

Stereocontrol in organic synthesis using silicon-containing compounds. A synthesis of a (\pm)-carbacyclin analogue with the geometry of the exocyclic double bond controlled by the protodesilylation of an allylsilane

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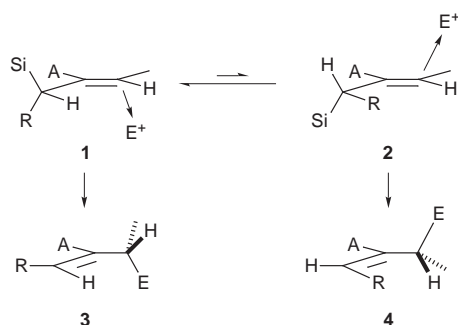
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The known ketone, 7-*tert*-butyldimethylsilyloxybicyclo[3.3.0]oct-8-en-2-one **11**, was converted in five steps into 3-(4'-methoxycarbonylbutylidene)-7-*tert*-butyldimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-one **13**. Reduction gave the diastereoisomeric pair of allylic alcohols **14** and **15**, both of which were converted into the allylsilane, 3-(1'-dimethylphenylsilyl-4'-methoxycarbonyl)butyl-7-*tert*-butyldimethylsilyloxy-8-cyanobicyclo[3.3.0]oct-2-ene **20**. Protodesilylation of the allylsilane gave a high level of selectivity (>96:4) in favour of the carbacyclin analogue, 5-(4'-methoxycarbonyl)butylidene-3-*tert*-butyldimethylsilyloxy-2-cyanobicyclo[3.3.0]octane **22**, having the exocyclic double bond with the *E*-configuration.

Introduction

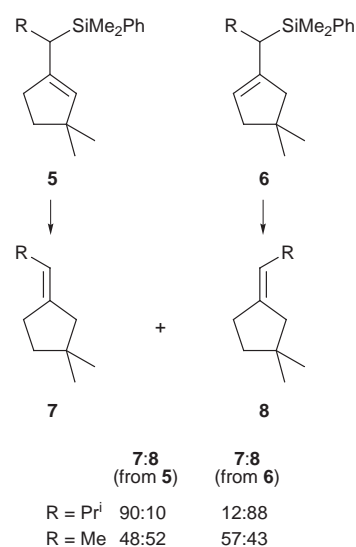
We and several other groups established that the stereochemistry of electrophilic attack on the double bond of an allylsilane was stereospecifically *anti*, usually in the sense **1**,¹⁻⁴ giving an alkene **3** with the R group and the A group *cis*, but with more or less of the reaction taking place from the alternative conformation **2**, creating an alkene **4** with the R group and the A group *trans* (Scheme 1). Most attention has naturally



Scheme 1

been paid to the stereochemistry at the new stereogenic centre,^{1,2} which is opposite in sense in the two products **3** and **4**, but it is sometimes possible to use the reaction to control double bond geometry. For example, dihydroxylation using osmium tetroxide, followed by convergent stereospecific elimination, can be made to give either the *cis* or the *trans* alkene.^{3,4} Alternatively, stereocontrol might be achieved by arranging for a high proportion of the reaction to take place in conformation **1**.

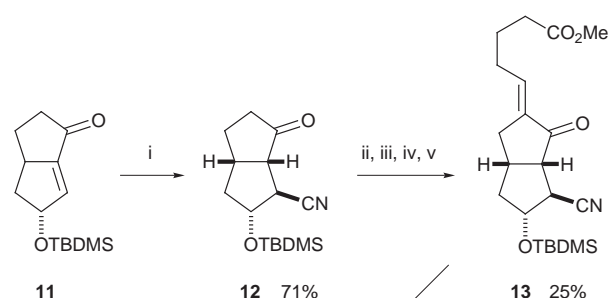
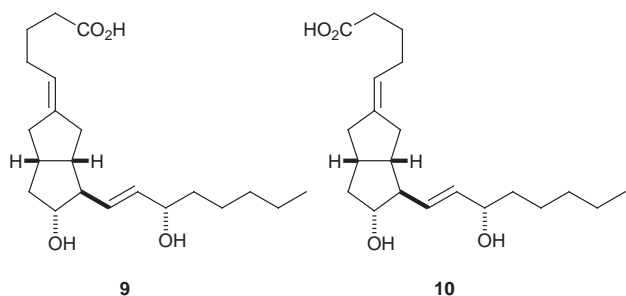
To test this possibility, we investigated the protodesilylation of allylsilanes, creating a double bond exocyclic to a five-membered ring.⁵ In summary, we found that protodesilylation of the allylsilanes **5** took place mainly in the sense **1** → **3** to give the *E*-alkenes **7**, provided that the group R was moderately large. Similarly, protodesilylation of the allylsilanes **6** gave the *Z*-alkenes **8** (Scheme 2). Thus when R was isopropyl, the selectivity for reaction taking place in the sense **1** over **2** was close to 90:10, both for **5** and for **6**, but when R was a methyl group the degree of selectivity was low and actually reversed in both cases, consistent with our earlier work,^{2,6} and that of Vedejs and



Scheme 2 Reagent: **i**, CF₃CO₂H, CDCl₃, 0 °C

McClure,⁴ and of Curran and Kim,⁷ establishing that electrophilic attack on the double bond of an allylsilane often takes place mainly from conformation **2** when the substituent on the double bond *cis* to the stereogenic centre is only a hydrogen atom, as here, and when, at the same time, the R group is methyl. A methyl group suffers only a weak A^{1,3} repulsion with the H atom on the double bond, but an isopropyl group suffers a much larger repulsion. The problem of having a small group like methyl on the stereogenic centre giving mixtures of geometrical isomers in the double bond is not, of course, restricted to allylsilane reactions—it turns up equally with allyl Grignard reactions, where selectivities (*E*:*Z*) ranging from 5:1 to 0.2:1 have been observed, depending upon the electrophile.⁸

At first sight this limitation does not bode well for our plan to use the protodesilylation of an allylsilane to control the geometry of the exocyclic double bond in a synthesis of a carbacyclin. *E*-Carbacyclin **9**⁹ is a prostacyclin analogue much more potent in inhibiting platelet aggregation than its *Z*-isomer **10**.^{10,11} Controlling the geometry of the exocyclic double bond in this molecule is therefore a significant challenge in synthesis, both because the geometry matters, and because it is not obvious how to set it up stereoselectively, given that it is remote from



