operating at 15.0 MHz. All spectra were recorded using tetramethylsilane as internal standard. ^{19}F-Spectra were recorded on a Bruker WM 250 spectrometer operating at 235.8 MHz. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Micromass 7070E instrument.

Capillary gas chromatography 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.

2-*Phenyl*-1,3-*dioxacyclohept*-5-*ene*.—*syn*-Butene-1,4-diol (50 ml; 53.5 g, 0.60 mol), freshly distilled benzaldehyde (51 ml; 53.0

g, 0.50 mol), and toluene-*p*-sulphonic acid (0.50 g) were heated under reflux in benzene (500 ml) with azeotropic removal of water. After 3.5 h production of water had ceased and the reaction mixture was allowed to cool. The mixture was then washed with sodium hydroxide (1M; 2 × 150 ml), dried (magnesium sulphate), filtered and evaporated to give 2-phenyl-1,3-dioxacyclohept-5-ene (*ca.* 95 g), which was used without further purification; ν_{max}(film) 3 080, 3 050, 3 020, 2 960, 2 930, 2 880, 2 840, 1 590, 1 490, 1 445, 1 380, 1 365, 1 345, 1 310, 1 295, 1 255, 1 205, 1 175, 1 090, 1 030, 1 000, 945, 920, 860, 785, 750, 740, 705, 650, and 640 cm^{-1}; δ(^{1}H, $CDCl_3$) 4.29–4.39 (4 H, m), 5.75 (2 H, s), 5.88 (1 H, s), and 7.30–7.62 (5 H, m).

4-*Benzyloxy*-syn-*but*-2-*en*-1-*ol*.—To dry ether (600 ml) under an argon atmosphere was added anhydrous aluminium chloride (100 g, 0.75 mol). The solution was cooled to 0 °C and lithium aluminium hydride (7.59 g, 0.20 mol) was added by means of a solid addition tube over 30 min. After being stirred at 0 °C for 30 min, a solution of crude 2-phenyl-1,3-dioxacyclohept-5-ene (67 g, 0.38 mol) in ether (100 ml) was added dropwise and the mixture was stirred at 0 °C for 30 min. The cooling bath was then removed and the reaction warmed to room temperature and stirred for a further 30 min. The solution was re-cooled to 0 °C and a 10% aqueous solution of sulphuric acid (600 ml) was added dropwise with stirring over 1 h. The organic layer was separated and washed with water (300 ml) and saturated aqueous sodium hydrogen carbonate (150 ml), dried ($MgSO_4$), filtered, and evaporated. The crude product was distilled to give 4-benzyloxy-*syn*-but-2-en-1-ol (52 g, 0.29 mol, 77%) as a colourless oil, b.p. 160–165 °C (0.5 mmHg); ν_{max}(film) 3 380, 3 060, 3 010, 2 910, 2 360, 1 610, 1 590, 1 495, 1 450, 1 410, 1 385, 1 365, 1 330, 1 310, 1 240, 1 210, 1 070, 1 025, 980, 940, 740, and 700 cm^{-1}; δ(^{1}H, $CDCl_3$) 3.80 (1 H, s), 4.05 (2 H, d, *J* 6.0 Hz), 4.09 (2 H, d, *J* 6.0 Hz), 4.50 (2 H, s), 5.60–5.83 (2 H, m), and 7.31 (5 H, s); *m*/*z* (CI, NH_3) 196 (M + NH_4^+) and 179 (M^+ + H).

4-*Benzyloxy*-syn-2,3-*epoxybutan*-1-*ol* (3).—To a solution of 4-benzyloxy-*syn*-but-2-en-1-ol (20.0 g, 0.112 mol) in dichloromethane (150 ml) was added vanadyl acetoacetonate (*ca.* 1 g) and the solution was cooled to 0 °C under an argon atmosphere. t-Butyl hydroperoxide (0.135 mmol; 31.0 ml of a 4.36M solution in toluene) was then added using a syringe over 5 min and the mixture was allowed to warm to room temperature over *ca.* 1 h. After four days, the reaction mixture was diluted with ether (100 ml) and washed with water (4 × 20 ml) and brine (20 ml). The product mixture was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel followed by distillation (Kugelrohr) gave 4-benzyloxy-*syn*-2,3-epoxybutan-1-ol (**3**) (18.20 g, 94 mmol, 84%), b.p. 220 °C (0.5 mmHg); ν_{max}(film) 3 380, 3 060, 3 000, 2 960, 2 900, 2 840, 1 600, 1 490, 1 445, 1 380, 1 360, 1 320, 1 290, 1 240, 1 200, 1 150, 1 090, 1 020, 975, 925, 870, 840, 740, and 690 cm^{-1}; δ(^{1}H, $CDCl_3$) 2.95 (1 H, br s, peak removed by D_2O shake), 3.14 (1 H, dt, *J* 6.0 and 4.5 Hz), 3.23 (1 H, dt, *J* 5.9 and 4.5 Hz), 3.53–3.71 (4 H, m), 4.47–4.57 (2 H, m), and 7.30 (5 H, s); *m*/*z* (CI, NH_3) 212 (M + NH_4^+) and 195 (M^+ + H).

