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The Stereoselective Addition of Organometallic Reagents to Electron-Deficient Alkylidenecyclohexanes; Alternative Linkages for Cholaphane Synthesis

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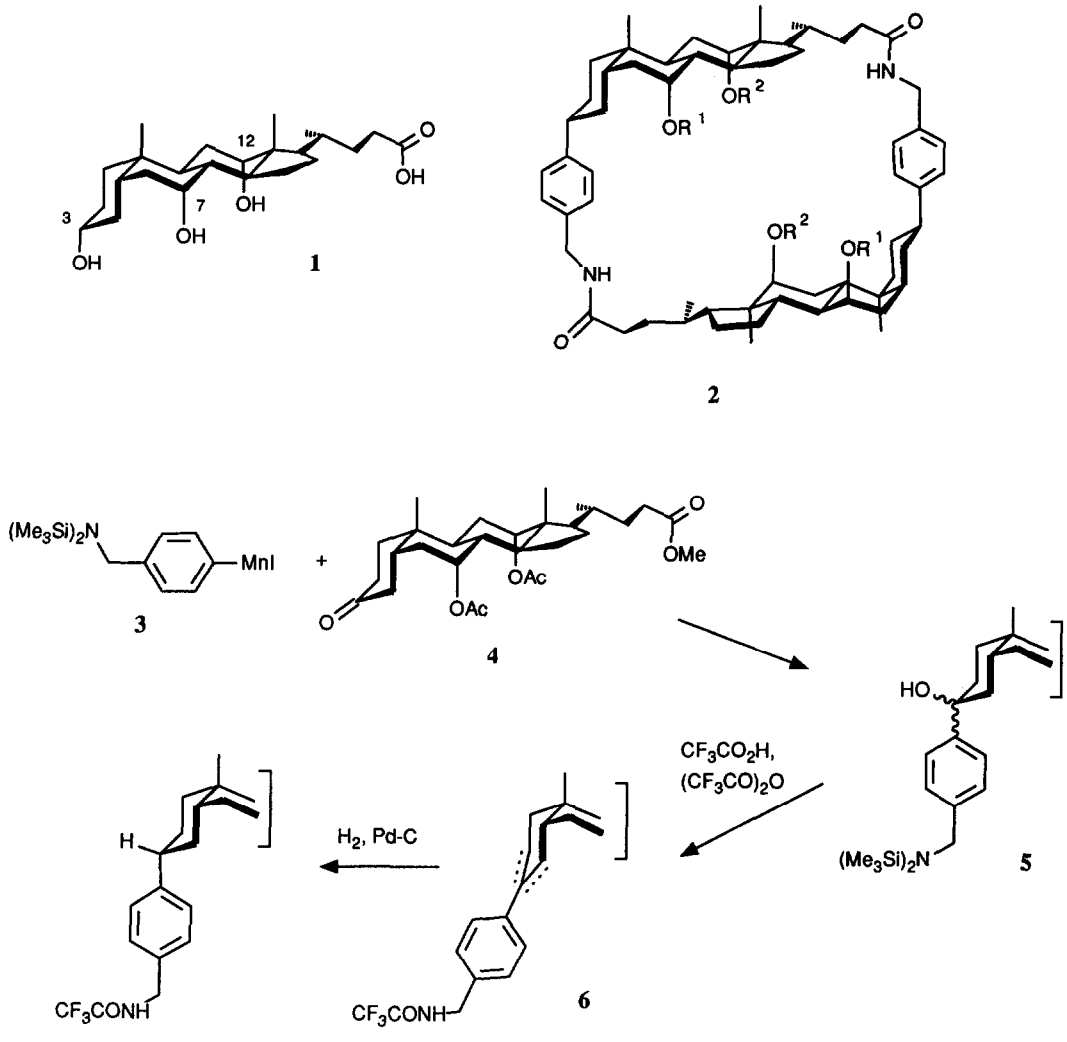
Abstract: *Knoevenagel condensations between t-butylcyclohexanone and malononitrile, Meldrum's acid and ethyl cyanoacetate gave electron-deficient alkenes which underwent equatorial-selective attack by chemoselective aryl organometallic reagents. Further transformations of the products were shown to be possible in some cases. The methodology is relevant to the synthesis of macrocyclic "cholaphane" receptors with externally-directed functional groups.*

Introduction

A degree of interest has arisen in the application of the inexpensive steroid cholic acid (**1**) as a building block in biomimetic/molecular recognition chemistry.[1,2] A few years ago we described the synthesis of the "cholaphanes" **2**, the first macrocyclic host molecules based on **1**.[1a] Although certain of these molecules proved remarkable in their ability to bind carbohydrate derivatives in organic solvents,[1b,c] the method used to synthesize them placed limitations on their further development. In the key sequence which introduced the aromatic spacer unit, carbon-carbon bond formation occurred *via* reaction of an organomanganese reagent **3** (chosen because of its inertness to ester groups) with a steroidal 3-keto group as in **4** (Scheme 1). Elimination of the stereoisomeric products gave alkenes **6** (mixture of regioisomers), and the necessary equatorial orientation of the spacer was achieved by hydrogenation from the (convex) β-face of the steroid.