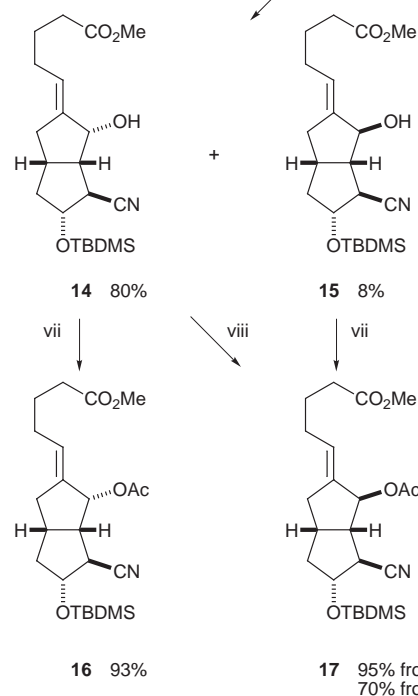
any resident steric influence. Although a few stereoselective syntheses have appeared,¹² the original Wittig route gave, as one might expect, both isomers in essentially equal amounts.^{11,13} Our own approach, based on the model reaction $5 \rightarrow 7$, would seem to be doomed—the methylene chain is likely to be more like a methyl group in its steric effect than an isopropyl, and is therefore unlikely to impart useful levels of stereocontrol. Nevertheless, we carried out the synthesis, for we were aware that other factors in our favour would come into play, and so they did. We reported this work in preliminary communications,¹⁴ and report it in full here.

Results and discussion

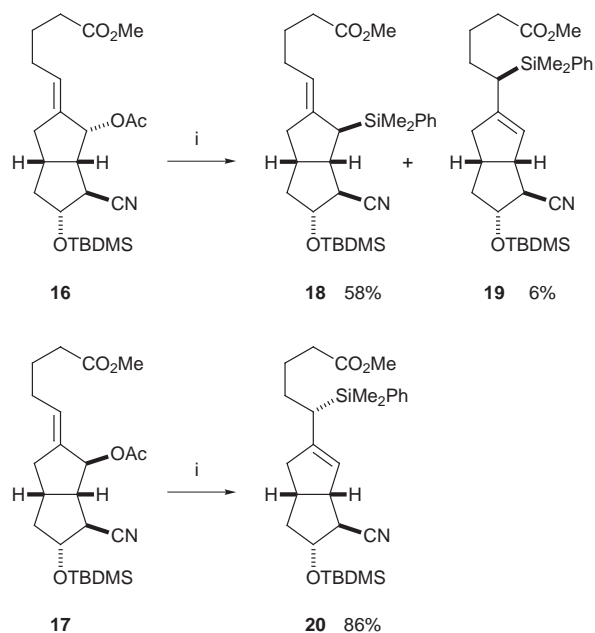
We chose not to deal with the problem of the lower side chain, which is, in any case, the main site of variation in the molecules being tested for clinical usefulness, and assembled instead a cyano analogue. We started from the known, racemic unsaturated ketone **11**,¹⁵ which was attacked *exo* on the bicyclic framework by cyanide ion to give the nitrile **12**. This addition took place under milder conditions than usual for this conventional procedure,¹⁶ as befits a bicyclooctenone with a bridgehead double bond. More recent methods for the conjugate addition of cyanide ion, based on trimethylsilyl cyanide in the presence of Lewis acids,¹⁷ were too harsh, giving elimination products lacking the silyloxy group or even more extensive decomposition. A conventional aldol sequence then gave the ketone **13**, with the usual *E*-geometry, but with an unimpressive overall yield, although this was only to be expected from an earlier report on aldol reactions on this type of bicyclooctanone.¹⁸ We were even less successful with phenylthioalkylation¹⁹ of the silyl enol ether derived from the ketone **12**.

Luche reduction²⁰ of the ketone **13** gave a separable mixture of the alcohols **14** and **15** in a ratio of 10:1, and acetylation gave the acetates **16** and **17**, respectively. The latter, the more important isomer, could also be made by a Mitsunobu reaction from the major alcohol **14** (Scheme 3). Acetic acid is not usually the best carboxylic acid to use in Mitsunobu reactions,²¹ but it worked well enough here.

The acetate **16** reacted with our silylcuprate reagent, using the solvent mixture that we had found best for secondary allylic acetates,²² giving a mixture of the regioisomeric allylsilanes **18** and **19**, with the latter, unfortunately, as the minor product, just as we had found earlier in the model series.²² In welcome contrast, the acetate **17** gave only the allylsilane **20**, which was discernibly different from the allylsilane **19** (Scheme 4). By analogy with our earlier work,³ these reactions can be relied upon to be stereospecifically *anti*. Presumably an allylsilane analogous to **18**, but with an *endo* silyl group, was not formed from the acetate **17**, because it would have involved *endo* attack on the bicyclo[3.3.0]octane system. Because of the success of this reaction, we were not obliged to use our other device for ensuring high levels of regioselectivity—the use of a silylcuprate reagent assembled on a carbamate group in place of the acetate.²² This was fortunate, for in this case we found that the *N*-phenyl carbamate derived from the alcohol **14** reacted with the silylcuprate reagent, assembled on the carbamate as usual, to give a low yield (12%) of the allylsilane **19** instead of **20**.