4-*Benzyloxy*-1-*trimethylsilyloxy*-syn-2,3-*epoxybutane* (**6**).—To a solution of 4-benzyloxy-*syn*-2,3-epoxybutan-1-ol (**3**) (2.04 g, 10.5 mmol) in THF (5 ml) at 0 °C under an argon atmosphere was added chlorotrimethylsilane (1.47 ml; 1.25 g, 11.6 mmol). Triethylamine (1.76 ml; 1.27 g, 12.6 mmol) was added dropwise using a syringe resulting in formation of a white precipitate. The mixture was allowed to reach room temperature over 1 h and was stirred overnight. Ether (150 ml) was added and the solution was washed with water (2 × 30 ml) and brine (20 ml), dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure. The product was purified by distillation (Kugelrohr) to give 4-benzyloxy-1-trimethylsilyloxy-*syn*-2,3-epoxybutane as a colourless oil (2.3 g, 8.65 mmol, 82%), b.p. 180 °C (2 mmHg); ν_{max}(film) 3 080, 3 040, 3 010, 2 940, 2 880, 2 840, 1 600, 1 490, 1 400, 1 385, 1 360, 1 320, 1 300, 1 250, 1 200, 1 155, 1 135, 1 085, 1 015, 970, 920, 860, 835, 740, and 690 cm^{-1}; δ(^{1}H, $CDCl_3$) 0.12 (9 H, s), 3.14 (1 H, dt, *J* 6.2 and 4.5 Hz), 3.24 (1 H, dt, *J* 6.7 and 4.0 Hz), 3.56–3.76 (4 H, m), 4.51–4.61 (2 H, m), and 7.24–7.34 (5 H, m); *m*/*z* (CI, NH_3) 284 (M + NH_4^+) and 267 (M + H^+) (Found: C, 63.0; H, 8.45. $C_{14}H_{22}O_3Si$ requires: C, 63.12; H, 8.32%).

Payne Rearrangement of (**3**) *in Aqueous Base*.—To a solution of the epoxy alcohol (**3**) (0.10 g, 0.52 mmol) in ether (5 ml) was added aq. sodium hydroxide (1M; 5 ml) and the resulting two-phase mixture was stirred vigorously at room temperature for 30 min. The layers were then separated and the aqueous phase extracted with ether (10 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Capillary GC analysis of the crude product mixture showed two components, one identified as the starting material (**3**). ^{1}H NMR analysis of the crude product mixture showed new signals at δ 2.70–2.80 (*ca.* 1.2 H, m) and 3.00–3.15 (*ca.* 0.6 H, m), characteristic of a terminal epoxide. The new product was therefore identified as the Payne rearranged epoxide.

Payne Rearrangement Experiments.—General procedure. (*a*) To a solution of epoxy alcohol (**3**) (0.20 g, 1.04 mmol) in THF (5 ml) at 0 °C under an argon atmosphere was added, dropwise, butyl-lithium (1.43M solution in hexane; 1.04 mmol, 0.72 ml) and the reaction mixture was stirred for 5 min. The temperature of the alkoxide solution was then adjusted as required and the complexing agent added using a syringe. Analysis was carried out by mixing a small sample (*ca.* 0.5 ml) with ether (0.5 ml) and saturated aqueous ammonium chloride (2–3 drops, enough to cause white precipitate to dissolve). Capillary gas chromatography of the crude sample was then carried out on an OV351 column.

(*b*) To a solution of epoxy alcohol (**3**) (0.20 g, 1.0 mmol) in THF (4 ml) at 0 °C under an argon atmosphere was added, dropwise, butyl-lithium (1.46M solution in hexane; 1.0 mmol, 0.68 ml). After 5 min, the metal salt (2.0 mmol) was added from a solid addition tube and the solution allowed to warm to 25 °C and stirred for the required time. A small sample (0.5 ml) was then removed and diluted with ether (1.0 ml) and saturated aqueous ammonium chloride (2–3 drops). Capillary GC analysis of the crude sample was then carried out on an OV351 column.