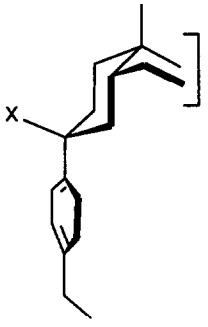
There was a sense in which this procedure appeared somewhat wasteful. C3 in **4** may be viewed as



Scheme 1

being "doubly functionalised", and still retains functionality in intermediates **5** and **6**. We felt that it should be possible to design a sequence in which the functionality could be carried through to the final product, i.e. a method of developing the steroidal C3 into a partial structure **7**. Potentially this would have two advantages. Firstly, the externally-directed functionality in the resulting cholaphanes could be used as a point of attachment (e.g. to a polymeric support) or to control the solubility properties. With regard to the latter, this would be especially important if we were to develop water-soluble cholaphanes capable of hydrophobic binding. Secondly, provided the group X were fairly bulky, it would restrict the conformation of the aromatic

spacer as shown in **7**, such that it would lie roughly parallel to the C_2-axis of the macrocycle.[3] This would lower the flexibility of the cholaphane framework, and provide a better-defined cavity (including a greater surface for hydrophobic binding, where relevant).



X = (a) functionalised, preferably variable
(b) bulky

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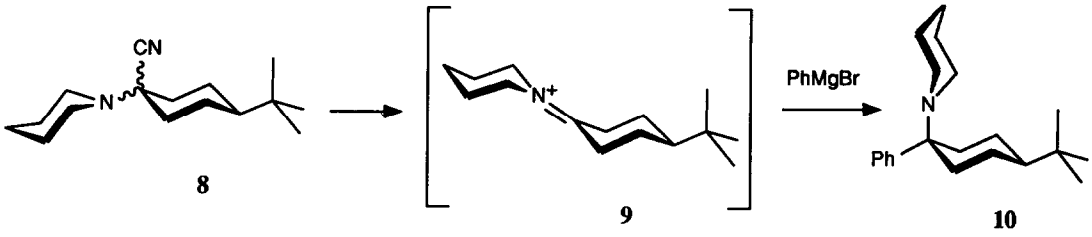
In order to realise these ideas, it was obviously desirable to undertake a series of model studies on a simple, conformationally-biassed cyclohexanone. We now give details of the results of such studies. One of the methods described herein has already been employed in the synthesis of a cholaphane,[2] and applications of the others are under investigation.

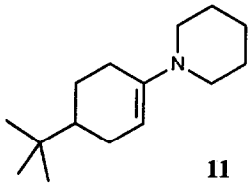
Results and Discussion

The task of devising the new C3 linkage did not seem trivial, given the need for (a) stereoselectivity, (b) chemoselectivity (once again, we would wish to restrict ourselves to reagents which are inert to ester groups) and (c) a high-yielding process. However, we were encouraged by the fact that the equatorial orientation would be required for the aryl substituent, as it seemed likely that addition reactions of aryl organometallics would generally favour this result (even though, in the particular case of additions to carbonyl groups, the selectivity is very low[4]). Initially our attention was drawn to iminium ions as substrates, as it was known that both isomers of aminonitrile **8** react with phenylmagnesium bromide to give moderate yields of amine **10** with excellent stereoselectivity,[5] presumably *via* iminium ion **9**[6] (Scheme 2). We hoped that more chemoselective, less basic organometallics might perform at least as well (especially with pre-generated iminium ions), and might give much better yields because of lower levels of enamine formation by C-deprotonation. Accordingly, we prepared the tetrafluoroborate of **9** from enamine **11** and treated it with phenyllithium, phenylmagnesium bromide, the organocerium reagent[7] derived from phenyllithium and $CeCl_3$, and the higher-order cuprate[8] $Ph_2Cu(CN)Li_2$. Unfortunately, although all these reactions gave detectable amounts of amine **10**, the yields were too low for our purposes (26% for the first two reagents, < 7% for the others).

We next considered the addition of an aryl organometallic to an exocyclic electron-deficient carbon-carbon double bond. While there appeared to be no direct precedent for this type of reaction in a stereochemically biassed system, analogous additions involving methyl organometallics had been found to be (to varying extents) equatorial-selective.[9] Moreover, it seemed that doubly-activated substrates of the general form **12** should (a) be available *via* the Knoevenagel reaction,[10] and (b) bear strong steric and electronic resemblances to the iminium ion **9** which was already known to have the desired stereochemical preference.