Scheme 3 Reagents: i, KCN, NH₄Cl, H₂O, DMF; ii, LDA; iii, MeO₂C(CH₂)₃CHO; iv, MeSO₂Cl, Et₃N; v, DBU; vi, NaBH₄, CeCl₃; vii, Ac₂O, Et₃N, DMAP; viii, AcOH, EtO₂CN=NCO₂Et, Ph₃P

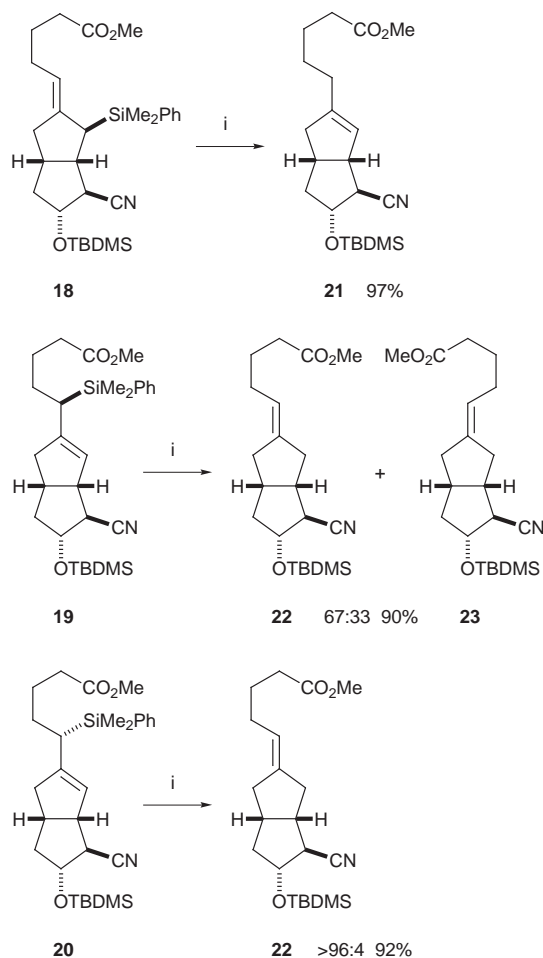


Scheme 4 Reagent: i, (PhMe₂Si)₂CuLi·LiCN, THF, Et₂O, pentane

This appears to be an unprecedented *anti* S_N2' reaction of a cuprate, but it is probable that it is a result of a *syn* 1,3-shift of the carbamate anion, away from the hindered *endo* position on the bicyclic framework, followed by an S_N2 reaction, with the

usual inversion. We did not pursue this problem, since we had by this time found the Mitsunobu alternative for achieving convergence.

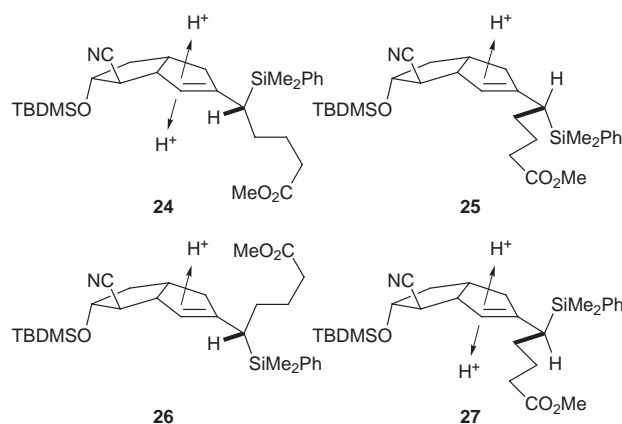
Protodesilylation of the allylsilane **18** merely moved the double bond regioselectively into the ring **21**, as expected,²³ but the protodesilylations of the two allylsilanes **19** and **20** were not equally stereoselective with respect to the double bond geometry exocyclic to the ring. Protodesilylation of the diastereoisomer **19** gave a mixture of the *E*- and *Z*-isomers **22** and **23** (Scheme 5) in a ratio of about 2:1, which looked, on the face of



Scheme 5 Reagent: i, CF₃CO₂H, CH₂Cl₂, 0 °C

it, very much what one might have expected from the model series (Scheme 2) if we assume that a methylene chain is a little more effective than a methyl group in causing the conformation **1** rather than **2** to be populated. However, the allylsilane **20** gave very largely (>96:4, GC supported by ¹³C NMR) the *E*-isomer **22**, exactly as we had hoped. The assignment of configuration to the alkenes **22** and **23** was easy by comparison of the ¹³C NMR spectra with those reported for the *E*- and *Z*-isomers of the carbacyclin iloprost.²⁴ Although our work with the model compounds would suggest that a methylene chain will not be an effective group in controlling the double bond geometry, we have somehow achieved an extraordinarily high level of control with one of the diastereoisomers but not the other.

The allylsilane **19** that does not give good stereocontrol will probably adopt most readily a conformation close to that shown as **24**, with the hydrogen atom eclipsing, or partly eclipsing, the double bond (Scheme 6). Protodesilylation in this conformation will lead to the *E*-isomer **22**, but it will involve attack by the proton either *syn* to the silyl group or *endo* on the bicyclic system. Since neither of these pathways is likely to be favourable, it is not surprising that this diastereoisomer does not lead cleanly to the *E*-carbacyclin **22**. The alternative conformation **25**, which will lead to the *Z*-isomer **23**, although probably not



Scheme 6

present in as high a concentration, can be protonated in the stereoelectronically favourable sense, that is *exo* on the bicyclic system and *anti* to the silyl group. With the allylsilane **20** that does give good stereocontrol, everything is favourable for the formation of the *E*-isomer **22**: the more populated conformation **26** is protonated *exo* on the bicyclic system and *anti* to the silyl group. The higher-energy conformation **27** of this diastereoisomer, if it were to give any of the *Z*-isomer **23**, would have to be protonated either *endo* on the bicyclic system or *syn* to the silyl group, and the combination of unfavourable factors effectively suppresses this pathway.

We note finally that the convergent synthesis of the acetate **17**, the stereospecific and highly regioselective synthesis of the allylsilane **20**, and the highly stereospecific protodesilylation conspire to make the four-step sequence from the enone **13** to the carbacyclin analogue **22** reasonably efficient (50%).

Experimental

Ether refers to diethyl ether.

