Stereocontrol with phosphine oxides: synthesis of optically active cyclopropyl ketones

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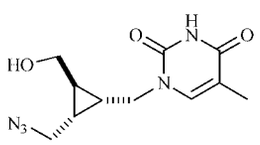
Treatment of β-keto γ′-hydroxy phosphine oxides, or silylated hemiacetal derivatives of these compounds, with potassium *tert*-butoxide in *tert*-butyl alcohol leads to the formation of cyclopropyl ketones. The synthesis of optically active 1,2-di- and 1,2,3-trisubstituted cyclopropyl ketones is described. The reaction is kinetically controlled and the ring-closure is generally stereospecific. A model is described to explain the stereochemical course of the reaction.

Introduction

Cyclopropanes are an interesting structural feature of many biologically active molecules.[1] For example, cyclopropyl nucleoside analogues[2] like **1** have potential antiviral activity, and



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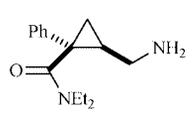

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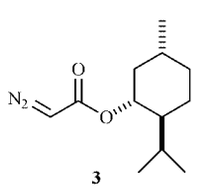

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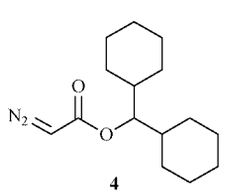

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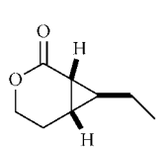

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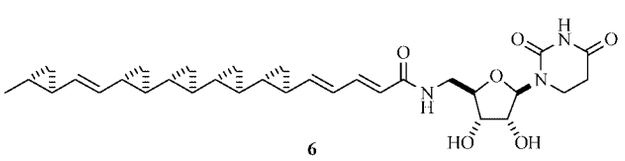

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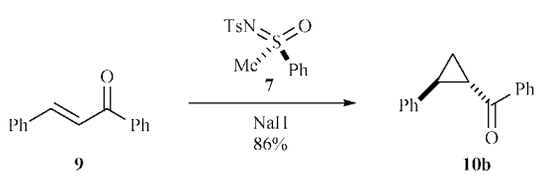
cyclopropyl amide **2** is an NMDA (*N*-methyl D-aspartic acid) receptor agonist.[3] Conformationally restricted cyclopropyl amino acids[4] have valuable properties when incorporated into peptides, and have been the subject of a recent review.[5]

Optically active di- and trisubstituted cyclopropyl esters† are most usually synthesised by the metal-catalysed addition of carbene equivalents to alkenes in the presence of chiral ligands,[7] but good enantioselectivities are usually accompanied by poor diastereoselectivities[8] unless very bulky diazoacetates (*e.g.* **3** and **4**) are used.[9] Other workers[10] have circumvented these problems by studying certain intramolecular cyclopropanations which generally give *exo* products (such as **5**). Asymmetric versions of the Simmons–Smith cyclopropanation reaction (using chiral auxiliaries and chiral reagents) have been developed[11] and several of these methods have been exploited in work[12] leading to the total synthesis[13] of FR-900848 (**6**).[14]

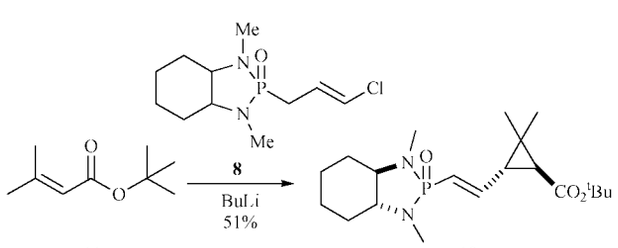
Homochiral nucleophiles have been used as chiral auxiliaries in the synthesis of cyclopropanes. In 1971, Johnson added the anion of sulfoximine **7** to chalcone and obtained an 84% yield of cyclopropyl ketone **10b** with "49% optical purity" and complete diastereoselectivity (Scheme 1).[15] More recently,



9 **7** **10b**

Scheme 1

Hanessian has synthesised a wide variety of tri- and tetrasubstituted cyclopropyl carbonyl compounds (*e.g.* **12**) using the anion of chiral chloroallyl phosphonamide **8** (Scheme 2).[16]



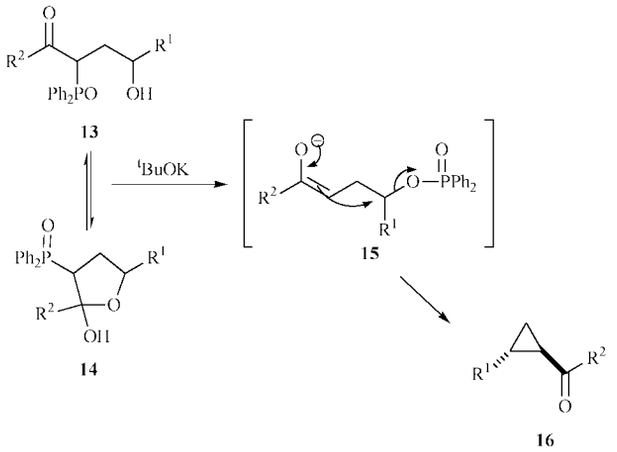
11 **8** **12**

Scheme 2

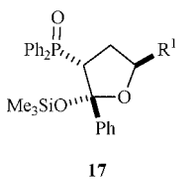
Previously, we discovered that treatment of hydroxyketones **13** with potassium *tert*-butoxide in *tert*-butyl alcohol initiated a remarkable cascade of events leading to the formation of cyclopropyl ketones **16**.[17] We believe that rearrangement of the hydroxyketones **13** by phosphinoyl transfer was followed by ring-closure of the enolates **15** to give cyclopropyl ketones **16** (Scheme 3). The reaction was successful with a variety of substituents and the yields and stereoselectivities observed were generally excellent. Others have observed similar reactions with diphenylphosphinoyl enamines[18] and other phosphorus-stabilised anions[19] and ylides.[20]

The silyl ethers[21] **17** are protected versions of the hydroxyketones **13**. In this paper we describe the synthesis of optically active cyclopropyl ketones (such as **16**) from the silyl ethers **17**. The stereochemical course of the reaction is discussed in detail.

† For use of cyclopropyl esters as intermediates in natural product synthesis, see ref. 6.



Scheme 3



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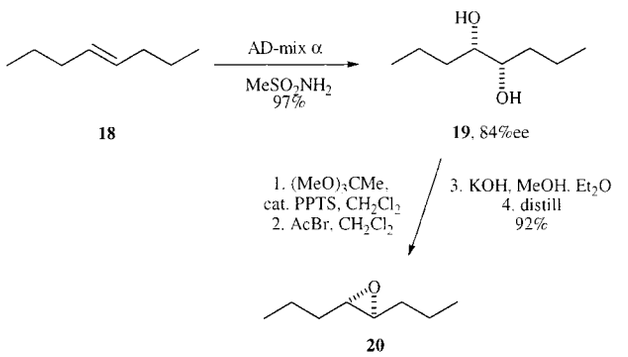
Synthesis of the starting materials

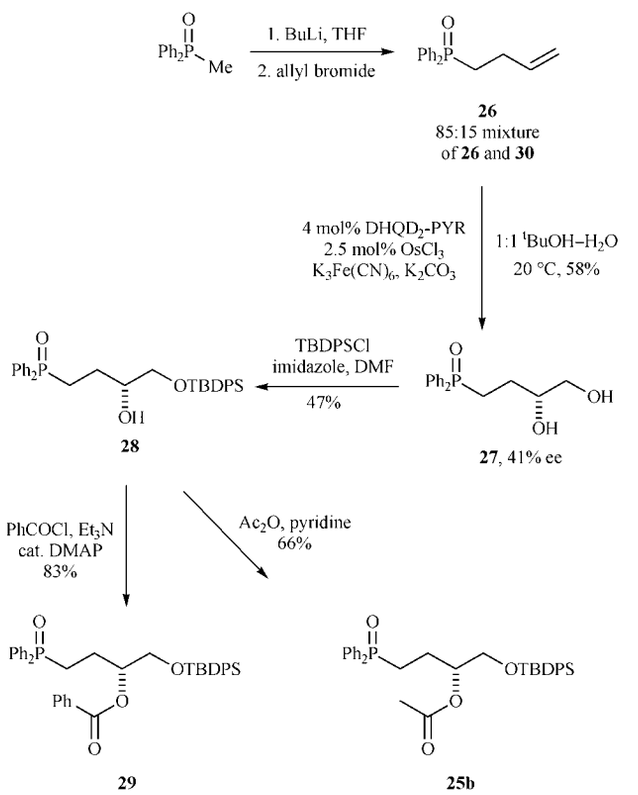
The optically active epoxide **20** was synthesised using methodology introduced by Sharpless (Scheme 4). Dihydroxylation[22] of the alkene **18** with AD-mix α (in the presence of methanesulfonamide) gave the diol **19** in 97% yield and 84% ee, which