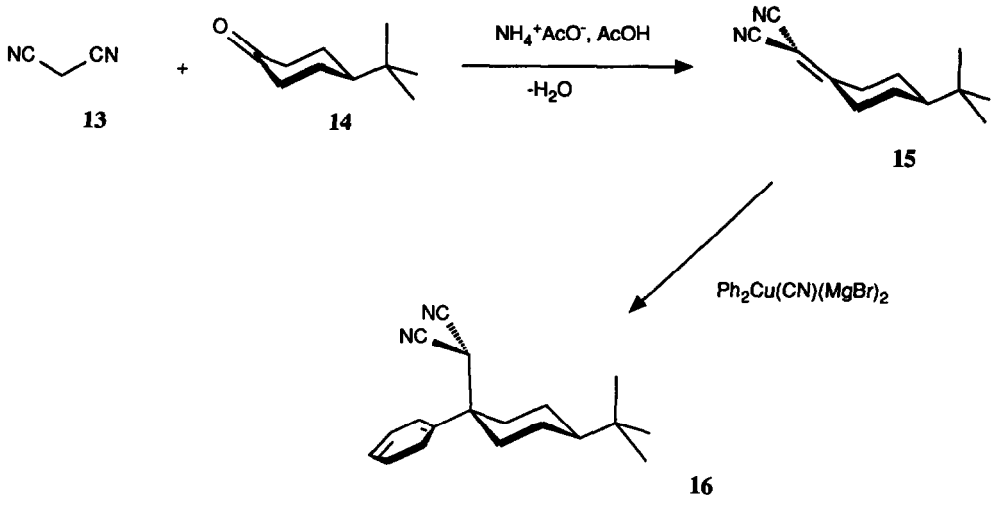
Scheme 2



Although a wide variety of active methylene compounds can be employed in the Knoevenagel condensation with aldehyde substrates, the method is more limited when applied to ketones. In the latter case the reaction only works well with a few of the more reactive agents, such as malononitrile (**13**), esters of cyanoacetic acid, and isopropylidene malonate (Meldrum's acid).[11,12] We chose malononitrile for our first investigations in this area. As shown in Scheme 3, treatment of t-butylcyclohexanone (**14**) with **13** in refluxing benzene, in the presence of ammonium acetate and acetic acid and with azeotropic removal of water,[13] gave dicyanoalkene **15** in 82% yield.

In considering the next step, we noted that while the "doubly activated" nature of **15** would promote addition, the effect would be countered by steric hindrance at the site of attack.[14] We thus decided to take advantage of the increased reactivity of higher-order organocuprate reagents.[8] **15** was treated with a two-fold excess of a reagent composed of two parts phenylmagnesium bromide[15] to one part cuprous cyanide, with a dimethoxyethane/ether mixture as solvent (Scheme 3). We were pleased to find that a single addition product was formed in essentially quantitative yield, there being no sign of a second stereoisomer. A provisional assignment, based on the chemical shift of the t-butyl group,[16] indicated that the desired stereoselectivity had indeed been obtained, i.e. the product was **16**. Conclusive evidence was obtained by X-ray crystallography, which also confirmed that the conformation about the C-phenyl bond was as expected. A notable feature of the crystals was that they contained three crystallographically distinct molecules in the unit cell, one of which is shown as Figure 1. Although all had the same gross features they varied in detail. In particular the dihedral angles corresponding to C(11)-C(10)-C(1)-C(7) in Figure 1 took the values 76.9, 84.4 and 88.7°, giving a useful (if low-resolution) picture of the degree of torsional freedom available to the aromatic ring.

In some respects we had clearly fulfilled our aims, given that the C-Aryl linkage in **16** met our structural requirements and could be introduced under mild conditions with excellent yield and stereoselectivity. Indeed, as described elsewhere,[2] we were able to apply the method to the synthesis of a



Scheme 3

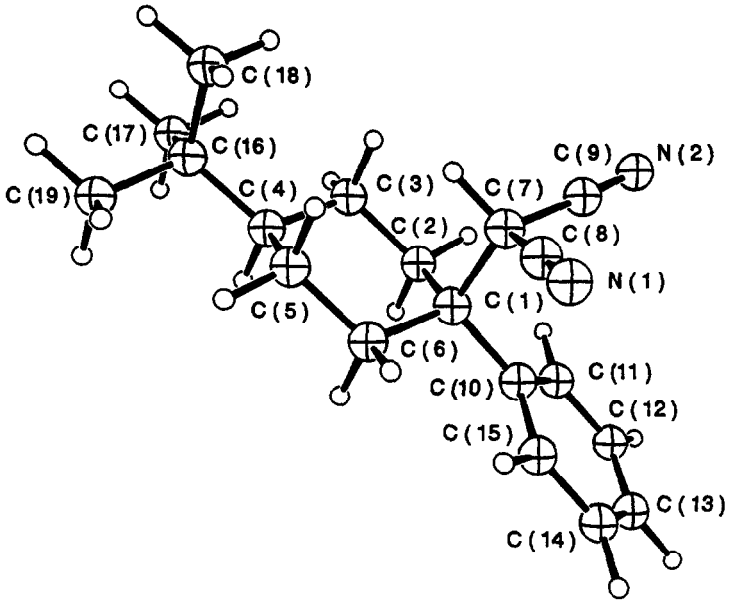
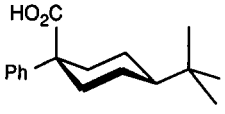


Figure 1: X-ray crystal structure of **16**

new cholaphane with greater rigidity than our initial examples. However, in order to complete the task we needed to demonstrate that the dicyanomethyl group in **16** could undergo clean conversion into other functionality. Unfortunately, this proved highly troublesome. Various reducing agents were tried, but failed to give clean conversion into a bis(aminomethyl)methyl unit, while **16** was untouched by hydrolytic conditions such as NaOMe/MeOH, H_2O_2/OH^-, and $HCl/H_2O/THF$. Oxidation with potassium permanganate[17] did not give the expected product **17**, and reactions aimed at **18** (employing guanidine/NaOEt)[18] and **19** (hydrazine/EtOH)[19] were also unsuccessful. The failure of many of these attempts may have been due to the unusually crowded environment of the cyano groups in **16**.