Payne Rearrangement–nucleophilic Trapping Experiments Using Organocopper Reagents.—General procedure. To a solution of the epoxy alcohol (**3**) and lithium chloride in THF at −78 °C under an argon atmosphere was added dropwise butyl-lithium (1 equiv. relative to the epoxyalcohol). The solution was stirred for 5 min at −78 °C and then allowed to warm to 0 °C. After *ca.* 10 min, a solution of the organocopper reagent was added using a cannula and the mixture was allowed to warm to room temperature over 2 h. The reaction was then stirred for a further 10–14 h after which time saturated aqueous ammonium chloride (5 ml) was added cautiously and the reaction stirred for 1–2 h to aid removal of copper residues. Ether (20 ml) was then added and the organic layer separated. The aqueous phase was further extracted with ether (2 × 20 ml) and the combined extracts were dried over ($MgSO_4$), filtered, and the solvent removed under reduced pressure.

Nucleophilic trapping using methylcopper. To a suspension of copper(I) iodide (1.34 g, 7.04 mmol) in THF (5 ml) at 0 °C under an argon atmosphere was added methyl-lithium (1.4M solution in ether; 6.70 mmol, 4.80 ml) dropwise over *ca.* 5 min. After a

further 10 min the yellow suspension of methyl copper was added using a cannula to a solution of alkoxide generated as above from epoxy-alcohol (**3**) (0.65 g, 3.35 mmol) and butyl-lithium (1.56M solution in hexane; 3.35 mmol, 2.15 ml) in THF (10 ml) containing lithium chloride (0.90 g, 21.4 mmol). The reaction was quenched after 16 h using the above work-up procedure to give 1-benzyloxy-2,3-dihydroxypentane (0.66 g, 3.14 mmol, 94%) as a colourless oil; ν_{max}(film) 3 400, 3 100, 3 060, 3 030, 2 970, 2 930, 2 870, 1 600, 1 500, 1 465, 1 445. 1 385, 1 370, 1 320, 1 285, 1 210, 1 180, 1 120, 1 100, 1 075, 1 030, 1 020, 980, 905, 830, 750, 730, 710, and 695 cm^{-1}; δ(^{1}H, $CDCl_3$) 0.90 (3 H, t, *J* 6.0 Hz), 1.37–1.53 (2 H, m), 3.20 (2 H, br s, peak removed by D_2O shake), 3.40–3.65 (4 H, m), 4.48 (2 H, s), and 7.29 (5 H, s). The compound was further characterised as the diacetate (prepared under standard conditions using acetic anhydride in pyridine solution), a colourless oil, ν_{max}(film) 3 080, 3 060, 3 020, 2 970, 2 930, 2 860, 1 740, 1 495, 1 450, 1 425, 1 370, 1 305, 1 240, 1 225, 1 100, 1 070, 1 030, 960, 900, 850, 750, 740, and 695 cm^{-1}; δ(^{1}H, $CDCl_3$) 0.89 (3 H, t, *J* 7.6 Hz), 1.48–1.68 (2 H, m), 2.00 (3 H, s), 2.05 (3 H, s), 3.50–3.66 (2 H, m), 4.45–4.55 (2 H, m), 5.06 (1 H, dt, *J* 7.8 and 4.5 Hz), 5.20 (1 H, dt, *J* 6.1 and 4.5 Hz), and 7.26–7.33 (5 H, m); *m/z* (CI, NH_3), 312 (M + NH_4^+). An analytically pure sample was obtained by flash column chromatography on silica-gel and distillation (Kugelrohr), b.p. 200 °C (0.5 mmHg) (Found: C, 65.05; H, 7.5. $C_{16}H_{22}O_5$ requires: C, 65.29; H, 7.53%).

Nucleophilic trapping using lithium methyl(cyano)cuprate. To a suspension of copper(I) cyanide (0.35 g, 3.91 mmol) in THF (5 ml) at 0 °C under an argon atmosphere was added methyl-lithium (1.4M solution in ether; 3.86 mmol, 2.76 ml) dropwise over *ca.* 5 min. The colourless solution was stirred for 10 min at 0 °C and then warmed to 25 °C over 30 min. It was then cooled to 0 °C and added using a cannula to a solution of the alkoxide generated as above from the epoxy alcohol (**3**) (0.50 g, 2.58 mmol) and butyl-lithium (1.56M solution in hexane; 2.58 mmol, 1.65 ml) in THF (10 ml) containing lithium chloride (0.90 g, 21.4 mmol). The reaction was quenched after 12 h using the above work-up procedure to give 1-benzyloxypentane-2,3-diol (0.51 g, 2.45 mmol; 95%) as a colourless oil whose ^{1}H NMR and IR spectra were identical to those obtained using methyl copper.