Scheme 4

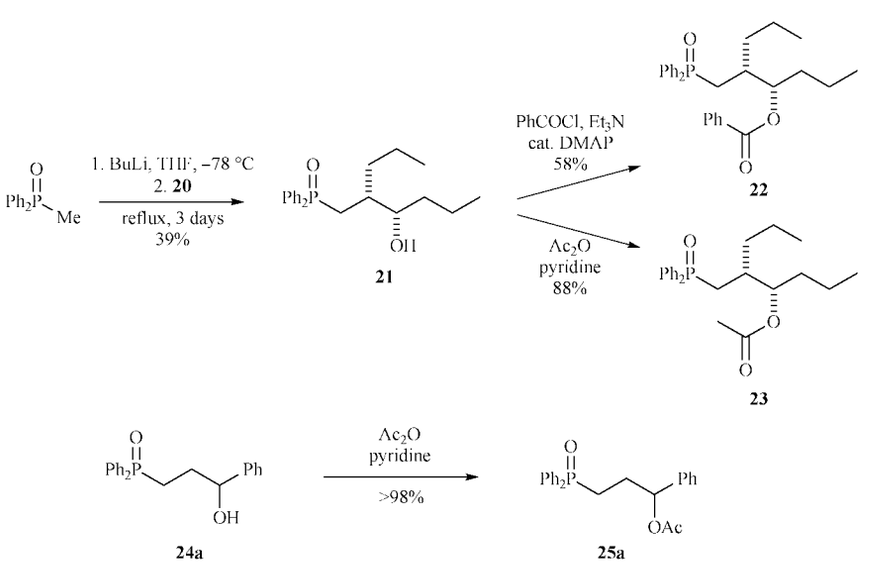
was converted into the epoxide **20**.[23] The epoxide **20** was opened with the lithium derivative of methyldiphenylphosphine oxide; the reaction was rather sluggish and gave the diphenylphosphinoyl alcohol **21** in only 39% yield after refluxing for 3 days in THF (Scheme 5). The diphenylphosphinoyl alcohols[24] **21** and **24** were converted into the benzoate **22** and the acetates **23** and **25** using standard methods.

The homoallylic phosphine oxide **26**, synthesised by allylation of methyldiphenylphosphine oxide, was converted into the diphenylphosphinoyl diol **27** by asymmetric dihydroxylation (Scheme 6).‡ The low enantiomeric excess (41% ee) of **27** compared with that of the diol[25] **31** (>95% ee) reflects the fact that **26** lacks an alkene substituent which can fit neatly into the

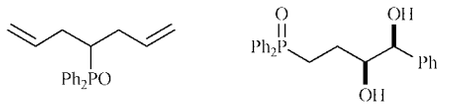


Scheme 6

‡ The dimeric ligand $DHQD_2$-PYR has been recommended for the asymmetric dihydroxylation of terminal alkenes (ref. 22).



Scheme 5

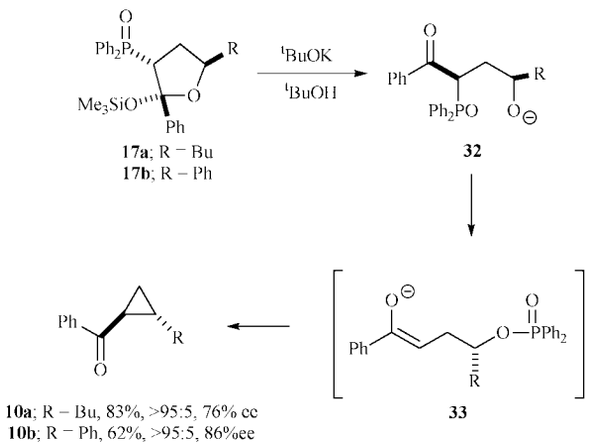


30 **31**

chiral pocket formed by the $DHQD_2$-PYR ligand.[26] The primary alcohol of **27** was protected as a TBDPS ether (→**28**) and the remaining alcohol was acylated under standard conditions.

Synthesis of optically active disubstituted cyclopropyl ketones

Treatment of silyl ethers **17** with *tert*-butoxide in *tert*-butyl alcohol triggered the formation of the cyclopropyl ketones **10** in good yield (Scheme 7).[21],§ We propose that desilylation and



17a; R = Bu
17b; R = Ph

32

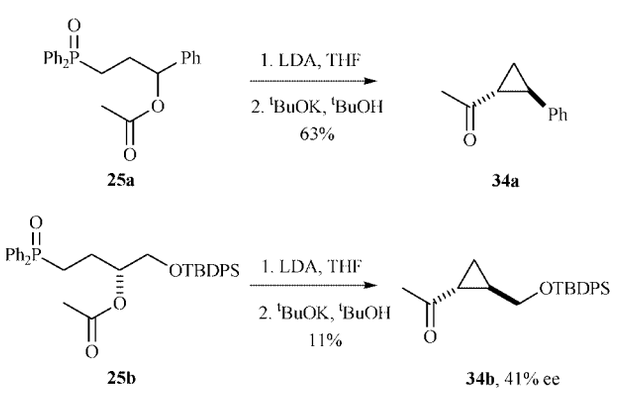
10a; R = Bu, 83%, >95:5, 76% ee
10b; R = Ph, 62%, >95:5, 86%ee

33

Scheme 7

ring-opening (**17**→**32**) is followed by the sequence of events outlined earlier: alkoxy ketones **32** rearrange (by transfer of the phosphorus acyl group from carbon to oxygen) to enolates **33** which cyclise to give the optically active cyclopropyl ketones **10** in good yield.

The study was extended to the intramolecular acylation reactions of diphenylphosphinoyl acetates **25**, molecules which can potentially enolise (Scheme 8). The acetates **25** were treated



25a **34a**

25b **34b**, 41% ee

Scheme 8

with two equivalents of LDA at −78 °C. The chlorotrimethylsilane trap was omitted because we did not want to isolate either silyl enol ethers or acyl transfer products (such as **17**). The crude reaction mixtures were treated with potassium *tert*-butoxide in *tert*-butyl alcohol and the cyclopropyl ketones **34** were isolated. We have previously synthesised racemic enolisable cyclopropyl ketones in a similar way.[17]

§ The cyclopropyl ketone *trans*-**10b** epimerised to a 67:33 mixture of *trans*- and *cis*-**10b** on standing in $CDCl_3$ for three weeks.

Table 1 Attempted epimerisation of the cyclopropyl ketone *trans*-**10b**

Entry	Conditions	Product **10b** ratio *trans*:*cis*
1	*p*-TsOH, $CHCl_3$	54:46
2	^{t}BuOK (10 eq.), ^{t}BuOH	>98:2

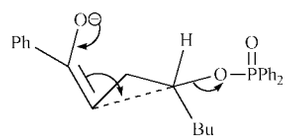
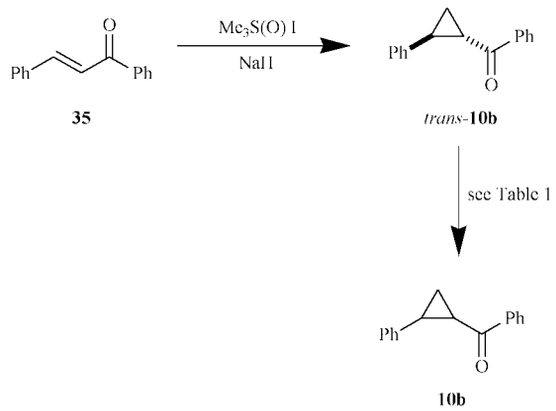


Fig. 1

Probing the stereochemical course of the formation of cyclopropyl ketones

At this stage of the investigation, an important question remained unanswered: was the formation of cyclopropyl ketones under thermodynamic or kinetic control? Scheme 9 and



35

trans-**10b**

see Table 1

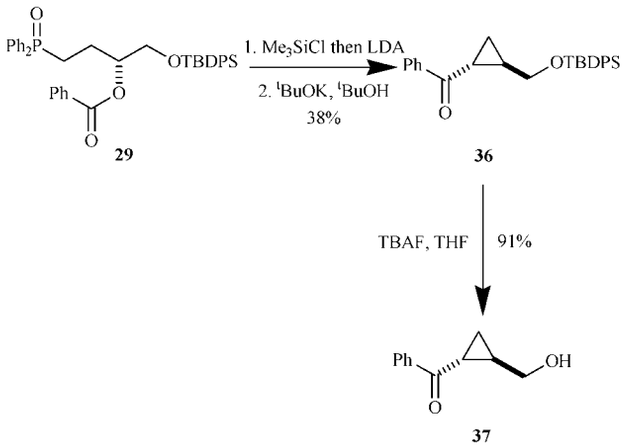
10b

Scheme 9

Table 1 describe some experiments which were designed to probe this question. We synthesised a diastereomerically pure sample of racemic **10b** using a method reported by Corey.[27] Cyclopropyl ketone **10b** was then subjected to conditions which might reasonably have led to its epimerisation.¶ After stirring for 2 weeks with one equivalent of toluene-*p*-sulfonic acid, **10b** was isolated as an equilibrium (54:46) mixture of *trans* and *cis* isomers. In contrast, **10b** was recovered unchanged after stirring for 6 hours at 50 °C with ten equivalents of potassium *tert*-butoxide, conditions which were considerably harsher than those used to synthesise optically active **10b** from **17b**. Taken together, these results indicate that the cyclisations **17**→**10** must be kinetically controlled; under the conditions of the cyclisation, enolisation of **10b** is clearly not possible. The cyclisations of enolates **33** are stereoselective because the two substituents prefer to be *trans* on the forming three-membered ring (Fig. 1). Favourable intramolecular displacement reactions of enolates which lead to the formation of cyclopropyl ketones are well known to proceed with high levels of diastereoselectivity.[16,29]