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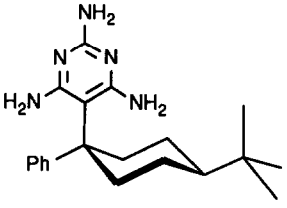

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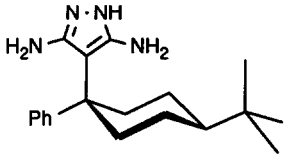
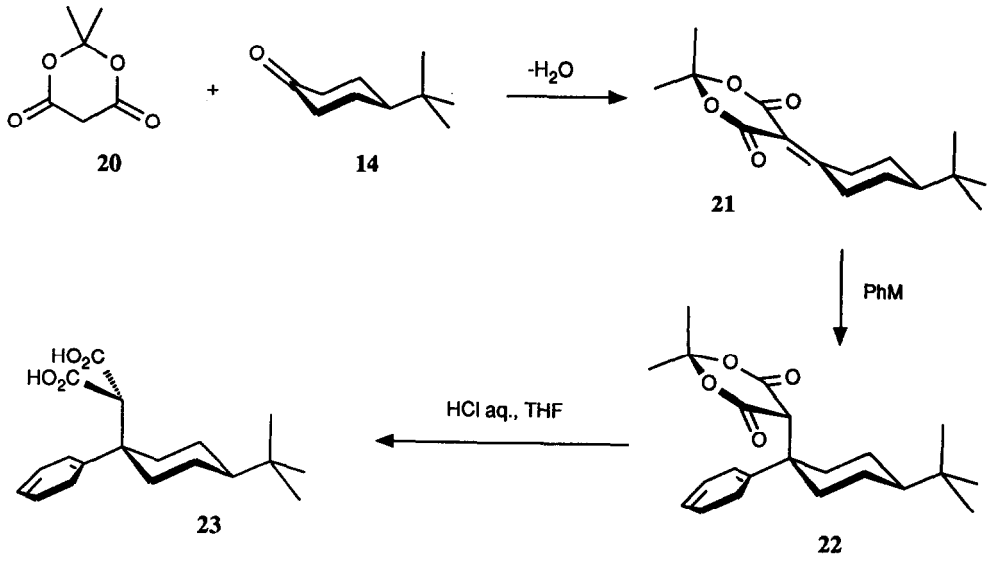


19

As mentioned above, it was known that isopropylidene malonate (**20**) would undergo the Knoevenagel condensation with ketones in good yields.[11] Provided the sequence through to adduct **22** could be carried through without incident (Scheme 4) it seemed unlikely that further transformations would cause serious difficulty. A number of methods were tried for the condensation of **20** with **14**, culminating in a procedure employing ammonium acetate, acetic acid and molecular sieves in toluene which gave **21** in a yield of 87% after crystallisation. This material was treated with $Ph_2CuCN(MgBr)_2$ in THF giving, as expected, a single addition product **22** in good yield (85% after crystallisation).[20] Once again, the stereochemistry was confirmed by an X-ray crystal structure in which the torsional restriction on the C-aryl bond was evident (Figure 2; dihedral C(8)-C(7)-C(1)-C(17) = 89.6°). Having become aware of the successful addition of organomanganese species to alkylidenemalonates,[21] we also treated **21** with the reagent derived from phenylmagnesium bromide and manganese chloride in THF. Adduct **22** was isolated in 75% yield. As before, we were able to find no indication of the presence of the alternative stereoisomer. Finally, we confirmed that further transformations on **22** would indeed be possible by removing the isopropylidene protection with aqueous acid. The malonic acid fragment in the product **23** would clearly serve as a satisfactory water-solubilising group if placed in the context of X in **7**. Usefully, the compound **22** was stable to lithium hydroxide in aqueous THF, the conditions used to hydrolyse the C24 methyl ester in cholaphane precursors, prior to cyclodimerisation.

While the above sequence did provide a satisfactory solution to our problem (which may well be applied in some cases), further work revealed a difficulty. Although the Knoevenagel condensation between **22** and ketones works well in many cases, it is not invariably successful and is difficult to "force" because of product instability (e.g. to silica gel). Accordingly, we felt we should also explore the third option mentioned earlier, i.e. esters of cyanoacetic acid. A disadvantage would be that the adducts would have an extra asymmetric centre, but as exemplified in Scheme 5, we felt that dealkoxycarbonylation followed by reduction (hopefully more succesful than with **16**) would give an *exo*-directed group which would serve our purpose.[22]