(5*SR*,7*RS*)-7-*tert*-Butyldimethylsilyloxybicyclo[3.3.0]oct-8-en-2-one **11**

1,2-Epoxyoct-3-ene, prepared in 89% yield from cycloocta-1,3-diene (160 mmol) was converted into bicyclo[3.3.0]oct-7-en-2-ol (71%) using lithium diethylamide, and into the bicyclic ketone using chromic acid.²⁵ Treatment with *N*-bromosuccinimide gave the bromohydrin, which was protected as its *tert*-butyldimethylsilyl ether. β -Elimination of the bromide using DBU, and chromatography (SiO₂, hexane–EtOAc, 4:1) gave the ketone (29% overall based on the epoxide), which had ¹³C NMR and IR in agreement with the literature;¹⁵ $\delta_{\text{H}}(\text{CDCl}_3)$ 6.35 (1 H, dd, *J* 3 and 2, HC=C), 5.20 (1 H, ddt, *J* 8, 7 and 2, HCOSi), 3.06–2.98 (1 H, m, bridgehead H), 2.72 (1 H, dt, *J* 8 and 5, *endo* CH_AH_BCO), 2.53–2.22 (3 H, m, *exo* CH_AH_BCO, *endo* Hs), 1.65–1.41 (2 H, m, *exo* Hs), 0.81 (9 H, s, Me₃C) and 0.05 (6 H, s, Me₂Si).

(1*SR*,5*SR*,7*RS*,8*SR*)-7-*tert*-Butyldimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-one **12**

Potassium cyanide (26.0 mmol) was added to a solution of the ketone **11** (20.0 mmol) and ammonium chloride (20.0 mmol) in a mixture of DMF (90 cm³) and water (10 cm³) at 60 °C and stirred for 4 h. The mixture was diluted with ether and washed with aqueous ammonium chloride and brine. The organic layer was dried (MgSO₄) and evaporated under reduced pressure to give a yellow oil. Chromatography (SiO₂, CH₂Cl₂) gave the ketone (71%); *R*_f(CH₂Cl₂) 0.25; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2240 (C≡N) and 1740 (C=O); $\delta_{\text{H}}(\text{CDCl}_3)$ 4.41 (1 H, dt, *J* 5 and 2.5, HCOSi), 3.15–3.01 (2 H, m, HCC≡N and *endo* CH_AH_BC=O), 2.9 (1 H, dd, *J* 9 and 2, bridgehead CHC=O), 2.49–2.17 (4 H, m, *exo* CH_AH_BC=O, *endo* Hs and bridgehead H), 1.89 (1 H, dddd, *J* 10, 8, 5 and 4, *exo* H β to C=O), 1.60 (1 H, ddd, *J* 15, 2.5 and 1.5,

exo H), 0.80 (9 H, s, Me₃C) and 0.04 (6 H, s, Me₂Si); δ_{C} (CDCl₃) 216.25 (C=O), 119.84 (C≡N), 77.44 (COSi), 54.15, 41.18, 41.56, 37.10, 36.65, 26.57 (3 × CH₂, 3 × CH), 25.44 (Me₃C), 17.74 (Me₃C), -5.21 (SiMe_AMe_B), -5.26 (SiMe_AMe_B); *m/z* 264 (17%, M - Me), 222 (100%, M - Bu') (Found: M⁺ - 15, 264.1439. C₁₄H₂₂NO₂Si requires *M*, 264.1420). The expected *exo* configuration of the cyano group was supported by the small coupling constant (2.5) between the proton adjacent to the silyloxy group at δ 4.41 and the proton adjacent to the cyano group.

Methyl 5-hydroxypentanoate

Sulfuric acid (conc., 0.1 cm³) was added to a stirred solution of δ -valerolactone (120 mmol) in methanol (250 cm³) and the mixture refluxed for 4 h. The mixture was cooled to 0 °C and sodium hydrogen carbonate (1.50 g) added. After the mixture had been stirred for 10 min, it was filtered through Celite and the solvent removed under reduced pressure to give the ester (94%) identical (¹H NMR) to that reported.²⁶

Methyl 5-oxopentanoate

The ester (80 mmol) was added to a solution of pyridinium chlorochromate (120 mmol) in dichloromethane (350 cm³) at 0 °C and allowed to warm to room temperature. The mixture was stirred for 2 h and diluted with ether, filtered through Celite and solvent removed under reduced pressure. The residue was redissolved in ether and the filtration process repeated to remove the remaining chromium residues. The product was purified by column chromatography (hexane-EtOAc, 3:1) to give the aldehyde (57%), identical (IR and ¹H NMR) to the known compound.²⁶

(E)(1SR,5SR,7RS,8SR)-3-(4'-Methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-one 13
LDA (1.1 mol dm⁻³ in THF, 6.0 cm³) was added dropwise to a solution of the ketone **12** (6.0 mmol) in THF (5 cm³) under argon at -78 °C and stirred for 20 min. Methyl 5-oxopentanoate (9.0 mmol) was added and the solution stirred for a further 3 min, after which acetic acid (6.6 mmol) was added. The mixture was warmed to room temperature and then diluted with ether, washed with ammonium chloride, dried (MgSO₄) and evaporated under reduced pressure. The residue was dissolved in dichloromethane, triethylamine (12.0 mmol) and methanesulfonyl chloride (12.0 mmol) were added at 0 °C, and the mixture was stirred for 1 h. DBU (12 mmol) was then added and the mixture stirred for a further 1 h, allowing it to warm to room temperature. After dilution with ether, the mixture was washed with aqueous ammonium chloride and brine, dried (MgSO₄) and evaporated under reduced pressure. The residue was chromatographed (SiO₂, EtOAc-hexane, 1:2) to give the ketone (25%); *R*_f(EtOAc-hexane, 1:2) 0.41; ν_{max} (film)/cm⁻¹ 2230 (C≡N), 1740 (COOMe), 1720 (C=O) and 1650 (C=C); δ_{H} (CDCl₃) 6.53 (1 H, tt, *J* 8 and 3, HC=C), 4.43 (1 H, q, *J* 4, HCO₂Si), 3.67 (3 H, s, MeO), 3.14-2.81 (4 H, m, ring Hs) and 2.51-2.29 (2 H, m, ring Hs), 2.33 (2 H, t, *J* 7, CH₂COOMe), 2.15 (2 H, q, *J* 7, CH₂CH₂C=C), 1.80 (2 H, quintet, *J* 7, CH₂CH₂C=C), 1.66-1.50 (1 H, m, remaining ring H), 0.77 (9 H, s, Me₃C), 0.02 (3 H, s, SiMe_AMe_B) and 0.01 (3 H, s, SiMe_AMe_B); δ_{C} (CDCl₃) 203.69 (C=O), 173.45 (COOMe), 137.38 (C=C), 136.97 (C=C), 120.18 (C≡N), 77.31 (COSi), 51.58 (MeO), 55.36, 42.80, 42.06, 33.65, 33.39, 32.36, 29.02, 23.40 (5 × CH₂, 3 × CH), 25.37 (Me₃C), 17.70 (Me₃C), -5.22 (SiMe_AMe_B) and -5.27 (SiMe_AMe_B); *m/z* 376 (13%, M - Me) and 334 (100, M - Bu') (Found: M⁺ - 15, 376.1968. C₂₁H₃₃NO₄Si requires *M* - 15, 376.1944).