Nucleophilic trapping using lithium butyl(cyano) cuprate. To a suspension of copper(I) cyanide (0.64 g, 7.09 mmol) in THF (10 ml) at 0 °C under argon was added butyl-lithium (1.56M solution in hexane; 6.40 mmol, 4.13 ml) dropwise over *ca.* 5 min. After a further 10 min the solution was added using a cannula to a solution of the alkoxide generated as above from the epoxy alcohol (**3**) (0.50 g, 2.57 mmol) and butyl-lithium (1.56M solution in hexane; 2.57 mmol, 1.65 ml) in THF (10 ml) containing lithium chloride (0.80 g, 19.0 mmol). The reaction was quenched after 16 h using the above work-up procedure to give 1-benzyloxyoctane-2,3-diol (0.58 g, 2.30 mmol, 90%) as a colourless oil; ν_{max}(film) 3 400, 3 080, 3 060, 3 020, 2 920, 2 860, 1 490, 1 445, 1 370, 1 200, 1 100, 1 025, 940, 910, 730, and 700 cm^{-1}; δ(^{1}H, $CDCl_3$) 0.80–0.95 (3 H, m), 1.10–1.53 (8 H, m), 3.00–3.30 (2 H, br s, peak removed by D_2O), 3.40–3.65 (4 H, m), 4.48 (2 H, s), and 7.25 (5 H, s); *m/z* (CI, NH_3) 270 (M + NH_4^+) and 253 (M + H^+). An analytical sample was obtained by flash column chromatography on silica gel (Found: C, 71.0; H, 9.65. $C_{15}H_{24}O_3$ requires: C, 71.39; H, 9.59%). This compound was further characterised as the diacetate (prepared under standard conditions using acetic anhydride in pyridine solution); ν_{max}(film) 3 080, 3 060, 3 020, 2 960, 2 940, 2 860, 1 740, 1 495, 1 450, 1 370, 1 225, 1 100, 1 025, 950, 890, 850, 740, and 700 cm^{-1}; δ(^{1}H, $CDCl_3$) 0.86 (3 H, t, *J* 6.8 Hz), 1.20–1.34 (6 H, m), 1.44–1.60 (2 H, m), 2.01 (3 H, s), 2.08 (3 H, s), 3.51 (2 H, d, *J* 5.1 Hz), 4.44–4.54 (2 H, m), 5.16–5.21 (2 H, m), and 7.27–7.33 (5 H, m); δ(^{13}C, $CDCl_3$) 13.94 (q), 20.85 (q), 22.41 (t), 24.70 (t), 30.48 (t) 31.52 (t), 68.42 (t), 71.92 (d), 72.34 (d), 127.7 (d), 128.4 (d), 137.8 (s), and 170.2 (s); *m/z* (CI, NH_3) 354 (M + NH_4^+) and 337 (M^+ + H).

Nucleophilic trapping using phenylcopper. To a solution of copper(I) bromide–dimethyl sulphide complex (0.826 g, 4.02 mmol) in THF (5 ml) at −78 °C under an argon atmosphere was added phenyl-lithium (1.0M solution in ether, lithium bromide complex; 4.02 mmol, 4.02 ml) dropwise over *ca.* 5 min. The resulting solution was stirred for 5 min and allowed to warm to 0 °C. After 10 min the solution of phenylcopper was added using a cannula to a solution of the alkoxide generated as above from epoxy alcohol (**3**) (0.52 g, 2.68 mmol) and methyl-lithium (1.40M solution in ether; 2.68 mmol, 1.92 ml) in THF (5 ml) containing lithium chloride (1.0 g, 23.8 mmol). The reaction was quenched after 16 h using the above work-up procedure to give 1-benzyloxy-4-phenylbutane-2,3-diol (0.67 g, 2.46 mmol, 92%) as a colourless oil which was shown by ^{1}H NMR spectroscopy to be a single regioisomer. A sample was further purified by flash column chromatography on silica gel; although considerable material loss (40–50%) was observed this did, however, furnish an analytically pure product which could be recrystallised to give colourless needles, m.p. 87–89 °C (ethyl acetate–light petroleum); ν_{max}(Nujol mull) 3 400, 3 020, 2 920, 2 850, 1 465, 1 375, 1 335, 1 310, 1 220, 1 130, 1 090, 1 050, 1 035, 1 010, 970, 940, 780, 760, 745, and 700 cm^{-1}; δ(^{1}H, $CDCl_3$) 2.58 (1 H, d, *J* 4.3 Hz, peak removed by D_2O shake), 2.64 (1 H, d, *J* 5.9 Hz, peak removed by D_2O shake), 2.86 (2 H, d, *J* 6.9 Hz), 3.56–3.68 (3 H, m), 3.85 (1 H, dt, *J* 2.7 and 6.9 Hz), 4.44–4.54 (2 H, m), and 7.19–7.32 (5 H, m); δ(^{13}C, $CDCl_3$) 39.96 (t), 70.96 (d), 72.90 (t), 73.28 (d), 73.66 (t), 126.4, 127.8, 127.9, 128.5, 129.4 (d), 137.5, and 138.2 (s); *m/z* (EI) 272.1411 (M^+) (Calc. $C_{17}H_{20}O_3$, 272.1412) (Found: C, 74.79; H, 7.42. $C_{17}H_{20}O_3$ requires: C, 74.97; H, 7.40%).