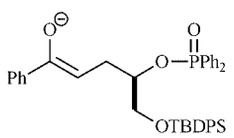
The stereospecificity of the formation of the cyclopropyl ketones was studied in two different ways. The optically active benzoate **29** was derived from the diol **27** which had 41% ee. Intramolecular acylation of the diphenylphosphinoyl benzoate **29** was followed by conversion into the cyclopropyl ketone **36** (Scheme 10). The silyl ether **36** was converted into the alcohol **37** whose enantiomeric excess was determined to be 43% ee by Mosher's method.[30] Within the limits of experimental error, the

¶ The epimerisation of similar cyclopropyl ketones has previously been studied (ref. 28).



29 36 37

Scheme 10



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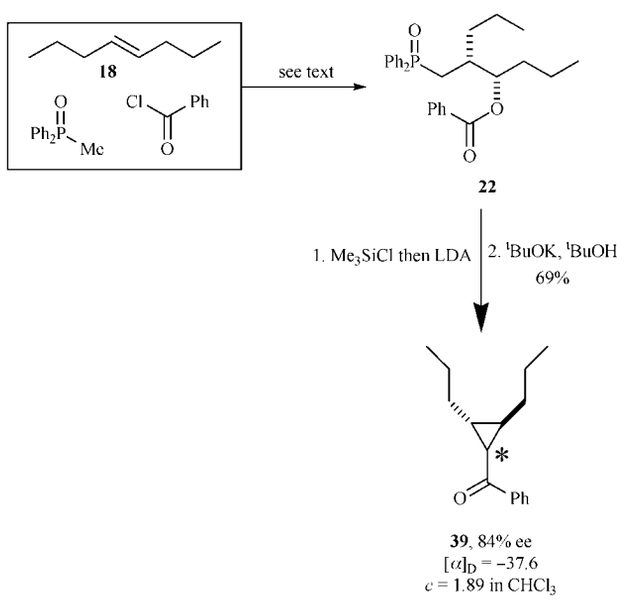
enantiomeric excess of the cyclopropyl ketone **37** was the same as its precursor (**27**), implying that the cyclisation **38**→**36** proceeded with strict inversion of configuration.

In a similar manner, the diphenylphosphinoyl benzoate **22** was transformed into the corresponding cyclopropyl ketone (Scheme 11). The product of the reaction was certainly the



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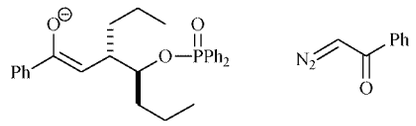
Scheme 11

diastereoisomer **39**; this is the only chiral diastereoisomer (an $[\alpha]_D^{20}$ of −37.6 was measured) and the only diastereoisomer with diastereotopic methyl groups. During the course of the cyclisation, the issue of stereo*selectivity* does not arise because no new stereogenic centres are formed.‖ The cyclisation of the enolate **40** is therefore a particularly interesting test of stereo*specificity* since the isolation of more than one diastereoisomer would certainly mean that the intramolecular S_N2 reaction of **40** did not proceed with strict inversion of configuration.

‖ The carbon marked with an asterisk in **39** is, according to Mislow,[31] chirotopic (it is in a chiral environment) but not stereogenic.



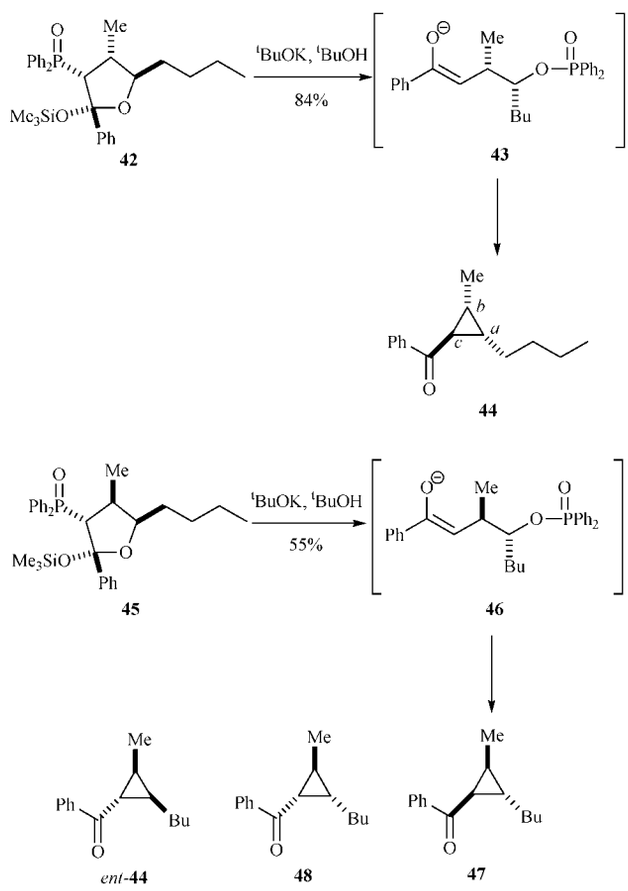
40 41

We only isolated one diastereoisomer. The cyclisation was stereospecific.

The benzoate **22** was synthesised from the reagents in the box (Scheme 11). The geometry of the alkene **18** is retained in the cyclopropyl ketone **39** (the propyl groups are *trans* on the cyclopropyl ring) because there are *four* inversions in the reaction sequence: two during the synthesis of the epoxide **20** (Scheme 4),[23] another when the epoxide is opened (**20**→**21**, Scheme 5) and a fourth when the cyclopropane ring is formed. One stereogenic centre is inverted three times (stereochemically equivalent to one inversion) and the other just once. The enantiomeric excess, introduced by Sharpless AD reaction, remains because there are no achiral intermediates. Moreover, the combination of methyldiphenylphosphine oxide and benzoyl chloride is an interesting alternative to the diazoketone **41**.

Synthesis of trisubstituted cyclopropyl ketones

Our method is particularly well suited to the synthesis of optically active cyclopropyl ketones with a chiral centre at each corner of the three-membered ring; treatment of the silyl ether[21] **42** with potassium *tert*-butoxide gave cyclopropyl ketone **44** as a 94 : 6 mixture of diastereomers in 84% yield (Scheme 12). This is



42 43 44 45 46 ent-44 48 47

Scheme 12

a result of the highly stereoselective cyclisation of enolate **43** in which both alkyl groups are *trans* to the forming phenyl ketone (Fig. 2). This favourable cyclisation is not available to **46**, and therefore the reaction of silyl ether **45** was much less selective: a

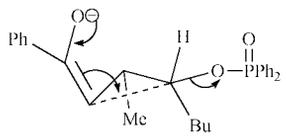


Fig. 2

62 : 27 : 11 mixture of cyclopropyl ketones **47**, **48** and *ent*-**44** was obtained in a relatively poor 55% yield. In this case, we believe that the loss of stereospecificity stems from a competing S_N1 mechanism. Other reactions suffer loss of stereospecificity when cyclisation is unfavourable;[32] some of these results may be explained by neighbouring group participation which is competitive with cyclisation. The synthesis of cyclopropyl ketone **44** is particularly interesting because the formation of each stereogenic centre is controlled by a different factor: centre (a) is controlled by the inversion of a displacement reaction (**43**→**44**), centre (b) is already present in the silyl ether **42** and centre (c) is determined by which face of the enolate reacts.