(E)(1SR,2RS,5SR,7RS,8SR)-3-(4'-Methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-ol 14 and **(E)(1SR,2SR,5SR,7RS,8SR)-3-(4'-methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-ol 15**
Sodium borohydride (1.67 mmol), cerium(III) chloride (1.7

mmol) and the ketone (1.5 mmol) were stirred in methanol (2.5 cm³) at 0 °C for 5 min. Aqueous ammonium chloride was added and the mixture extracted with ether. The ether was washed with brine, dried (MgSO₄) and evaporated under reduced pressure. The residue was chromatographed (SiO₂, hexane-EtOAc, 2:1) to give the alcohol **14** (80%); *R*_f(hexane-EtOAc, 2:1) 0.33; ν_{max} (CH₂Cl₂)/cm⁻¹ 3500 (OH), 2230 (C≡N), 1740 (C=O) and 1650 (C=C); δ_{H} (CDCl₃) 5.50 (1 H, t, *J* 7, HC=C), 4.48 (1 H, d, *J* 6, HCOH), 4.27 (1 H, td, *J* 8 and 6, HCO₂Si), 3.66 (3 H, s, Me), 2.80-2.72 (2 H, m, ring Hs), 2.58-2.48 (1 H, m, ring H), 2.36-2.11 (3 H, m, ring Hs), 2.30 (2 H, t, *J* 7, CH₂COOMe), 2.07 (2 H, q, *J* 7, CH₂CH₂C=C), 1.71 (2 H, quintet, *J* 7, CH₂CH₂C=C), 1.30-1.19 (1 H, m, ring H), 0.88 (9 H, s, Me₃C), 0.12 (3 H, s, SiMe_AMe_B) and 0.08 (3 H, s, SiMe_AMe_B); *m/z* 393 (4%, M⁺), 336 (51, M - Bu') and 318 (100, M - Bu' - H₂O) (Found: M⁺, 393.2316. C₂₁H₃₅NO₄Si requires *M*, 393.2335), and the alcohol **15** (8%); *R*_f(hexane-EtOAc, 2:1) 0.20; ν_{max} (CH₂Cl₂)/cm⁻¹ 3500 (OH), 2230 (C≡N), 1740 (C=O) and 1650 (C=C); δ_{H} (CDCl₃) 5.59 (1 H, t, *J* 7, HC=C), 4.27 (1 H, s, HCOH), 4.22 (1 H, td, *J* 8 and 6, HCO₂Si), 2.81-2.48 (3 H, m, ring Hs), 2.40 (3 H, m, ring Hs), 2.31 (2 H, t, *J* 7, CH₂COOMe), 2.25 (2 H, q, *J* 7, CH₂CH₂C=C), 1.72 (2 H, quintet, *J* 7, CH₂CH₂), 1.27-1.16 (1 H, m, ring H), 0.87 (9 H, s, Me₃C), 0.11 (3 H, s, SiMe_AMe_B) and 0.08 (3 H, s, SiMe_AMe_B); *m/z* 336 (21%, M - Bu') and 75 (100) (Found: M⁺ - 57, 336.1637. C₂₁H₃₅NO₄Si requires *M* - 57, 336.1631).

(E)(1SR,2RS,5SR,7RS,8SR)-3-(4'-Methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-yl acetate 16

The alcohol **14** (0.6 mmol), acetic anhydride (0.7 mmol), triethylamine (0.7 mmol) and *N,N*-dimethylaminopyridine (0.7 mmol) were kept in dichloromethane (1 cm³) for 2 h at room temperature. Aqueous ammonium chloride was added and the mixture extracted with ether. The ether was washed with brine, dried (MgSO₄) and evaporated under reduced pressure. The residue was chromatographed (SiO₂, hexane-EtOAc, 3:1) to give the acetate (93%); *R*_f(2:1 hexane-EtOAc) 0.47; ν_{max} (CH₂Cl₂)/cm⁻¹ 2230 (C≡N), 1740 (C=O × 2) and 1650 (C=C); δ_{H} (CDCl₃) 5.50 (1 H, dd, *J* 8 and 1, HCOAc), 5.41 (1 H, tq, *J* 7 and 2, HC=C), 4.18 (1 H, td, *J* 9 and 7, HCO₂Si), 3.66 (3 H, s, MeO), 2.86 (1 H, dt, *J* 10 and 8, CHCHOAc), 2.49-2.41 (2 H, m, ring Hs), 2.32-2.03 (3 H, m, ring Hs), 2.30 (2 H, t, *J* 7, CH₂COOMe), 2.17 (3 H, s, MeC=O), 2.08 (2 H, q, *J* 7, CH₂CH₂C=C), 1.71 (2 H, quintet, *J* 7, CH₂CH₂C=C), 1.25-1.17 (1 H, m, ring H), 0.87 (9 H, s, Me₃C), 0.11 (3 H, s, SiMe_AMe_B) and 0.07 (3 H, s, SiMe_AMe_B); *m/z* 420 (7%, M - Me) and 378 (100, M - Bu') (Found: M⁺ - 15, 420.2218. C₂₃H₃₇NO₅Si requires *M* - 15, 420.2206).