Nucleophilic trapping using dilithium bis(prop-2-enyl)(cyano) cuprate. To a solution of prop-2-enyl-lithium at 0 °C, prepared from 2-bromopropene (1.31 ml, 1.78 g, 14.7 mmol) and lithium (0.123 g, 17.67 mmol) was added copper(I) cyanide (0.46 g, 5.15 mmol). The reaction mixture was stirred for 10 min, then warmed to room temperature and stirred for 1 h, after which time it was added using a syringe to a solution of the alkoxide at 0 °C generated as above from epoxy alcohol (**3**) (0.50 g, 2.58 mmol) and methyl-lithium (2.58 mmol; 1.84 ml of a 1.4M solution in ether). The resulting mixture was allowed to warm to room temperature after 1 h and was then stirred for a further 14 h after which time work-up was carried out as above to give 6-benzyloxy-2-methylhex-1-ene-4,5-diol (0.52 g, 2.20 mmol, 86%); δ(^{1}H, $CDCl_3$) 1.70 (3 H, s), 2.20 (2 H, d, *J* 6.0 Hz), 3.40–3.90 (6 H, m), 4.48 (2 H, s), 4.75 (1 H, s), 4.83 (1 H, s), and 7.20–7.37 (5 H, m). The crude product was further characterised as the diacetate (prepared under standard conditions using acetic anhydride in pyridine solution); ν_{max}(film) 3 060, 3 020, 2 970, 2 940, 2 860, 1 740, 1 640, 1 600, 1 450, 1 375, 1 310, 1 270, 1 220, 1 105, 1 045, 1 025, 960, 950, 900, 740, 715, and 700 cm^{-1}; δ(^{1}H, $CDCl_3$) 1.74 (3 H, s), 1.97 (3 H, s), 2.06 (3 H, s), 1.97 (3 H, s), 2.06 (3 H, s), 2.18–2.28 (2 H, m), 3.51 (2 H, d, *J* 5.6 Hz), 4.43–4.53 (2 H, m), 4.70 (1 H, br s), 4.78 (1 H, br s), 5.16 (1 H, q, *J* 4.2 Hz), 5.37 (1 H, dt, *J* 7.0 and 5.4 Hz), and 7.22–7.34 (5 H, m); δ(^{13}C, $CDCl_3$) 20.39 (q), 20.45 (q), 21.88 (q), 38.95 (t), 67.85 (t), 69.27 (d), 71.88 (d), 72.82 (t), 113.7 (t), 127.4, 128.0 (d), 137.4 (s), 140.3 (s), 169.6 (s), and 169.7 (s); *m/z* (CI, NH_3) 338 (M + NH_4^+) and 321 (M + H^+).

Oct-7-en-2-yn-1-ol.—Lithium wire (4.83 g, 0.696 mol, 2% sodium) was added to a solution of iron(II) nitrate (*ca.* 1 g) in liquid ammonia (400 ml). The reaction was stirred until the blue colour dissipated and then for a further 30 min. A solution of prop-2-yn-1-ol (78.34 ml, 17.74 g, 0.316 mol) in THF (30 ml) was then added over 30 min and the resultant solution was stirred for 2 h. A solution of 5-bromopent-1-ene (25 ml; 31.45 g, 0.211 mol) in THF (25 ml) was then added and stirring was continued