Summary

β-Keto γ′-hydroxy phosphine oxides **13**, and related silylated derivatives **17**, **42** and **45**, can be transformed into cyclopropyl ketones by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol. The stereochemical course of this transformation has been determined in detail and the method has been applied to the synthesis of optically active 1,2-di- and 1,2,3-trisubstituted cyclopropyl ketones. Optically active cyclopropyl carbonyl compounds have also been synthesised using asymmetric metal-catalysed cyclopropanations with chiral ligands[7,8,10,11] and using a phosphonamide chiral auxiliary.[16] Our reaction sequence combines the best features of these two approaches: a catalytic asymmetric method, the Sharpless AD reaction, was used to induce asymmetry and the formation of the cyclopropane ring was highly diastereoselective because the ring-closure involved anionic chemistry.[16,29]

Experimental

General methods have been described previously.[21b]

(4*R*,5*R*)-Octane-4,5-diol 19

By the method described by Sharpless,[22] (*E*)-oct-4-ene (5.56 cm^3, 35.7 mmol), AD-mix α (50 g) and methanesulfonamide (3.39 g, 35.7 mmol) gave a crude product after mechanical stirring for 16 h. Flash chromatography, eluting with 1 : 1 hexane–ether, gave the diol[33] **19** (5.02 g, 97%) as a liquid, $[a]_D^{20}$ −23.9 (*c* 1.34 in $CHCl_3$) (lit.[33] +32.2, *c* 2.3 in EtOH) (Found: M^+, 146.1308. $C_8H_{18}O_2$ requires *M*, 146.1307); ν_{max}/cm^{-1}(neat) 3362 (OH); δ_H (400 MHz; $CDCl_3$) 3.34 (2 H, m, C*H*OH), 3.08 (2 H, m, OH), 1.5–1.3 (8 H, m) and 0.89 (6 H, t, *J* 7.1, 2 Me); δ_C (50 MHz; $CDCl_3$) 74.2$^+$ (CHOH), 35.6$^-$, 18.8$^-$ and 14.0$^+$ (Me); *m*/*z* 146.1 (10%, M^+), 103.1 (60, M^+ − Pr) and 73.1 (100, CHOHPr). Integration of the 500 MHz ^1H NMR spectrum of the Mosher's diesters of this material showed it to have 84% ee.

(4*R*,5*R*)-4,5-Epoxyoctane 20

By the method described by Sharpless,[23] trimethyl orthoacetate (4.20 cm^3, 32.9 mmol), (4*R*,5*R*)-octane-4,5-diol **19** (4.20 g, 28.7 mmol), pyridinium toluene-*p*-sulfonate (71 mg, 0.29 mmol), acetyl bromide (2.47 cm^3, 33.3 mmol) and potassium carbonate (6.76 g, 48.7 mmol) gave a crude product which was washed with water (3 × 100 cm^3) to give the epoxide[34] **20** (3.38 g, 92%) as a liquid. $[a]_D^{20}$ −24.9 (*c* 1.70 in ether; 84% ee) (Found: MH^+, 129.1277. $C_8H_{16}O$ requires MH, 129.1279); ν_{max}/cm^{-1} ($CHCl_3$) no characteristic peaks; δ_H (400 MHz; $CDCl_3$) 2.65 (2 H, t, *J* 4.7, C*H*O), 1.6–1.4 (8 H, m) and 0.95 (6 H, t, *J* 6.9, 2 Me); δ_C (50 MHz; $CDCl_3$) 58.7$^+$ (CHO), 34.2$^-$, 19.3$^-$ and 13.9$^+$ (Me); *m*/*z* 129.1 (10%, MH^+).

(2*S*,3*R*)-1-Diphenylphosphinoyl-2-propylhexan-3-ol 21

n-Butyllithium (15 cm^3 of a 1.6 mol dm^{-3} solution in hexanes, 24.0 mmol) was added dropwise to methyldiphenylphosphine oxide (4.21 g, 19.5 mmol) in dry THF (100 cm^3) at 0 °C. After 15 min, (4*R*,5*R*)-4,5-epoxyoctane **20** (2.5 g, 19.5 mmol) was added dropwise, and the reaction was stirred for a further 4 h at 20 °C, refluxed for 3 days, quenched with saturated ammonium chloride solution (100 cm^3), extracted with dichloromethane (3 × 100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product, which was purified by flash chromatography, eluting with 2% methanol in EtOAc, to give the *alcohol* **21** (2.66 g, 39%) as an oil, R_f 0.50 (EtOAc); $[a]_D^{20}$ +8.3 (*c* 1.55 in $CHCl_3$; 84% ee) (Found: M^+, 344.1913. $C_{21}H_{29}O_2P$ requires *M*, 344.1905); ν_{max}/cm^{-1} ($CHCl_3$) 3325 (br, OH), 1438 (P–Ph) and 1160 (P=O); δ_H (400 MHz; $CDCl_3$) 7.8–7.7 (4 H, m), 7.55–7.4 (6 H, m, Ph_2PO), 4.54 (1 H, d, *J* 8.1, OH), 3.62 (1 H, m, C*H*OH), 2.41 (1 H, dt, *J* 9.9 and 15.3, PCH_AH_B), 2.21 (1 H, ddd, *J* 3.3, 9.1 and $^2J_{PH}$ 15.4, PCH_AH_B), 1.95 (1 H, m), 1.54–1.1 (8 H, m), 0.90 (3 H, t, *J* 6.9, Me) and 0.76 (3 H, t, *J* 7.2, Me); δ_C (100 MHz; $CDCl_3$) 134–128.5 (m, Ph_2PO), 73.0$^+$ (d, $^3J_{PC}$ 2.4, CHOH), 39.9$^+$ (d, $^2J_{PC}$ 3.7, PCH_2CH), 36–34 (m), 30.3$^-$ (d, $^1J_{PC}$ 69.4, PCH_2), 21–19 (m), 14.2$^+$ (Me) and 14.0$^+$ (Me); *m*/*z* 344.1 (1%, M^+), 301.1 (75, M^+ − Pr) and 202.1 (100, Ph_2POH).

4-Diphenylphosphinoylbut-1-ene 26

By the same general method, *n*-butyllithium (47.0 cm^3 of a 1.3 mol dm^{-3} solution in hexane, 61.1 mmol), methyldiphenylphosphine oxide (12.0 g, 55.6 mmol) and allyl bromide (5.4 cm^3, 61.1 mmol) with lithiation at −78 °C and stirring for 2 h gave a crude product which was purified by flash chromatography, eluting with 2% methanol in EtOAc, gave the *homoallylic phosphine oxide* **26** (487 mg, 63%, 85 : 15 mixture of *mono* and *bis* allylated products) as an oil; R_f 0.30 (EtOAc) (Found: M^+, 256.1017. $C_{16}H_{17}OP$ requires *M*, 256.1017); ν_{max}/cm^{-1} ($CHCl_3$) 1640 (C=C), 1438 (P–Ph) and 1170 (P=O); δ_H (400 MHz; $CDCl_3$) 7.73–7.65 (4 H, m), 7.5–7.35 (6 H, m, Ph_2PO), 5.76 (1 H, m, C*H*=CH_2), 4.97 (1 H, dd, *J* 1.0 and 16.9, CH=CH_AH_B), 4.92 (1 H, dd, *J* 1.0 and 10.1, CH=CH_AH_B) and 2.62–2.38 (4 H, m); δ_C (100 MHz; $CDCl_3$) 137.4$^+$ (d, $^3J_{PC}$ 15.7, C*H*=CH_2), 133–128 (m, Ph_2PO), 115.2 (CH=CH_2), 29.0$^-$ (d, $^1J_{PC}$ 70.6, PCH_2) and 25.5$^-$ (d, $^2J_{PC}$ 2.5); *m*/*z* 256.1 (70%, M^+), 202.1 (100, Ph_2POH) and 201.0 (100, Ph_2PO).

(2*R*)-4-Diphenylphosphinoylbutane-1,2-diol 27

By the method previously described,[25] 4-diphenylphosphinoylbut-1-ene **26** (6.83 g, 26.7 mmol, 85 : 15 *mono* : *di* allylated material), potassium carbonate (11.1 g, 80.4 mmol), potassium ferricyanide (26.3 g, 80.0 mmol), osmium trichloride (200 mg, 0.67 mmol) and $DHQD_2$-PYR (941 mg, 1.06 mmol, 4.0 mol%) gave a crude product after stirring for 1 day. Flash chromatography, eluting with 20% methanol in EtOAc, gave the *vicinal diol* **27** (3.84 g, 58% of possible yield) as an oil, R_f 0.44 (30% methanol in EtOAc); $[a]_D^{20}$ −0.7 (*c* 2.89 in $CHCl_3$); (Found: $M^+ - H_2O$, 272.0963. $C_{16}H_{19}O_3P$ requires $M - H_2O$, 272.1071); ν_{max}/cm^{-1} ($CHCl_3$) 3348 (OH), 1438 (P–Ph) and 1178 (P=O); δ_H (400 MHz; $CDCl_3$) 7.7–7.55 (4 H, m), 7.5–7.25 (6 H, m, Ph_2PO), 4.94 (1 H, d, *J* 3.9, CHO*H*), 4.66 (1 H, m, CH_2OH), 3.64 (1 H, m, C*H*OH), 3.45 (1 H, m, CH_AH_BOH), 3.35 (1 H, m, CH_AH_BOH), 2.52 (1 H, m, PCH_AH_B), 2.25 (1 H, m, PCH_AH_B) and 1.65 (2 H, m); δ_C (100 MHz; $CDCl_3$) 133–128 (m, Ph_2PO), 72.0$^+$ (d, $^3J_{PC}$ 12.5, CHOH), 66.3$^-$ (CH_2OH), 25.6$^-$ (d, $^1J_{PC}$ 72.1, PCH_2) and 25.2$^-$ (d, $^2J_{PC}$ 2.9); *m*/*z* 272.1 (5%, $M^+ - H_2O$), 259.1 (80, $M^+ - CH_2OH$) and 202.1 (100, Ph_2POH). Integration of the 235 MHz ^{19}F NMR spectrum of the Mosher's ester of this material showed it to have 41% ee.