Scheme 4

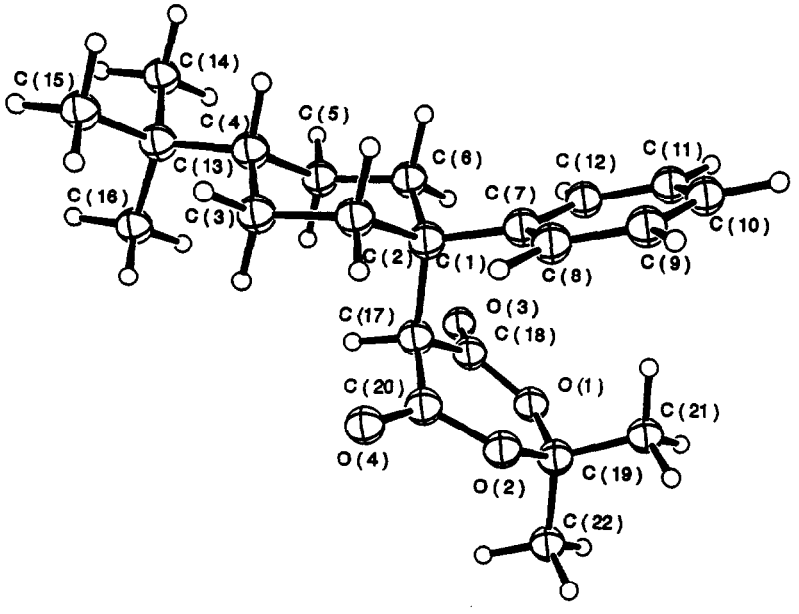
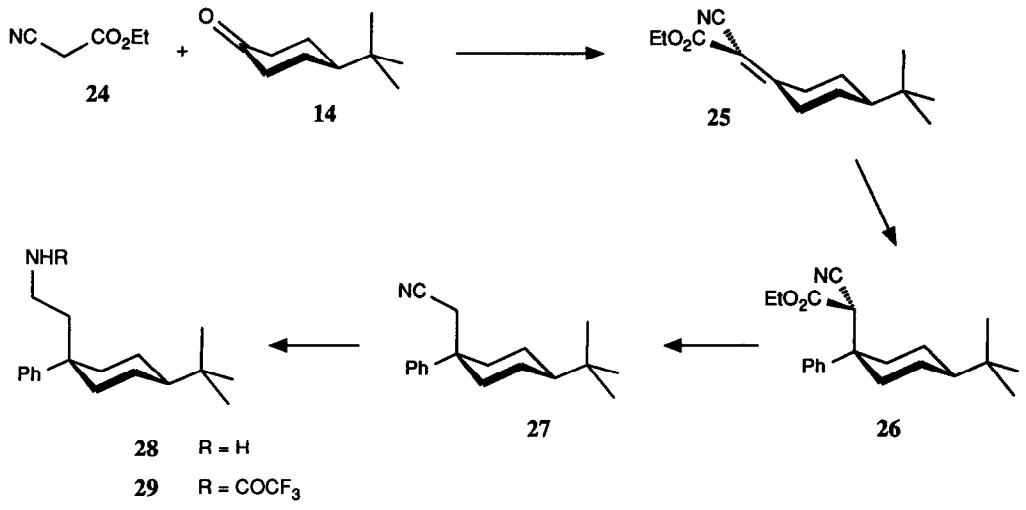


Figure 2: X-ray crystal structure of **22**



Scheme 5

We thus attempted the sequence in Scheme 5 and found that it could be carried through without difficulty. Condensation of ethyl cyanoacetate (**24**) with **14** was accomplished using the method developed for **21**, giving the product **25**[9b] in 87% yield. Treatment of **25** with $Ph_2Cu(CN)(MgBr)_2$ in THF gave adduct **26** in 91% yield, the stereochemistry being inferred from our previous experience and from ^1H NMR data. Dealkoxycarbonylation with sodium chloride in wet DMSO[23] at 160 °C gave nitrile **27** in 91% yield, and reduction with $NaBH_4/CoCl_2$ in methanol[24] gave amine **28**, characterised as its trifluoroacetyl derivative **29** (78% yield).

In conclusion, we have demonstrated several mild and high-yielding methods for converting the carbonyl group of a conformationally-biassed cyclohexanone into a quaternary carbon bearing an equatorial aromatic ring and various axially-directed substituents. This methodology is well-suited to the construction of "cholaphanes" with externally-directed functionality, and provides access to rigid structural fragments which may be applicable in other architectures.

Experimental

^1H NMR spectra were recorded on a Bruker MSL 300 spectrometer at 300 MHz or, where indicated, on Bruker AC 400 (400 MHz) or WP 80 (80 MHz) instruments. ^{13}C NMR spectra were recorded on the MSL 300 or AC 400 spectrometers. All spectra were recorded in $CDCl_3$, with TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodiobenzophenone. Dichloromethane and hexane were dried by distillation from calcium hydride. Methanol was dried by distillation from magnesium. Analytical TLC was performed on aluminium sheets coated with silica gel 60 (0.2 mm layer thickness).

4-Dicyanomethylene-t-butylcyclohexane (**15**).- A mixture of 4-t-butylcyclohexanone (**14**) (4.01 g, 26.0 mmol), malononitrile (**13**) (1.72 g. 26.0 mmol), ammonium acetate (0.39 g) and acetic acid (1.2 ml) in dry benzene (8 ml) was heated under reflux in a flask fitted to a Dean and Stark apparatus. After 3 hours the reaction mixture was cooled then washed with water (3 x 20 ml) and brine (20 ml). The solution was dried over magnesium sulphate and evaporated under reduced pressure to give brown crystals (4.82 g). The product was purified by passage through a silica gel plug using hexane-ethyl acetate (4:1) as eluent, and then recrystallized from hexane to give off-white crystals of the unsaturated dinitrile **15**[25] (4.33 g, 82%), m.p. 82-33 °C; δ_H (80 MHz) 0.88 (9 H, s, t-butyl), 1.1 - 1.5 (3 H, m, 4-H and axial 3,5-H), 1.9 - 2.6 (4 H, m, axial 2,6-H and equatorial 3,5-H), 3.07 (2 H, br d, *J* 13 Hz, equatorial 2,6-H); ν_{max}(film from THF) 2233 (conj. CN), and 1600 cm^{-1} (conj. alkene); TLC R_f 0.40 in hexane-ethyl acetate (5:1).