for 2.5 h. Saturated aqueous ammonium chloride (150 ml) was then cautiously added followed by ether (100 ml) and the resultant mixture was allowed to warm to room temperature overnight. The organic phase was separated, and the product extracted with ether (2 × 100 ml). The combined extracts were dried ($MgSO_4$), filtered, and the solvent removed at atmospheric pressure through a Vigreux column. The residue was distilled through a 6-in fractionation column to give oct-7-en-2-yn-1-ol (**8**) (21.02 g, 0.169 mol; 80%) as a colourless oil, b.p. 80–84 °C (1.0 mmHg); ν_{max}(film) 3 340, 3 090, 3 000, 2 950, 2 860, 2 300, 2 240, 1 650, 1 460, 1 435, 1 420, 1 355, 1 330, 1 230, 1 140, 1 020, and 920 cm^{-1}; δ(^1H, $CDCl_3$) 1.61 (2 H, quintet, *J* 7.3 Hz), 2.10–2.39 (5 H, m), 4.25 (2 H, t, *J* 2.1 Hz), 4.95–5.10 (2 H, m), and 5.71–5.87 (1 H, m); δ(^{13}C, $CDCl_3$), 18.20 (t), 27.91 (t), 32.85 (t), 50.85 (t), 78.90 (d), 85.60 (d), 115.2 (t), and 137.9 (d); *m/z* (CI, NH_3) 142 ($M + NH^+$) and 125 ($M + H^+$), no parent ion observed with EI.

(Z)-*Octa*-2,7-*dien*-1-*ol* (**9**).—To a solution of oct-7-en-2-yn-1-ol (**8**) (9.46 g, 76.3 mmol) in methanol (10 ml) was added Lindlar catalyst (200 mg). Hydrogen was bubbled through the stirred solution and the reaction was followed by capillary gas chromatography. After 24 h the product consisted of 36% starting material and 64% of the desired product. After a further 16 h, no starting material was present, and the major product was contaminated with 5% of another compound, probably an over-reduced by-product [tentatively characterised by a signal at δ 3.63 (t, *J* 6.5 Hz), characteristic of alkan-1-ols]. The reaction mixture was filtered and methanol removed through a fractionation column. The residue was distilled to give (*Z*)-octa-2,7-dien-1-ol (**9**) (8.95 g, 71 mmol; 93%) as a colourless oil, b.p. 94–96 °C (20 mmHg); ν_{max}(film) 3 320, 3 080, 3 010, 2 980, 2 920, 2 860, 1 655, 1 640, 1 450, 1 435, 1 410, 1 340, 1 310, 1 210, 1 030, 980, 910, and 830 cm^{-1}; δ(^1H, $CDCl_3$) 1.46 (2 H, quintet, *J* 7.3 Hz), 2.01–2.11 (4 H, m), 3.14 (1 H, br s, removed by D_2O shake), 4.15 (2 H, d, *J* 5.9 Hz), 4.93–5.04 (2 H, m), 5.43–5.63 (2 H, m), and 5.71–5.87 (1 H, m); δ(^{13}C, $CDCl_3$) 26.84 (t), 28.82 (t), 33.26 (t), 58.26 (t), 114.7 (t), 129.1 (d), 132.0 (d), 132.0 (d), and 138.5 (d); *m/z* (CI, NH_3) 144 ($M + NH_4^+$) and 126 (M^+) (Found: C, 75.95; H, 11.4. $C_8H_{14}O$ requires C, 76.14; H, 11.18%)