(2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-4-diphenylphosphinoylbutan-2-ol 28

A solution of (2*R*)-4-diphenylphosphinoylbutane-1,2-diol **27** (2.12 g, 7.3 mmol), imidazole (1.73 g, 25.8 mmol) and *tert*-butylchlorodiphenylsilane (2.11 cm^3, 8.0 mmol) in DMF (15 cm^3) was stirred overnight, quenched with water (10 cm^3), extracted into dichloromethane (3 × 10 cm^3), dried ($MgSO_4$) and evaporated to give a crude product. Flash chromatography, eluting with 5% methanol in EtOAc, gave the silyl ether **28** (1.82 g, 47%) as an oil, R_f 0.32 (EtOAc); $[\alpha]_D^{20}$ +2.1 (*c* 1.58 in $CHCl_3$; 41% ee) (Found: $M^+ - Bu$, 471.1544. $C_{32}H_{37}O_3PSi$ requires $M - Bu$, 471.1545); ν_{max}/cm^{-1}($CHCl_3$) 1590 (Ph) and 1437 (P − Ph); δ_H (400 MHz; $CDCl_3$) 7.8–7.3 (20 H, m, Ph_2PO and 2 × Ph), 3.76 (1 H, m, C*H*OH), 3.57 (1 H, dd, *J* 4.9 and $^2J_{HH}$ 10.2, CH_AH_BOSi), 3.54 (1 H, dd, *J* 6.3 and $^2J_{HH}$ 10.2, CH_AH_BOSi), 3.42 (1 H, d, *J* 4.3, OH), 2.49 (1 H, m), 2.33 (1 H, m), 1.89 (1 H, m), 1.65 (1 H, m) and 0.99 (9 H, s, ^{t}Bu); δ_C (63 MHz; $CDCl_3$) 135.7^+, 133–127.5 (m, Ph_2PO and Ph), 71.8^+ (d, $^3J_{PC}$ 11.0, CHOH), 67.3^- (CH_2OSi), 26.9^+ (^{t}Bu), 26.1^- (d, $^1J_{PC}$ 72, PCH_2), 25.4^- (d, $^2J_{PC}$ 3.5) and 19.2^- (^{t}Bu); *m*/*z* 471.2 (100%, $M^+ - Bu$), 393.1 (65).

(2*S*,3*R*)-1-Diphenylphosphinoyl-2-propylhexan-3-yl benzoate 22

Triethylamine (1.82 g, 18.0 mmol) and benzoyl chloride (2.25 g, 15.9 mmol) were added dropwise to (2*S*,3*R*)-1-diphenylphosphinoyl-2-propylhexan-3-ol **21** (1.17 g, 3.4 mmol) and dimethylaminopyridine (100 mg, 0.84 mmol) in dry dichloromethane (30 cm^3) at room temperature. The reaction was stirred for 3 days, quenched with water, extracted with dichloromethane (3 × 60 cm^3), dried ($MgSO_4$) and evaporated to give a crude product. Flash chromatography, eluting with 2:1 EtOAc–hexane, gave the *benzoate ester* **22** (880 mg, 58%) as an oil, R_f 0.42 (EtOAc); $[\alpha]_D^{20}$ −2.5 (*c* 2.25 in $CHCl_3$; 84% ee) (Found: M^+, 448.2155. $C_{28}H_{33}PO_3$ requires *M*, 448.2167); ν_{max}/cm^{-1} ($CHCl_3$) 1712 (C=O), 1438 (P–Ph) and 1176 (P=O); δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, dd, *J* 1.8 and 8.0, *ortho*-PhCO), 7.75–7.1 (13 H, m, Ph_2PO and remaining Ph), 5.19 (1 H, td, *J* 3.2 and 9.7, C*H*OBz), 2.57 (1 H, ddd, *J* 2.9, 9.3 and $^2J_{HH}$ 12.5, PCH_AH_B), 2.30 (1 H, m, C*H*Pr), 2.18 (1 H, m, PCH_AH_B), 1.9–1.2 (8 H, m), 0.91 (3 H, t, *J* 7.0, Me) and 0.90 (3 H, t, *J* 7.0, Me); δ_C (100 MHz; $CDCl_3$) 165.9^- (C=O), 135–128 (m, Ph_2PO and Ph), 76.2^+ (d, $^3J_{PC}$ 10.0, C*H*OBz), 36.0^+ (d, $^2J_{PC}$ 2.7), 33.5^- (d, $^3J_{PC}$ 2.7), 31.5^-, 30.3^- (d, $^1J_{PC}$ 71.3, PCH_2), 20.1^-, 19.2^-, 14.1^+ (Me) and 13.9^+ (Me); *m*/*z* 448.2 (10%, M^+), 202.1 (60, Ph_2PO) and 105.0 (100, PhCO).

(2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-4-diphenylphosphinoylbutan-2-yl benzoate 29

By the same general method, (2*R*)-1-(*tert*-butyldiphenylsilyloxy)-4-diphenylphosphinoylbutan-2-ol **28** (825 mg, 1.56 mmol), dimethylaminopyridine (64 mg, 0.53 mmol) and benzoyl chloride (0.32 cm^3, 2.6 mmol) gave a crude product after stirring for 16 h. Flash chromatography, eluting with 3:2 EtOAc–hexane, gave the *benzoate ester* **29** (821 mg, 83%) as an oil, R_f 0.46 (EtOAc); $[\alpha]_D^{20}$ +1.6 (*c* 3.18 in $CHCl_3$; 41% ee) (Found: MH^+, 633.2595. $C_{32}H_{37}O_3P$ requires *MH*, 633.2590); ν_{max}/cm^{-1} ($CHCl_3$) 1714 (C=O), 1438 (P–Ph) and 1178 (P=O); δ_H (400 MHz; $CDCl_3$) 8.02 (2 H, dd, *J* 1.4 and 8.5, *ortho*-Bz), 7.75–7.2 (23 H, m, Ph_2PO and remaining 3 × Ph), 5.29 (1 H, quin, *J* 5.8, C*H*OBz), 3.81 (1 H, dd, *J* 5.1 and $^2J_{HH}$ 11.0, CH_AH_BOSi), 3.77 (1 H, dd, *J* 4.6 and $^2J_{HH}$ 11.0, CH_AH_BOSi), 2.38 (2 H, m), 2.11 (2 H, m) and 0.93 (9 H, s, ^{t}Bu); δ_C (63 MHz; $CDCl_3$) 166.1^- (C=O), 135.8^+, 133–127.5 (m, Ph_2PO and Ph × 3), 74.8^+ (d, $^3J_{PC}$ 15.4, CHOBz), 64.7^- (CH_2OSi), 26.9^+ (^{t}Bu), 25.9^- (d, $^1J_{PC}$ 72.1, PCH_2), 23.2^- and 19.1^- (^{t}Bu); *m*/*z* 633.4 (90%, MH+), 575.3 (80, M − Bu) and 555.3 (80, M − Ph).

(2*S*,3*R*)-1-Diphenylphosphinoyl-2-propylhexan-3-yl acetate 23

(2*S*,3*R*)-1-Diphenylphosphinoyl-2-propylhexan-3-ol **21** (1.00 g, 2.90 mmol) was dissolved in pyridine (8 cm^3) and acetic anhydride (8 cm^3), and the reaction mixture was stirred for 16 h. The reaction was diluted with EtOAc (60 cm^3), washed with dilute hydrochloric acid solution (2 × 60 cm^3), saturated aqueous sodium bicarbonate solution (60 cm^3), brine (60 cm^3) and saturated aqueous copper nitrate solution (60 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. Flash chromatography, eluting with 2:1 EtOAc–hexane, gave the *acetate* **23** (990 mg, 88%) as an oil, R_f 0.41 (EtOAc); $[\alpha]_D^{20}$ −27.4 (*c* 1.10 in $CHCl_3$; 84% ee) (Found: M^+, 386.2006. $C_{23}H_{31}PO_3$ requires *M*, 386.2011); ν_{max}/cm^{-1} ($CHCl_3$) 1727 (C=O), 1438 (P–Ph) and 1172 (P=O); δ_H (400 MHz; $CDCl_3$) 7.8–7.7 (4 H, m), 7.55–7.4 (6 H, m, Ph_2PO), 4.98 (1 H, td, *J* 3.2 and 9.3, C*H*OAc), 2.48 (1 H, m, PCH_AH_B), 2.12 (1 H, m, PCH_AH_B), 2.07 (3 H, s, Ac), 1.7–1.1 (9 H, m), 0.87 (3 H, t, *J* 7.6, Me) and 0.82 (3 H, t, *J* 7.1, Me); δ_C (100 MHz; $CDCl_3$) 170.5^- (C=O), 133.5–128.5 (m, Ph_2PO), 75.3^+ (d, $^3J_{PC}$ 9.9, C*H*OAc), 35.8^+, 33.6^- (d, $^3J_{PC}$ 2.9), 31.2^-, 30.0^- (d, $^1J_{PC}$ 71.4, PCH_2), 22.1^+ (Ac), 20.0^-, 19.0^-, 14.0^+ (Me) and 13.8^+ (Me); *m*/*z* 386.2 (40%, M^+), 271.1 (M^+ − CHOAcPr) and 201.1 (60, Ph_2POH).