r-4-*t-Butyl*-c-1-*dicyanomethyl*-t-1-*phenylcyclohexane* (**16**).- A suspension of copper (I) cyanide (91.4 mg, 1.02 mmol) in dry dimethoxyethane (1 ml) was vigorously stirred at 0 °C under an atmosphere of argon. To this was added a solution of phenylmagnesium bromide (2.04 mmol; 1.65 M in ether). The mixture was allowed to warm to room temperature, giving a light-brown coloured solution over a dark brown gum. After 45 minutes a solution of the unsaturated dinitrile **15** (98.8 mg, 0.488 mmol) in dry DME (2.5 ml) was added, resulting in a chocolate coloured suspension. After stirring for 12 hours, saturated aqueous ammonium chloride solution (1 ml) was added to the mixture and the resultant slurry was washed with ether. The extract was dried with magnesium sulphate and evaporated under reduced pressure to give yellow crystals (0.153 g). The crystals were dissolved in hot hexane, and passed onto a small column of silica gel. Elution with hexane (to remove a fast-running impurity, probably biphenyl) followed by hexane-ethyl acetate (5:1) gave, after evaporation of the solvent, white crystals of *adduct* **16** (0.126 g, 99%). An analytical sample was prepared by recrystallisation from hexane-ethyl acetate, m.p. 123-124 °C (Found: C, 81.37; H, 8.60; N, 10.02. $C_{19}H_{24}N_2$ requires C, 81.38; H, 8.63; N, 9.99%); ν_{max} (film from THF) 2252 cm^{-1} (CN); δ_H (400 MHz) 0.92 (9 H, s, t-butyl), 1.12 (3 H, m, 4-H and axial 3,5-H), 1.78 (2 H, t, *J* 12 Hz, axial 2,6-H), 1.95 (2 H, br d, *J* 13 Hz, equatorial 3,5-H), 2.69 (2 H, br d, *J* 14 Hz, equatorial 2,6-H), 4.35 [1 H, s, $CH(CN)_2$], and 7.45 (5 H, m, aromatic); TLC R_f 0.42 in hexane-ethyl acetate (5:1).

Isopropylidene (4-t-butylcyclohexylidene)malonate (**21**).- To toluene (10 ml) containing acetic acid (0.14 g) and ammonium acetate (0.05 g) was added 4-t-butylcyclohexanone (**14**) (2 g, 12.96 mmol) followed by isopropylidene malonate (**20**) (1.88 g, 12.96 mmol) and 4 Å molecular sieves (2.5 g). After three hours the molecular sieves were filtered off and washed with diethyl ether (30 ml). The combined filtrate plus washings was extracted with aqueous saturated sodium hydrogen carbonate (3 x 30 ml), then water (30 ml) and dried with anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave crude product (3.3 g). Recrystallisation from hexane gave white crystals of *alkylidenemalonate* **21** (3.16 g, 87%), m.p. 123.5-124 °C (Found: C, 68.61; H, 8.51. $C_{16}H_{24}O_4$ requires C, 68.54; H, 8.63%); $\nu_{max}(CHCl_3)$ 3001, 2965, 2872, 1762, 1729 (C=O), 1595 (C=C), 1293, 1264, 1241, 1205, 1166, 1017 cm^{-1}; δ_H (80 MHz) 0.88 (9 H, s, t-butyl), 1.1 - 1.8 (3 H, m, axial 3,5-H and 4-H), 1.75 (6 H, s, 2 x CH_3), 1.9 - 2.4 (4 H, m, axial 2,6-H and equatorial 3,5-H), 3.79 (2 H, br d, *J* 13 Hz, equatorial 2,6-H); TLC R_f 0.32 in hexane-ethyl acetate (85:15).

r-4-*t-Butyl*-c-1-(4,4-*dimethyl* -3,5-*dioxa*-2,6-*dioxocyclohexyl*)-t-1-*phenylcyclohexane* (**22**)*: (A) Using an organomanganese reagent.*- A suspension of $MnCl_2$ (1.13 g, 8.95 mmol) in dry THF (20 ml) was vigorously

stirred at -30 °C under an atmosphere of argon. To this was added a solution of phenylmagnesium bromide (8.95 mmol; 0.895 M in THF). After 30 minutes the mixture was allowed to warm to room temperature, giving a brown emulsion. After 2 hours a solution of alkylidenemalonate **21** (0.5 g, 1.79 mmol) in dry THF (10 ml) was added at 0 °C. The mixture was left stirring over night then aqueous HCl (30 ml, 2 M) and diethyl ether (50 ml) was added. The aqueous layer was separated and extracted with diethyl ether (2 x 30 ml). The combined organic layers were washed with aqueous saturated sodium bicarbonate (2 x 50 ml) then water (50 ml) and dried over sodium sulphate. Removal of the solvent under reduced pressure followed by recrystallisation from hexane gave white crystals of **22** (0.48 g, 75%) (for characterisation, see below).