syn-2(S), 3(R)-*Epoxyoct*-7-*en*-1-*ol* (**10**).—Dichloromethane (150 ml) was added using a cannula to activated 4 Å molecular sieves (10 g) under an argon atmosphere. The flask was cooled to −20 °C and titanium tetraisopropoxide (18.9 ml, 18.0 g, 63.5 mmol) was added using a syringe. The solution was then stirred vigorously and (+)-diethyl tartrate (13.1 ml; 15.7 g, 76.2 mmol) was added using a syringe. After 10 min, (*Z*)-octa-2,7-dien-1-ol (**9**) (8.16 g, 64.8 mmol) was added and the solution stirred for a further 10 min. Finally, t-butyl hydroperoxide (4.74M solution in CH_2Cl_2; 0.130 mmol, 27.4 ml) was added by syringe over 10 min. The reaction was transferred to a thermostatic cold bath at −20 °C, allowed to stand for 6 days, and was then allowed to reach 0 °C over 15 min; it was then decanted into a solution of iron(II) sulphate (32.5 g) and tartaric acid (13.0 g) in distilled water (130 ml) at 10 °C (cooled by an ice–water bath). The molecular sieves were washed with dichloromethane (2 × 10 ml) and the washings added to the rest of the reaction mixture. The mildly exothermic reaction which ensued was monitored using a thermometer and after the temperature had begun to fall the cooling bath was removed and the mixture was stirred at room temperature for 30 min. The organic layer was separated, the aqueous phase extracted with ether (2 × 100 ml), and the combined extracts were evaporated. Ether (50 ml) was added and the solution cooled to 0–5 °C. A precooled solution of sodium hydroxide (6 g) in saturated brine (130 ml) was added and vigorous stirring continued at *ca.* 3 °C for 1 h. The aqueous phase was separated and extracted with ether (2 × 100 ml), and the combined organic extracts were dried (magnesium sulphate), filtered, and the solvent removed under reduced pressure. The residue was distilled through a fractionation column into an ice-cooled receiver to give a white solid which melted on warming to room temperature to give *syn*-2(S), 3(*R*)-epoxyoct-7-en-1-ol (**10**) (7.15 g, 50.4 mmol; 78%) as a colourless oil, b.p. 82–85 °C (0.5 mmHg); $[\alpha]_D^{16} = -3.51$, (*c* = 3.45 in $CHCl_3$); ν_{max}(film), 3 380, 3 080, 2 970, 2 860, 1 640, 1 460, 1 415, 1 270, 1 230, 1 200, 1 140, 1 040, 1 000, 910, 855, 840, 825, 760, and 700 cm^{-1}; δ(^1H, $CDCl_3$) 1.50–1.73 (4 H, m), 2.07–2.16 (2 H, m), 2.80 (1 H, br s, peak removed by D_2O shake), 3.00–3.10 (1 H, m), 3.16 (1 H, dt, *J* 6.9 and 4.2 Hz), 3.64 (1 H, dd, *J* 7.0 and 12.1 Hz), 3.84 (1 H, dd, *J* 12.1 and 3.90 Hz), 4.94–5.07 (2 H, m), and 5.72–5.88 (1 H, m); δ(^{13}C, $CDCl_3$) 25.85 (t), 27.35 (t), 33.34 (t), 57.09 (d), 57.13 (d), 60.81 (t), 115.0 (t), and 138.1 (d); *m/z* (CI, NH_3) 160 ($M + NH_4^+$) and 142 (M^+) (Found: C, 67.2; H, 10.05. $C_8H_{14}O_2$ requires C, 67.57; H, 9.93%). ^1H NMR spectroscopy of the product showed that little (<5%) Payne rearranged epoxide was present. The enantiomeric excess was found to be ⩾94% by lanthanide shift studies on the acetate using Eu(hfc)$_3$.

Nucleophilic Trapping of Epoxy Alcohol (**10**) *using* $(MeLi)_{1.2}CuCN$ *and Lithium Chloride*.—To a solution of the epoxy alcohol (**10**) (2.0 g, 14.08 mmol) in THF (20 ml) containing lithium chloride (3.6 g, 85.7 mmol) at −78 °C under an argon atmosphere was added dropwise, butyl-lithium (1.47M solution in hexane; 14.08 mmol, 9.58 ml) over 5 min. The resulting solution was stirred for 5 min at −78 °C and warmed to 0 °C. After a further 10 min a solution of the cuprate generated from copper(I) cyanide (4.14 g, 46.5 mmol) and methyl-lithium (1.4M solution in ether; 55.8 mmol, 39.9 ml) at 0 °C in THF (20 ml) was added using a cannula to the alkoxide and after a further 30 min the resulting mixture was allowed to reach room temperature. The reaction was stirred for 4 days after which time saturated aqueous ammonium chloride (20 ml) was cautiously added followed by ether (50 ml). The organic layer was separated, the aqueous phase extracted with ether (2 × 30 ml), and the combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a mixture of essentially two diols, (**11**) and (**12**) (2.02 g, 12.8 mmol, 91%) as shown by capillary gas chromatography analysis [(**11**), 68.5%, (**12**), 31.5%]. The two products were separated by flash-column chromatography on silica gel. The major fraction was identified as the desired product (**13**), a colourless oil, $[\alpha]_D^{20} =$ 20.0, (*c* 1.22 in $CHCl_3$); ν_{max}(film) 3 380, 3 080, 2 940, 2 860, 1 640, 1 460, 1 440, 1 415, 1 380, 1 320, 1 260, 1 130, 1 070, 1 040, 1 000, 970, 910, and 830 cm^{-1}; δ(^1H, $CDCl_3$) 0.97 (3 H, t, *J* 7.4 Hz), 1.35–1.70 (6 H, m), 2.00–2.20 (2 H, m), 2.65 (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); δ(^{13}C, $CDCl_3$) 10.08 (q), 25.00 (t), 26.29 (t), 32.88 (t), 33.74 (t), 73.91 (d), 75.84 (d), 114.7 (t), and 138.7 (d); *m/z* (CI, NH_3) 176 ($M + NH_4^+$) and 159 ($M + H^+$), no parent ion observed with EI.