(E)(1SR,2SR,5SR,7RS,8SR)-3-(4'-Methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-yl acetate 17

Method A. The alcohol **15** was acetylated similarly to give the acetate (95%); *R*_f(hexane-EtOAc, 3:1) 0.25; ν_{max} (CH₂Cl₂)/cm⁻¹ 2230 (C≡N), 1740 (C=O × 2) and 1650 (C=C); δ_{H} (CDCl₃) 5.67 (1 H, t, *J* 7, HC=C), 5.27 (1 H, s, HCOAc), 4.23 (1 H, dt, *J* 8 and 7, HCO₂Si), 3.65 (3 H, s, MeO), 2.77-2.03 (7 H, m, 2 bridgehead Hs, 3 ring Hs and CH₂CH₂C=C), 2.29 (2 H, t, *J* 7, CH₂COOMe), 2.04 (3 H, s, MeC=O), 1.70 (2 H, quintet, *J* 7, CH₂CH₂C=C), 1.62-1.23 (2 H, m, ring Hs), 0.87 (9 H, s, Me₃C), 0.12 (3 H, s, SiMe_AMe_B) and 0.08 (3 H, s, SiMe_AMe_B); *m/z* 420 (4%, M - Me), 378 (52, M - Bu'), 117 (100) (Found: M⁺ - 15, 420.2220. C₂₃H₃₇NO₅Si requires *M* - 15, 420.2206).

Method B. Diethyl azodicarboxylate (4.8 mmol) was added to a solution of the alcohol **14** (1.6 mmol), triphenylphosphine (4.8 mmol) and acetic acid (4.8 mmol) in ether (2 cm³) at room temperature and stirred for 8 h. The mixture was washed with aqueous sodium hydrogen carbonate and brine, dried (MgSO₄) and evaporated under reduced pressure. The residue was

chromatographed (SiO₂, hexane–EtOAc, 3:1) to give the *acetate* (70%), identical (TLC, IR, ¹H NMR) with the other sample.

(E)(1SR,2RS,5SR,7RS,8SR)-3-(4'-Methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-yl N-phenyl carbamate

n-Butyllithium (1.6 mol dm⁻³ in hexane, 0.1 cm³) was added to a solution of the alcohol **14** (0.155 mmol) in THF (1.0 cm³) under argon at -78 °C and stirred for 10 min. Phenyl isocyanate (0.18 mmol) was added and the mixture warmed to room temperature over 1 h. The mixture was diluted with ether, washed with aqueous ammonium chloride and brine, dried (MgSO₄) and solvent evaporated under reduced pressure. The residue was chromatographed (SiO₂, hexane–EtOAc, 3:1) to give the *carbamate* (74%); *R*_f(hexane–EtOAc, 3:1) 0.27; *v*_{max}(CH₂Cl₂)/cm⁻¹ 3300 (NH), 1740 (C=O), 1690 (C=O), 1620 (C=C), 1600, 1580 and 1500 (Ph); *δ*_H(CDCl₃) 7.42–7.07 (5 H, m, Ph), 6.76 (1 H, s, NH), 5.58 (1 H, d, *J* 9, HCO₂CNHP), 5.50 (1 H, t, *J* 7, HC=C), 4.25 (1 H, td, *J* 9 and 7, HCOSi), 3.66 (3 H, s, MeO), 2.93 (1 H, dt, *J* 10 and 8, CHCHCN), 2.62–2.07 (7 H, m, ring Hs and side-chain CH₂C=C), 2.30 (2 H, t, *J* 7, CH₂COOMe), 1.71 (2 H, quintet, *J* 7, CH₂CH₂COOMe), 1.33–1.19 (1 H, m, ring H), 0.89 (9 H, s, Me₃C), 0.12 (3 H, s, SiMe_AMe_B) and 0.09 (3 H, s, SiMe_AMe_B); *m/z* 512 (3%, M⁺), 455 (30, M – Bu') and 119 (100) (Found: M⁺, 512.2743. C₂₈H₄₀N₂O₅Si requires *M*, 512.2707).

(E)(1SR,2SR,5SR,7RS,8SR)-2-Dimethylphenylsilyl-3-(4'-methoxycarbonylbutylidene)-7-tert-butylidimethylsilyl-8-cyanobicyclo[3.3.0]octane 18 and (E)(1'RS,1RS,5SR,7RS,8SR)-3-(1'-dimethylphenylsilyl-4'-methoxycarbonyl)butyl-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]oct-2-ene 19