3-Diphenylphosphinoyl-1-phenylpropyl acetate 25a

By the same general method, 3-diphenylphosphinoyl-1-phenylpropanol **24a** (2.97 g, 8.83 mmol) gave a crude product after 16 h. Flash chromatography, eluting with EtOAc, gave the *acetate* **25a** (3.28 g, 98%) as needles, mp 143–144 °C (from EtOAc–hexane); R_f 0.40 (EtOAc) (Found: C, 72.8; H, 6.15; P, 8.1; M^+, 378.1384. $C_{23}H_{31}PO_3$ requires C, 73.0; H, 6.15; P, 8.2%; *M*, 378.1385); ν_{max}/cm^{-1} ($CHCl_3$) 1737 (C=O), 1438 (P–Ph) and 1179 (P=O); δ_H (400 MHz; $CDCl_3$) 7.7–7.2 (15 H, m, Ph_2PO), 5.74 (1 H, t, *J* 6.0, C*H*OAc), 2.4–2.0 (4 H, m) and 2.02 (3 H, s, Ac); δ_C (100 MHz; $CDCl_3$) 170.1^- (C=O), 139.3^- (*ipso*-Ph), 133–126 (m, Ph_2PO and Ph), 75.6^+ (d, $^3J_{PC}$ 16.3, C*H*OAc), 28.1^- (d, $^2J_{PC}$ 1.9), 25.5^- (d, $^1J_{PC}$ 72.0, PCH_2) and 21.2^+ (Ac); *m*/*z* 378.1 (45%, M^+), 335.1 (100, M^+ − Ac) and 201.0 (80, Ph_2PO).

(2*R*)-1-(*tert*-Butyldiphenylsilyloxy)-4-diphenylphosphinoylbutan-2-yl acetate 25b

By the same general method, (2*R*)-1-(*tert*-butyldiphenylsilyloxy)-4-diphenylphosphinoylbutan-2-ol **24b** (702 mg, 1.33 mmol) gave a crude product after stirring for 16 h. Flash chromatography, eluting with 3:1 EtOAc–hexane, gave the *acetate* **25b** (614 mg, 66%) as an oil, R_f 0.46 (EtOAc); $[\alpha]_D^{20}$ +0.6 (*c* 1.86 in $CHCl_3$; 41% ee) (Found: $M^+ - {}^tBu$, 513.1562. $C_{34}H_{39}O_4PSi$ requires $M^+ - {}^tBu$, 513.1651); ν_{max}/cm^{-1} ($CHCl_3$) 1733 (C=O), 1438 (P–Ph) and 1178 (P=O); δ_H (400 MHz; $CDCl_3$) 7.75–7.3 (20 H, m, Ph_2PO and 2 × Ph), 5.01 (1 H, qd, *J* 5.3 and 6.5, C*H*OAc), 3.68 (1 H, dd, *J* 5.6 and $^2J_{HH}$ 10.8, CH_AH_BOSi), 3.63 (1 H, dd, *J* 4.7 and $^2J_{HH}$ 10.8, CH_AH_BOSi), 2.25 (2 H, m), 1.99 (3 H, s, Ac), 1.93 (2 H, m) and 0.98 (9 H, s, ^{t}Bu); δ_C (63 MHz; $CDCl_3$) 170.6^- (C=O), 136–127 (m, Ph_2PO and 2 × Ph), 74.1^+ (d, $^3J_{PC}$ 15.3, CHOAc), 64.5^- (CH_2OSi), 26.7^+ (^{t}Bu), 25.7^- (d, $^1J_{PC}$ 72.1, PCH_2), 22.9^-, 21.1^+ (Ac) and 19.2^- (^{t}Bu); *m*/*z* 513.2 (100%, $M^+ - {}^tBu$).

(1*R,2*R**)-(2-Phenylcyclopropyl)phenylmethanone 10b**

By the method of Corey,[27] sodium hydride (60% dispersion in oil, 212 mg, 5.3 mmol) was added to a solution of trimethylsulfoxonium iodide (1.14 g, 5.2 mmol) in DMSO (6 cm^3). After stirring for 10 min, chalcone (1.0 g, 4.8 mmol) was added dropwise, the reaction was stirred for 1 h at room temperature and 1 h at 50 °C, quenched with water (10 cm^3), extracted with ether (3 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product, which was purified by flash

chromatography, eluting with 3:1 hexane–ether, to give the cyclopropyl ketone **10b** as an oil, R_f 0.53 (2:1 hexane–ether) (Found: M^+, 222.1040. $C_{16}H_{14}O$ requires *M*, 222.1044); ν_{max}/cm^{-1} ($CHCl_3$) 1662 (C=O), 1599 (Ph) and 1579 (Ph); δ_H (400 MHz; $CDCl_3$) 8.02 (2 H, dd, *J* 1.5 and 8.5, *ortho*-PhCO), 7.58 (1 H, dt, *J*, 1.1 and 5.4, *para*-PhCO), 7.49 (2 H, t, *J* 5.8, *meta*-PhCO), 7.33 (2 H, t, *J* 7.2, Ph), 7.3–7.2 (3 H, m, Ph), 2.93 (1 H, ddd, *J* 4.1, 5.1 and 8.2, Ph(C=O)C*H*), 2.72 (1 H, ddd, *J* 4.1, 6.7 and 8.8, PhC*H*), 1.95 (1 H, ddd, *J* 4.2, 5.2 and 9.0) and 1.58 (1 H, ddd, *J* 4.1, 6.6 and 8.0); δ_C (100 MHz; $CDCl_3$) 198.5$^-$ (C=O), 140.5$^-$, 137.8$^-$, 128.9$^+$, 127.8$^+$, 126.2$^+$, 125.8$^+$, 30.0$^+$, 29.3$^+$ and 19.3$^-$; *m*/*z* 222.1 (45%, M^+), 105.0 (100, PhCO) and 77 (45, Ph).

(1*S*,2*S*)-(2-Butylcyclopropyl)phenylmethanone 10a

Potassium *tert*-butoxide (180 mg, 1.61 mmol) and the silylated hemiacetal[21b] **17a** (0.53 mmol) were dissolved in *tert*-butyl alcohol (15 cm^3) and stirred for 5 h. The reaction mixture was quenched with water (10 cm^3), extracted with ether (3 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. Flash chromatography, eluting with 4:1 hexane–EtOAc, to give the *cyclopropyl ketone* **10a** (100 mg, 83%, >95:5 mixture) as an oil, R_f 0.58 (2:1 hexane–ether); $[\alpha]_D^{20}$ +5.3 (*c* 2.14 in $CHCl_3$; 76% ee) (Found: M^+, 202.1356. $C_{14}H_{18}O$ requires *M*, 202.1458); ν_{max}/cm^{-1} ($CHCl_3$) 1662 (C=O), 1599 (Ph) and 1579 (Ph); δ_H (400 MHz; $CDCl_3$) 8.01 (2 H, dd, *J* 1.4 and 7.2, *ortho*-Ph), 7.50 (3 H, m, remaining Ph), 2.42 (1 H, td, *J* 4.4 and 8.2, Ph(CO)C*H*), 1.60 (1 H, m), 1.5–1.3 (8 H, m) and 0.90 (3 H, t, *J* 7.2, Me); δ_C (100 MHz; $CDCl_3$) 200.1$^-$ (C=O), 138.1$^-$ (*ipso*-Ph), 128.4$^+$, 127.9$^+$, 126.2$^+$, 33.1$^-$, 31.3$^-$, 27.2$^+$, 25.1$^+$, 20.4$^-$, 18.9$^-$ and 13.9$^+$ (Me); *m*/*z* 202.1 (45%, M^+), 105.0 (100, PhCO) and 77 (45, Ph).