(B) Using an organocopper reagent.- A suspension of copper (I) cyanide (3.58 g, 40 mmol) in dry THF (10 ml) was vigorously stirred at 0 °C under an atmosphere of argon. To this was added a solution of phenylmagnesium bromide (80 mmol; 2 M in THF). The mixture was allowed to warm to room temperature, giving a dark brown solution. After 30 minutes a solution of alkylidenemalonate **21** (5.0 g, 17.9 mmol) in dry THF (10 ml) was added at 0 °C. The mixture was left stirring overnight then aqueous saturated ammonium chloride (50 ml) was added. The aqueous layer was separated and extracted with diethyl ether (2 x 40 ml). The combined organic layers were washed with aqueous sodium chloride (50 ml, 20%) and dried over sodium sulphate. Removal of the solvent under reduced pressure followed by recrystallisation from hexane gave white crystals of *addition product* **22** (5.4 g, 85%), m.p. 139-140 °C (Found: C, 73.79; H, 8.14. $C_{22}H_{30}O_4$ requires C, 73.71; H, 8.44%); $\nu_{max}(CHCl_3)$ 2960, 2875, 1767, 1739 (C=O), 1365, 1295, 1282, 1233, 1199, 1185, 1090, 1074, 1003, 848, 791 cm^{-1}; δ_H (400 MHz) 0.65 (3 H, s, CH_3CCH_3), 0.91 (9 H, s, t-butyl), 1.11 (1 H, m, 4-H), 1.48 (3 H, s, CH_3CCH_3), 1.51 (4 H, m, axial 2,3,5,6-H), 1.87 (2 H, br d, *J* 10 Hz, equatorial 3,5-H), 3.03 (2 H, br d, *J* 10 Hz, equatorial 2,6-H), 3.88 [1 H, s, $CH(CO\text{-})_2$], 7.25 (5 H, m, phenyl); δ_C 23.18 (C-3), 26.35 (CH_3CCH_3), 27.50 [$(CH_3)_3C$], 30.57 (CH_3CCH_3), 32.45 [$C(CH_3)_3$], 35.25 (C-2), 45.56 (C-1), 47.23 (C-4), 49.38 (CH), 105.74 [$C(CH_3)_2$], 126.55, 127.45, 128.48 (aromatic CH), 143.90 (aromatic C), 165.06 (carbonyl).

r-4-*t-Butyl*-c-1-[*bis(hydroxycarbonyl)methyl*]-t-1-*phenylcyclohexane* (**23**).- THF (2 ml) was added to the malonate **22** (100 mg, 0.28 mmol) followed by aqueous HCl (1 ml, 2 M). The mixture was stirred for 12 hours. Aqueous saturated sodium chloride (3 ml) and diethyl ether (2 ml) were added. After separation of the organic layer, the aqueous layer was reextracted with diethyl ether (3 ml). The combined organic layers were washed with saturated sodium chloride (3 × 5 ml) and dried over sodium sulphate. Removal of the solvent under reduced pressure followed by heating under vacuum (1 mm Hg, oil bath temp. 100 °C) gave *diacid* **23** as a white solid (71 mg, 80%). An analytical sample was prepared by recrystallisation from hexane-ethyl acetate, m.p. 162-163 °C (Found: C, 71.48; H, 8.30. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23%); $\nu_{max}(CHCl_3)$ 3481, 2964, 2874, 1756 (C=O), 1367, 1235, 1186, 1111, 1028, 654 cm^{-1}; δ_H (80 MHz) 0.85 (9 H, s, t-butyl), 1.10-2.01 (7 H, m, cyclohexyl CH_2 and CH), 2.65 (2 H, br d, *J* 12 Hz, equatorial 2,6-H), 4.02 [1 H, s, $CH(CO\text{-})_2$], 7.23 (5 H, br m, phenyl), 8.25 (2 H, br s, COO*H*).

Ethyl (4-t-*butylcyclohexylidene*)*cyanoacetate* (**25**).- To toluene (50 ml) containing acetic acid (0.71 g) and ammonium acetate (0.25 g) was added 4-t-butylcyclohexanone (**14**) (10.12 g, 65.56 mmol) followed by ethyl cyanoacetate (**24**) (8.15 g, 72.1 mmol) and 4 Å molecular sieves (6 g). The reaction was heated to 50 °C