The allylic acetate **16** (0.55 mmol) and the silylcuprate reagent (1 mol dm⁻³ in THF, 1 cm³) were kept under nitrogen in a mixture of ether (1.5 cm³) and pentane (1.5 cm³) at 0 °C for 2 h. The mixture was diluted with ether, washed with aqueous ammonium chloride and brine, dried (MgSO₄) and solvent evaporated under reduced pressure. The residue was chromatographed to give the *allylsilane 18* (58%); *R*_f(CH₂Cl₂) 0.44; *v*_{max}(film)/cm⁻¹ 2230 (C≡N), 1740 (C=O), 1660 (C=C) and 1600 (Ph); *δ*_H(CDCl₃) 7.48–7.32 (5 H, m, Ph), 5.01 (1 H, td, *J* 7 and 1, HC=C), 4.12 (1 H, dt, *J* 8 and 6, HCOSi), 3.66 (3 H, s, MeO), 2.53 (1 H, ddd, *J* 9, 8 and 3, CHCHSi), 2.34–1.94 (8 H, m, ring Hs and CH₂CH₂C=C), 2.26 (2 H, t, *J* 7, CH₂CH₂COOMe), 1.62 (2 H, quintet, *J* 7, CH₂CH₂COOMe), 1.20 (1 H, dt, *J* 8 and 6, *exo* CH_AH_BCHOSi), 0.86 (9 H, s, Me₃C), 0.31 (6 H, s, SiMe_AMe_B or C or D), 0.09 (3 H, s, SiMe_AMe_B or C or D) and 0.05 (3 H, s, SiMe_AMe_B or C or D); *δ*_C(CDCl₃) 174.05 (C=O), 142.03, 133.68, 129.31 and 127.79 (aromatic Cs), 136.69 (HC=C), 121.39 (C≡N), 120.47 (HC=C), 76.30 (COSi), 51.44 (MeO), 47.12, 45.38, 41.65 and 38.35 (CHs), 42.15, 36.10, 33.39, 29.03 and 25.10 (CH₂s), 25.65 (Me₃C), 17.94 (Me₃C), -4.49, -4.58, -4.83 and -4.92 (4 × MeSi); *m/z* 511 (29%, M⁺) and 135 (100, PhMe₂Si⁺) (Found: M⁺, 511.2942. C₂₉H₄₅NO₃Si₂ requires *M*, 511.2938), and the *allylsilane 19* (6%); *R*_f(CH₂Cl₂) 0.40; *v*_{max}(film)/cm⁻¹ 2220 (C≡N), 1740 (C=O) and 1660 (C=C); *δ*_H(CDCl₃) 7.52–7.27 (5 H, m, Ph), 5.15 (1 H, d, *J* 2, HC=C), 4.10 (1 H, ddd, *J* 10, 9 and 6, HCOSi), 3.62 (3 H, s, MeO), 3.18 (1 H, td, *J* 8 and 2, allylic bridgehead H), 2.58–2.37 (1 H, m, bridgehead H), 2.30–1.12 (12 H, m, CH₂s and CHs), 0.90 (9 H, s, Me₃C), 0.29 (3 H, s, SiMe_AMe_B), 0.27 (3 H, s, SiMe_AMe_B or C or D), 0.12 (3 H, s, SiMe_AMe_B or C or D) and 0.08 (3 H, s, SiMe_AMe_B or C or D); *δ*_C(CDCl₃) 173.65 (C=O), 145.38, 133.87, 129.19 and 127.78 (aromatic C), 137.44 (HC=C), 122.78 (HC=C), 121.90 (C≡N), 76.68 (COSi), 52.43 (MeO), 51.44, 43.73, 36.00 and 30.91 (CHs), 42.78, 42.15, 33.81, 28.56 and 24.75 (CH₂s) and 25.70 (Me₃C), 17.97 (Me₃C), -4.17, -4.43, -4.83 and -4.88 (4 × MeSi); *m/z* 511 (37%, M⁺) and 135 (100, PhMe₂Si⁺) (Found: M⁺, 511.2907. C₂₉H₄₅NO₃Si₂ requires *M*, 511.2938).

The allylsilane **19** (12%) was the only identifiable product from the reaction of (E)(1SR,2SR,5SR,7RS,8SR)-3-(4'-methoxycarbonylbutylidene)-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]octan-2-yl *N*-phenyl carbamate with, successively, butyllithium, copper(I) iodide, triphenylphosphine and the silyllithium reagent for 2 h at 0 °C.²²

(E)(1'RS,1RS,5SR,7RS,8SR)-3-(1'-Dimethylphenylsilyl-4'-methoxycarbonyl)butyl-7-tert-butylidimethylsilyloxy-8-cyanobicyclo[3.3.0]oct-2-ene 20

The allylic acetate **17** (0.23 mmol) was similarly treated with the silylcuprate reagent to give the *allylsilane 20* (86%); *R*_f(CH₂Cl₂) 0.43; *v*_{max}(CH₂Cl₂)/cm⁻¹ 2230 (C≡N), 1740 (C=O) and 1630 (C=C); *δ*_H(CDCl₃) 5.12 (1 H, d, *J* 2, HC=C), 4.07 (1 H, td, *J* 9 and 6, HCOSi), 3.63 (3 H, s, MeO), 3.13 (1 H, td, *J* 9 and 2, allylic bridgehead H), 2.51–1.13 (9 H, m, ring Hs and CH₂CHSi), 2.37 (2 H, t, *J* 7, CH₂COOMe), 1.45 (2 H, quintet, CH₂CH₂COOMe), 0.90 (9 H, s, Me₃C), 0.29 (3 H, s, SiMe_AMe_B), 0.27 (3 H, s, SiMe_AMe_B or C or D), 0.12 (3 H, s, SiMe_AMe_B or C or D) and 0.08 (3 H, s, SiMe_AMe_B or C or D); *δ*_C(CDCl₃) 173.21 (C=O), 144.87, 133.77, 127.71 and 129.17 (aromatic C's), 137.49 (HC=C), 123.56 (HC=C), 122.20 (C≡N), 76.43 (COSi), 52.01 (MeO), 51.48, 41.43, 36.09 and 27.86 (remaining CHs), 43.41, 42.39 (2 CH₂s), 33.66 (CH₂COOMe), 31.40 and 24.78 (remaining CH₂s), 25.69 (MeC), 17.93 (Me₃C), -4.05, -4.33, -4.82 and -4.89 (4 MeSi); *m/z* 511 (40%, M⁺) and 135 (100%, PhMe₂Si⁺) (Found: M⁺, 511.2913. C₂₉H₄₅NO₃Si₂ requires *M*, 511.2938).

(E)(1RS,2SR,3RS,5SR)-7-(4'-Methoxycarbonyl)butyl-3-tert-butylidimethylsilyloxy-2-cyanobicyclo[3.3.0]oct-7-ene 21

Trifluoroacetic acid (0.10 mmol) and the allylsilane **18** (0.01 mmol) were kept in CH₂Cl₂ (1 cm³) at 0 °C for 2 h. The mixture was diluted with ether, washed with aqueous sodium hydrogen carbonate, dried (MgSO₄) and evaporated under reduced pressure. The residue was chromatographed (SiO₂, CH₂Cl₂) to give the endocyclic *alkene* (97%); *R*_f(CH₂Cl₂) 0.38; *v*_{max}(CH₂Cl₂)/cm⁻¹ 2230 (C≡N), 1740 (C=O) and 1650 (C=C); *δ*_H(CDCl₃) 5.33 (1 H, d, *J* 2, HC=C), 4.20 (1 H, ddd, *J* 10, 9 and 6, HCOSi), 3.66 (3 H, s, MeO), 3.23 (1 H, td, *J* 8 and 2, allylic bridgehead H), 2.67 (1 H, dtd, *J* 16, 9 and 3, remaining bridgehead H), 2.51 (1 H, dd, *J* 16 and 9, one allylic ring H), 2.36–2.29 (1 H, m, HCCN), 2.30 (2 H, t, *J* 7, CH₂COOMe), 2.17 (1 H, ddd, *J* 13, 9 and 6, *endo* CH_AH_BCHOSi), 2.06–1.98 (3 H, m, CH₂CH₂C=C and allylic ring H), 1.60 (2 H, quintet, *J* 7, CH₂CH₂COOMe), 1.43 (2 H, quintet, *J* 7, CH₂CH₂C=C), 1.32 (1 H, dt, *J* 13 and 10, *exo* CH_AH_BCHOSi), 0.87 (9 H, s, Me₃C), 0.11 (3 H, s, SiMe_AMe_B) and 0.08 (3 H, s, SiMe_AMe_B); *δ*_C(CDCl₃) 173.94 (C=O), 144.47 and 124.29 (HC=C), 122.04 (C≡N), 76.99 (COSi), 52.83 (MeO), 51.42, 43.28 and 36.91 (remaining CHs), 42.50, 41.78, 33.81, 30.44 and 27.04 (remaining CH₂s), 25.64 (Me₃C), 17.98 (Me₃C), -4.83 (SiMe_AMe_B) and -4.88 (SiMe_AMe_B); *m/z* 362 (3%, M – Me) and 320 (100, M – Bu') (Found: M⁺ – 15, 362.2171. C₂₁H₃₅NO₃Si requires *M* – 15, 362.2152).