(1*S*,2*S*)-(2-Phenylcyclopropyl)phenylmethanone 10b

By the same general method, silylated hemiacetal[21b] **17b** (60 mg, 0.12 mmol) gave a crude product which was purified by flash chromatography, eluting with 1:1 hexane–ether to give the cyclopropyl ketone[15,27] **10b** (16 mg, 62%, >95:5 mixture) as an oil. Standing in $CDCl_3$ for 3 weeks to give the cyclopropyl ketone **10b** (16 mg, 62%, 67:33 mixture) as an oil (Found: M^+, 222.1040. $C_{16}H_{14}O$ requires *M*, 222.1044); R_f 0.61 (1:1 hexane–ether); $[\alpha]_D^{20}$ +37.8 (*c* 0.12 in $CHCl_3$; 86% ee); ν_{max}/cm^{-1} ($CHCl_3$) 1662 (C=O), 1599 (Ph) and 1579 (Ph); δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, dd, *J* 1.5 and 8.5, *ortho*-Ph^{major}), 7.90 (2 H, dd, *J* 0.9 and 8.6, *ortho*-Ph^{minor}), 7.6–7.1 (8 H, m, remaining Ph), 3.09 (1 H, ddd, *J* 5.7, 7.3 and 9.1, Ph(CO)CH^{minor}), 2.90 (1 H, ddd, *J* 4.0, 5.2 and 8.1, Ph(CO)CH^{major}), 2.70 (1 H, ddd, *J* 4.1, 6.6 and 8.9, PhC$H^{major + minor}$), 2.13 (1 H, ddd, *J* 5.2, 5.8 and 7.0, minor), 1.93 (1H, ddd, *J* 4.1, 5.1 and 9.2, major), 1.55 (1 H, ddd, *J* 4.1, 6.6 and 8.0, major), 1.46 (1 H, ddd, *J* 4.8, 7.6 and 8.5, minor); *m*/*z* 222.1 (30%, M^+), 105.0 (100, PhCO) and 77 (55, Ph). The *trans* isomer was spectroscopically identical to that obtained previously.

(1*S*,2*S*,3*R*)-(2-Butyl-3-methylcyclopropyl)phenylmethanone 44

By the same general method, silylated hemiacetal[21b] **42** (273 mg, 0.54 mmol) gave a crude product which was purified by flash chromatography, eluting with 3:1 hexane–EtOAc, to give the *cyclopropyl ketone* **44** (97 mg, 84%, 96:4 mixture) as an oil, R_f 0.58 (2:1 hexane–ether); $[\alpha]_D^{20}$ −0.57 (*c* 0.96 in $CHCl_3$; 76% ee) (Found: M^+, 216.1520. $C_{15}H_{20}O$ requires *M*, 216.1514); ν_{max}/cm^{-1} ($CHCl_3$) 1655 (C=O), 1598 (Ph) and 1579 (Ph); δ_H (400 MHz; $CDCl_3$) 7.98 (2 H, dd, *J* 2.0 and 8.1, *ortho*-Ph), 7.6–7.4 (3 H, m, remaining Ph), 2.11 (1 H, t, *J* 4.3, Ph(CO)CH), 1.82 (1 H, dqd, *J* 3.1, 4.3 and 10.0), 1.76 (1 H, dtd, *J* 4.4, 7.1 and 8.7), 1.6–1.3 (6 H, m), 1.22 (3 H, d, *J* 6.2, Me) and 0.91 (3 H, t, *J* 7.1, Me); δ_C (100 MHz; $CDCl_3$) 200.0$^-$ (C=O), 138.2$^-$ (*ipso*-Ph), 132.4$^+$, 128.4$^+$, 127.8$^+$, 33.5$^+$, 32.4$^+$, 31.7$^-$, 27.1$^-$, 26.0$^+$, 22.4$^-$, 14.0$^+$ (Me) and 12.4$^+$ (Me); *m*/*z* 216.2 (15%, M^+), 105.0 (100, PhCO) and 77 (30, Ph).

(1*S*,2*S*,3*S*)-(2-Butyl-3-methylcyclopropyl)phenylmethanone 47

By the same general method, silylated hemiacetal[21b] **45** (112 mg, 0.22 mmol) gave a crude product which was purified by flash chromatography, eluting with 3:1 hexane–EtOAc, to give the *cyclopropyl ketones* **47**, **48** and *ent*-**44** (26 mg, 55%, 62:27:11 mixture) as an oil, R_f 0.58 (2:1 hexane–ether); $[\alpha]_D^{20}$ +68.7 (*c* 0.60 in $CHCl_3$; 76% ee) (Found: M^+, 216.1520. $C_{15}H_{20}O$ requires *M*, 216.1514); ν_{max}/cm^{-1} ($CHCl_3$) 1661 (C=O), 1598 (Ph) and 1479 (Ph); δ_H (400 MHz; $CDCl_3$, major isomer) 7.98 (2 H, dd, *J* 1.1 and 7.2, *ortho*-Ph), 7.6–7.4 (3 H, m, remaining Ph), 2.41 (1 H, dd, *J* 4.9 and 8.5, Ph(CO)CH), 1.8–1.2 (8 H, m), 1.18 (3 H, d, *J* 6.0, Me) and 0.81 (3 H, t, *J* 7.3, Me); δ_C (100 MHz; $CDCl_3$) 199.0$^-$ (C=O), 139.2$^-$ (*ipso*-Ph), 132.3$^+$, 128.4$^+$, 127.9$^+$, 35.9$^+$, 32.1$^+$, 31.9$^-$, 25.9$^-$, 23.3$^+$, 22.3$^-$, 18.3$^+$ (Me) and 14.0$^+$ (Me); *m*/*z* 216.2 (15%, M^+), 105.0 (100, PhCO) and 77 (30, Ph).

The minor isomer was identical spectroscopically to the cyclopropyl ketone **44**. The other isomer was identified by the cyclopropane ring coupling constants: in particular, 2.44 [1 H, dd, *J* 4.9 and 9.0, Ph(CO)CH].

(2*R*,3*R*)-(2,3-Dipropylcyclopropyl)phenylmethanone 39

A stock solution of LDA was prepared by the dropwise addition of *n*-butyllithium (1.2 cm^3 of a 1.7 mol dm^{-3} solution in hexanes) to a stirred solution of diisopropylamine (202 mg, 2.0 mmol) in dry THF (8.6 cm^3) at 0 °C. LDA (5.4 cm^3 of a 0.5 mol dm^{-3} solution in THF) was added dropwise to a stirred solution of (2*S*,3*R*)-1-diphenylphosphinoyl-2-propylhexan-3-yl benzoate **22** (603 mg, 1.34 mmol) and chlorotrimethylsilane (0.63 cm^3, 5.0 mmol) gave a crude product. By the general method described above, potassium *tert*-butoxide (450 mg, 4.0 mmol) gave a crude product, which was purified by flash chromatography, eluting with 5:1 hexane–ether to give the *cyclopropyl ketone* **39** (225 mg, 69%) as an oil, R_f 0.65 (3:1 hexane–ether); $[\alpha]_D^{20}$ −37.6 (*c* 1.89 in $CHCl_3$; 84% ee) (Found: M^+, 230.1671. $C_{16}H_{22}O$ requires *M*, 230.1671); ν_{max}/cm^{-1} ($CHCl_3$) 1662 (C=O); δ_H (400 MHz; $CDCl_3$) 7.97 (2 H, br d, *J* 7.1, *ortho*-Ph), 7.51 (1 H, tt, *J* 1.2 and 6.4, *para*-Ph), 7.41 (2 H, br t, *J* 6.5, *meta*-Ph), 2.47 (1 H, dd, *J* 4.9 and 8.3, Ph(CO)C*H*), 1.9–1.5 (10 H, m), 0.92 (3 H, t, *J* 7.1, Me) and 0.83 (3 H, t, *J* 7.2, Me); δ_C (100 MHz; $CDCl_3$) 198.9$^-$ (C=O), 139.2$^-$ (*ipso*-Ph), 132.3$^+$, 128.4$^+$, 127.9$^+$ (Ph), 35.6$^-$, 34.4$^+$, 31.7$^+$, 28.8$^+$, 28.5$^-$, 22.9$^-$, 22.6$^-$, 14.0$^+$ (Me) and 13.9$^+$ (Me); *m*/*z* 230.2 (20%, M^+), 187.1 (100, M^+ − Pr) and 105.0 (90, PhCO).

(1*R*,2*R*)-[2-(*tert*-Butyldiphenylsilyloxy)methylcyclopropyl]-phenylmethanone 36

By the general method described above, (2*R*)-1-*tert*-butyldiphenylsilyloxy-4-diphenylphosphinoyl butan-2-yl benzoate **29** (776 mg, 1.23 mmol), LDA (5.0 cm^3 of a 0.5 mol dm^{-3} solution in THF, 2.5 mmol), chlorotrimethylsilane (0.62 cm^3, 4.9 mmol) and potassium *tert*-butoxide (413 mg, 3.70 mmol) gave a crude product, which was purified by flash chromatography, eluting with 4:1 hexane–ether to give the *cyclopropyl ketone* **36** (190 mg, 38%) as an oil, R_f 0.53 (2:1 hexane–ether); $[\alpha]_D^{20}$ −8.4 (*c* 1.01 in $CHCl_3$; 43% ee) (Found: $M^+ - {}^t$Bu, 357.1311. $C_{27}H_{30}O_2Si$ requires $M^+ - {}^t$*Bu*, 357.1311); ν_{max}/cm^{-1} ($CHCl_3$) 1666 (C=O); δ_H (400 MHz; $CDCl_3$) 8.02 (2 H, dd, *J* 1.0 and 6.3, *ortho*-Bz), 7.7 (4 H, m), 7.6–7.35 (10 H, m), 3.92 (1 H, dd, *J* 4.6 and $^2J_{HH}$ 10.9, CH_AH$_B$OSi), 3.65 (1 H, dd, *J* 6.1 and $^2J_{HH}$ 10.9, CH$_A$*H*$_B$OSi), 2.68 (1 H, td, *J* 4.4 and 8.0, Ph(CO)C*H*), 1.86 (1 H, m), 1.51 (1 H, m), 1.30 (1 H, m) and 1.09 (9 H, ^{t}Bu); δ_C (100 MHz; $CDCl_3$) 199.7$^-$ (C=O), 138.1$^-$ (*ipso*-Ph), 135.6$^+$, 135.5$^+$, 134.8$^-$ (*ipso*-Ph), 134–125 (m), 64.9$^-$ (CH_2OSi), 27.8$^+$, 26.9$^+$

(^{t}Bu), 23.2$^+$ and 20.7$^-$ (^{t}Bu); *m*/*z* 357.1 (80%, M$^+$ − ^{t}Bu) and 199.1 (100, Ph_2SiOH).