Nucleophilic Trapping of the Epoxy Alcohol (**10**) *Using Lithium Methyl(cyano)cuprate and Lithium Chloride*.—To solution of alkoxide generated as above from the epoxy alcohol (**10**) (0.50 g, 3.52 mmol) and butyl-lithium (1.56M solution in hexane; 3.52 mmol, 2.26 ml) in THF (10 ml) containing lithium chloride (0.90 g, 21.4 mmol) was added a solution of lithium methyl(cyano) cuprate generated from copper(I) cyanide (0.63 g, 7.04 mmol) and methyl-lithium (7.04 mmol, 5.03 ml of a 1.4M solution in ether) in THF (5 ml) at 0 °C. After 5 min the reaction was allowed to warm to room temperature and stirred for 16 h. Saturated aqueous ammonium chloride (5 ml) and ether (20 ml) were then added and the organic layer was separated. The aqueous phase was extracted with ether (2 × 20 ml), and the combined extracts were dried ($MgSO_4$), filtered, and solvent

removed under reduced pressure. The products were identified by comparison of the ^1H NMR spectrum of the crude reaction mixture with those of pure products isolated from nucleophilic trapping reactions using $(MeLi)_{1.2}CuCN$ (*vide supra*) and methyl-lithium. In this case, 60% reaction was observed and <5% of the undesired regioisomers formed. In very similar experiments the reaction mixture was stirred for 48 h at 25 °C before work-up resulting in a slightly greater extent of reaction (*ca.* 70%). Further, when the alkoxide was stirred for 24 h at room temperature prior to addition of the cuprate little difference was made to the selectivity or extent of the reaction. The use of a larger excess of cuprate reagent also did not greatly affect the selectivity (<10% unwanted regioisomers) or the extent of the reaction (maximum *ca.* 80%). When the reaction was carried out at 10 °C rather than room temperature then again little effect on the selectivity or extent of reaction was observed. Finally, the use of a large excess (6 equiv.) of MeCuCNLi and prolonged reaction times (4–6 days) also did not significantly improve the selectivity or extent of reaction.

It proved impossible to separate the starting material from the desired diol by chromatography on silica gel or alumina, or by distillation; however the undesired regioisomers were readily removed by chromatography on silica gel (ether–light petroleum, 1:3). For this reason the crude product mixture was used without purification in the next step of the synthesis.

Preparation of (+)-exo-*Brevicomin* (**7**).—A suspension of $CuCl_2 \cdot 2H_2O$ (1.14 g, 6.73 mmol) and $PdCl_2$ (75 mg) in THF (2 ml) was stirred for 90 min at room temperature. A solution of the crude product mixture [0.53 g, *ca.* 3.35 mmol, from the epoxy alcohol (**10**) (0.52 g, 3.66 mmol)] from the above reaction in THF (3 ml) was then added and the resulting mixture was stirred for 16 h. Water (3 ml) was added and the product extracted with ether (2 × 25 ml), and the combined extracts were allowed to stand overnight. The aqueous residue was acidified using 1M hydrochloric acid (1 ml) and stirred overnight after which time it was extracted with ether (2 × 20 ml). The extracts were combined and washed with saturated brine (5 ml), dried ($MgSO_4$), and filtered. The solvent was removed through a fractionation column at atmospheric pressure, and the residue purified by flash-column chromatography on silica gel (pentane eluant). The fractions containing the desired product were identified by capillary gas chromatography. Solvent was removed through a fractionation column and the residue distilled (Kugelrohr) to give (+)-*exo*-brevicomin (**7**) [0.18 g, 1.34 mmol, 31% overall from the epoxy alcohol (**10**)] as a colourless oil, b.p. 90–110 °C (100 mmHg); $([\alpha]_D^{18} = 67.5°$, *c* 1.05 in ether; $[\alpha]_D^{18} = 65.1°$, *c* 0.756 in $CHCl_3$). The purity of the product was >98% by capillary gas chromatography; ν_{max}(film) 2 940, 2 880, 2 850, 1 460, 1 380, 1 350, 1 330, 1 300, 1 270, 1 260, 1 240, 1 200, 1 175, 1 140, 1 105, 1 080, 1 070, 1 050, 1 030, 1 015, 1 005, 990, 970, 930, 900, 880, 855, 845, 790, and 770 cm^{-1}; $\delta(^1H, CCl_4)$ 0.88 (3 H, t, *J* 7.4 Hz), 1.31 (3 H, s), 1.33–1.92 (8 H, m), 3.79 (1 H, t, *J* 6.4 Hz), and 3.99 (1 H, s); $\delta(^{13}C, CCl_4)$ 9.71 (q), 17.20 (t), 24.93 (q), 27.91 (t), 28.41 (t), 34.88 (t), 77.60 (d), 80.54 (d), and 107.1 (s); *m/z* (EI) (Found: 156.1146; Calc. for $C_9H_{16}O_2$, 156.1150).

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