(E and Z)(1SR,2SR,3RS,5SR)-5-(4'-Methoxycarbonyl)butylidene-3-tert-butylidimethylsilyloxy-2-cyanobicyclo[3.3.0]octane 22 and 23

Trifluoroacetic acid (0.10 mmol) and the allylsilane **19** (0.01 mmol) were kept in CH₂Cl₂ (1 cm³) at 0 °C for 2 h, and a similar work-up gave a mixture of the *E*- and *Z*-alkenes (90%, *E*:*Z* 67:33); *R*_f(CH₂Cl₂) 0.37; *v*_{max}(CH₂Cl₂)/cm⁻¹ 2230 (C≡N), 1740 (C=O) and 1650 (C=C); *E*-isomer **22**: *δ*_H(CDCl₃) 5.28 (1 H, t, *J* 7, HC=C), 4.18 (1 H, td, *J* 9 and 7, HCOSi), 3.65 (3 H, s, MeO), 2.63–2.44 (3 H, m, bridgehead Hs and allylic ring H), 2.35–2.14 (3 H, m, HCCN, *endo* CH_AH_BCHOSi, and allylic ring H), 2.29 (2 H, t, *J* 7, CH₂COOMe), 2.10–1.93 (4 H, m, CH₂CH₂C=C and allylic ring Hs), 1.65 (2 H, quintet, *J* 7, CH₂CH₂COOMe), 1.21 (1 H, dt, *J* 13 and 8, *exo* CH_AH_BCHOSi), 0.87 (9 H, s, Me₃C), 0.11 (3 H, s, SiMe_AMe_B) and 0.08

(3 H, s, SiMe_AMe_B); δ_{C} (CDCl₃) 174.03 (C=O), 140.51 (HC=C) 122.27 (HC=C), 121.74 (C≡N), 76.74 (COSi), 51.44 (MeO), 44.15, 43.45 and 38.41 (bridgehead Cs and CHCN), 42.00 (CH₂CHOSi), 38.73 (CH₂ trans to side chain), 34.75 (CH₂ cis to side chain), 33.39 (CH₂COOMe), 28.71 (CH₂CH₂C=C), 25.66 (Me₃C), 24.89 (CH₂CH₂COOMe), 17.95 (Me₃C), -4.82 (SiMe_AMe_B) and -4.89 (SiMe_AMe_B); *Z*-isomer **23**: δ_{H} (CDCl₃) 5.26 (1 H, t, *J* 7, HC=C), 4.18 (1 H, td, *J* 9 and 7, HCOSi), 3.66 (3 H, s, MeO), 2.63–1.93 (10 H, m, ring Hs and CH₂CH₂C=C), 2.30 (2 H, t, *J* 7, CH₂COOMe), 1.68 (2 H, quintet, *J* 7, CH₂CH₂C=C), 1.22 (1 H, dt, *J* 13 and 8, *exo* CH_AH_BCHOSi), 0.87 (9 H, s, Me₃C), 0.11 (3 H, s, SiMe_AMe_B) and 0.08 (3 H, s, SiMe_AMe_B); δ_{C} (CDCl₃) 170.04 (C=O), 140.51 (HC=C) 122.30 (HC=C), 121.81 (C≡N), 77.00 (COSi), 51.49 (MeO), 44.85, 44.11 and 37.59 (2 bridgehead CHs and CHCN), 41.45 (CH₂CHOSi), 40.07 (CH₂ trans to side chain), 33.41 (CH₂COOMe), 33.40 or 29.69 (CH₂ cis to side chain), 28.74 (CH₂CH₂C=C), 25.67 (Me₃C), 24.88 (CH₂CH₂C=C), 17.98 (Me₃C), -4.80 (SiMe_AMe_B) and -4.86 (SiMe_AMe_B); *m/z* 362 (12%, *M* - Me) and 320 (100, *M* - Bu').

The assignment of configuration rests mainly on the comparisons of the chemical shifts of the ring allylic methylene carbons of our compounds *E*-**22** (34.75 and 38.73) and *Z*-**23** (40.07 and 33.41 or 29.69) with those reported²⁴ for *E*-iloprost (35.88 and 38.14 or 38.11) and *Z*-iloprost (41.23 and 32.59 or 32.50), with the upfield signals from the methylene carbon *syn* to the methoxycarbonylpropyl sidechain.

(E)(1SR,2SR,3RS,5SR)-5-(4'-Methoxycarbonylbutylidene)-3-tert-butylidimethylsilyloxy-2-cyanobicyclo[3.3.0]octane 22

Trifluoroacetic acid (0.10 mmol) and the allylsilane **20** (0.01 mmol) were kept in CH₂Cl₂ (1 cm³) at 0 °C for 2 h, and a similar work-up gave the *E*-alkene (92%, *E*:*Z* > 96:4) identical (¹H NMR, ¹³C NMR) with the sample above (Found: *M*⁺ - 15, 362.2130. C₂₁H₃₅NO₃Si requires *M* - 15, 362.2152).

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