(1*S*,2*S*)-1-(2-Phenylcyclopropyl)ethanone 34a

LDA (5.0 cm^3 of a 0.5 mol dm^{-3} solution in THF, 2.5 mmol) was added dropwise to a stirred solution of (1*S*)-3-diphenylphosphinoyl-1-phenylpropan-1-yl acetate **25a** (473 mg, 1.25 mmol) in dry THF (10 cm^3) at −78 °C. The reaction mixture was stirred for 20 min, quenched at −78 °C with saturated ammonium chloride solution, warmed to room temperature, extracted with dichloromethane (3 × 15 cm^3), dried ($MgSO_4$) and evaporated to give a crude product. By the general method described above, the crude product and potassium *tert*-butoxide (380 mg, 3.4 mmol) gave a crude product, which was purified by flash chromatography, eluting with 2:1 hexane–ether, to give the *cyclopropyl ketone* **34a** (126 mg, 63%) as an oil, R_f 0.38 (2:1 hexane–ether) (Found: M$^+$, 160.0878. $C_{16}H_{22}O$ requires *M*, 160.0888); ν_{max}/cm^{-1} ($CHCl_3$) 1678 (C=O), 1631 (Ph) and 1604 (Ph); δ_H (400 MHz; $CDCl_3$) 7.29 (2 H, br t, *J* 7.6, *meta*-Ph), 7.21 (1 H, br t, *J* 7.6, *para*-Ph), 7.09 (2 H, br d, *J* 7.2, *ortho*-Ph), 2.52 (1 H, ddd, *J* 4.0, 6.8 and 8.9, AcC*H*), 2.30 (3 H, s, Me), 2.21 (1 H, td, *J* 5.1 and 10.2, PhC*H*), 1.68 (1 H, td, *J* 4.6 and 8.9) and 1.38 (1 H, ddd, *J* 4.3, 6.8 and 7.8); δ_C (100 MHz; $CDCl_3$) 208.1$^-$ (C=O), 140.3$^-$ (*ipso*-Ph), 128.8$^+$, 126.5$^+$, 126.0$^+$ (Ph), 32.9$^+$, 31.2$^+$, 29.1$^+$ and 19.2$^-$; *m*/*z* 160.1 (30%, M$^+$) and 117.1 (100, M − Ac).

(1*R*,2*R*)-1-[2-(*tert*-Butyldiphenylsilyloxy)methylcyclopropyl]-ethanone 34b

By the same general method, (2*R*)-1-*tert*-butyldiphenylsilyloxy-4-diphenylphosphinoylbutan-2-yl acetate **25b** (580 mg, 1.02 mmol), LDA (5.1 cm^3 of a 0.5 mol dm^{-3} solution in THF, 2.5 mmol) and potassium *tert*-butoxide (342 mg, 3.05 mmol) gave a crude product, which was purified by flash chromatography, eluting with 2:1 hexane–ether to give the *cyclopropyl ketone* **34b** (40 mg, 11%) as an oil, R_f 0.24 (3:1 hexane–ether); $[\alpha]_D^{20}$ −14.4 (*c* 2.08 in $CHCl_3$; 43% ee) (Found: M$^+$ − ^{t}Bu, 295.1158. $C_{22}H_{28}O_2Si$ requires *M* − ^{t}*Bu*, 295.1154); ν_{max}/cm^{-1} ($CHCl_3$) 1691 (C=O) and 1589 (Ph); δ_H (400 MHz; $CDCl_3$) 7.75–7.6 (4 H, m), 7.5–7.35 (6 H, m), 3.79 (1 H, dd, *J* 4.8 and $^2J_{HH}$ 11.0, CH_AH$_B$OSi), 3.53 (1 H, dd, *J* 6.0 and $^2J_{HH}$ 10.9, CH$_A$*H*$_B$OSi), 2.19 (3 H, s, Me), 1.87 (1 H, td, *J* 4.5 and 8.5, AcC*H*), 1.75 (1 H, m), 1.20 (1 H, m), 1.09 (9 H, ^{t}Bu) and 0.89 (1 H, ddd, *J* 3.8, 6.4 and 8.2); δ_C (100 MHz; $CDCl_3$) 208.1$^-$ (C=O), 135.6$^+$, 135.2$^-$ (*ipso*-Ph), 134.8$^+$, 133.6$^-$ (*ipso*-Ph), 129.7$^+$, 129.6$^+$, 127.7$^+$ (2 × C), 64.6$^-$ (CH_2OSi), 30.4$^+$, 26.9$^+$ (^{t}Bu), 26.5$^+$, 26.4$^+$, 19.2$^-$ and 19.0$^-$; *m*/*z* 295.1 (30%, M$^+$ − ^{t}Bu) and 119.1 (Ph_2SiOH).

(1*R*,2*R*)-[(2-Hydroxymethyl)cyclopropyl]phenylmethanone 37

Tetra-*n*-butylammonium fluoride (0.7 cm^3 of a 1.0 mol dm^{-3} solution in THF, 0.7 mmol) was added dropwise to a stirred solution of the cyclopropyl ketone **36** (144 mg, 0.35 mmol) in dry THF (5 cm^3). The reaction was stirred for 1 h, water added, extracted with dichloromethane (3 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was purified by flash chromatography, eluting with 2:1 ether–hexane, to give the *alcohol* **37** (56 mg, 91%) as an oil, R_f 0.08 (1:1 hexane–ether); $[\alpha]_D^{20}$ −19.1 (*c* 0.25 in $CHCl_3$) (Found: M$^+$, 176.0836. $C_{11}H_{13}O_2$ requires *M*, 176.0837); ν_{max}/cm^{-1} ($CHCl_3$) 3448 (OH) and 1666 (C=O); δ_H (400 MHz; $CDCl_3$) 8.01 (2 H, td, *J* 1.1 and 6.8, *ortho*-Ph), 7.6–7.4 (3 H, m), 3.80 (1 H, dd, *J* 5.6 and $^2J_{HH}$ 11.4, CH_AH$_B$OH), 3.56 (1 H, dd, *J* 6.8 and $^2J_{HH}$ 11.4, CH$_A$*H*$_B$OH), 2.66 (1 H, td, *J* 4.2 and 8.4, Ph(CO)C*H*), 1.91 (2 H, m, OH and C*H*CH$_2$OH), 1.48 (1 H, *J* 3.1 and 8.6) and 1.07 (1 H, ddd, *J* 3.6, 6.4 and 8.2); δ_C (100 MHz; $CDCl_3$) 156.0$^-$ (C=O), 132.8$^+$, 128.5$^+$, 128.1$^+$, 64.6$^-$ (CH_2OH), 27.6$^+$, 22.7$^+$ and 15.7$^-$; *m*/*z* 176.1 (10%, M$^+$), 105.0 (100, PhCO) and 77.0 (75, Ph). Integration of the 500 MHz ^{1}H NMR spectrum of the Mosher's esters of this material showed it to have 43% ee.

Attempted epimerisation of cyclopropyl ketone 10b with potassium *tert*-butoxide in *tert*-butyl alcohol

Potassium *tert*-butoxide (336 mg, 3.0 mmol) was added to a solution of cyclopropyl ketone **10b** (66 mg, 0.30 mmol) in *tert*-butyl alcohol (4 cm^3). After stirring for 6 h at 50 °C, the reaction was quenched with water (4 cm^3), extracted with ether (3 × 5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product. Analysis of the 400 MHz ^{1}H NMR of the crude product indicated that no epimerisation had occurred.

Epimerisation of cyclopropyl ketone 10b with toluene-*p*-sulfonic acid in chloroform

Toluene-*p*-sulfonic acid heptahydrate (150 mg, 0.51 mmol) was added to a solution of cyclopropyl ketone **10b** (114 mg, 0.51 mmol) in chloroform (4 cm^3). After stirring for 14 days, the reaction was quenched with water (4 cm^3), extracted with ether (3 × 5 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give a crude product which was the cyclopropyl ketones **10b** (112 mg, 98%, 54:46 mixture of diastereomers) as an oil, spectroscopically identical to those obtained previously.

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