for three hours, then the molecular sieves were filtered off and washed with diethyl ether (30 ml). The filtrate plus washings was combined and washed with aqueous saturated sodium hydrogen carbonate (3 x 30 ml), then water (30 ml) and dried with anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave crude product (14.6 g). This was heated to 80 °C at 1 mmHg for 1 hour to give **25** as a low melting solid (14.1 g, 87%); TLC R_f 0.4 in hexane-ethyl acetate (85:15); ν_{max}(neat) 2965, 2872, 2229 (CN), 1729 (C=O), 1604 (C=C), 1469, 1449, 1336, 1218, 1091, 1030 cm^{-1} (lit[9b] ν_{max} 2225, 1720, 1600); δ_H 0.88 (9 H, s, t-butyl), 1.16 - 1.44 (3 H, m, axial 3,5-H and 4-H), 1.34 (3 H, t, *J* 7 Hz, CH_2CH_3), 2.05 (3 H, m, equatorial 3,5-H and axial 2- or 6-H), 2.31 (1 H, td, *J* 13, 4 Hz, axial 2- or 6-H), 3.10 (1 H, ddd, *J* 14, 6, 3 Hz, equatorial 2- or 6-H), 3.98 (1 H, ddd, *J* 14, 6, 3 Hz, equatorial 2- or 6-H), 4.26 (2 H, q, *J* 7 Hz, CH_2CH_3); δ_C 13.66 (CH_3), 27.03 [$(CH_3)_3C$], 28.38, 28.68, 30.76, (cyclohexyl CH_2), 31.99 [$C(CH_3)_3$], 36.14 (cyclohexyl CH_2), 46.66 (C_4H), 61.14 (OCH_2), 101.42 (C=C_1), 114.98 (CN), 161.42 [C(CN)(CO_2Et)], 179.35 (COOEt).

r-4-*t-Butyl*-c-1-(1-*cyano*-1-*ethoxycarbonylmethyl*)-t-1-*phenylcyclohexane* (**26**).- A suspension of copper (I) cyanide (5.71 g, 63.8 mmol) in dry THF (15 ml) was vigorously stirred at 0 °C under an atmosphere of argon. To this was added a solution of phenylmagnesium bromide (121.54 mmol; 1.52 M in THF). The mixture was allowed to warm to room temperature giving a dark brown solution. After 30 minutes a solution of cyanoacetate **25** (10 g, 40.51 mmol) in dry THF (10 ml) was added at -30 °C. The mixture was allowed to warm to room temperature, with stirring, over a period of 1 hour. Aqueous saturated ammonium chloride (50 ml) was added. The aqueous layer was separated and extracted with diethyl ether (2 x 50 ml). The combined organic layers were washed with aqueous sodium chloride (2 × 100 ml, 20%) and dried over sodium sulphate. Removal of the solvent under reduced pressure followed by recrystallisation from hexane gave white crystals of *addition product* **26** (12 g, 91%), m.p. 97.5-98 °C (Found: C, 77.46; H, 8.52; N, 4.11. $C_{21}H_{29}NO_2$ requires C, 77.02; H, 8.93; N, 4.28%); ν_{max}($CHCl_3$) 2965, 2846, 2247 (CN), 1746 (C=O), 1462, 1450, 1360, 1240, 1020, 850, 698, 612 cm^{-1}; δ_H 0.92 (9 H, s, t-butyl), 0.91 (3 H, t, *J* 7.2 Hz, CH_2CH_3), 1.08 (1 H, tt, *J* 13, 2.4 Hz, 4-H), 1.21 (1 H, qd, *J* 13, 2.8 Hz, axial 3- or 5-H), 1.36 (1 H, qd, *J* 13.5, 3 Hz, axial 3- or 5-H), 1.59 (1 H, td, *J* 14, 3.5 Hz, axial 2- or 6-H), 1.66 (1 H, td, *J* 13, 3.8 Hz, axial 2- or 6-H), 1.88 (2 H, m, equatorial 3,5-H), 2.60-2.90 (2 H, m, equatorial 2,6-H), 3.60-3.90 (2 H, m, OCH_2CH_3), 4.06 [1 H, s, CH(CN)(CO_2Et)], 7.22-7.46 (5 H, m, phenyl); δ_C 13.34 (OCH_2CH_3), 22.60, 22.80 (C-3 and C-5), 27.28 [$(CH_3)_3C$], 32.19 [$C(CH_3)_3$], 32.43, 36.60 (C-2 and C-6), 42.17 (C-1), 43.04 [CH(CN)(CO_2Et)], 46.96 (C-4), 61.92 (OCH_2CH_3), 115.96 (CN), 125.79, 127.16, 127.99 (aromatic CH), 143.44 (aromatic C) 164.89 (C=O).

r-4-*t-Butyl*-c-1-(1-*cyanomethyl*)-t-1-*phenylcyclohexane* (**27**).- Dimethyl sulphoxide (3.4 ml) was added to a flask containing the ethyl ester **26** (328 mg, 1 mmol), sodium chloride (20.4 mg, 0.34 mmol), water (37.4 mg) and some boiling chips. A reflux condenser was attached and the mixture was heated on an oil bath (oil bath temp. 160 °C). After 2 hours the mixture was allowed to cool to room temperature and water (10 ml) was added. The resulting precipitate was removed by suction filtration and washed with water (3 × 10 ml). Extraction of the product into ethyl acetate (5 ml) followed by drying over magnesium sulphate and removal of the solvent under reduced pressure gave *nitrile* **27** (230 mg, 90%). An analytical sample was prepared by recrystallisation from hexane, m.p. 120.5-122 °C (Found: C, 85.01; H, 9.80; N, 5.29. $C_{18}H_{25}N$ requires C, 84.71; H, 9.87; N, 5.49%); ν_{max} (film from THF) 2952, 2866, 2246 (CN), 1598, 1582, 1495, 1445, 1422, 1364, 1235, 1026, 771, 710 cm^{-1}; δ_H 0.84 (9 H, s, t-butyl), 0.97 (1 H, tt, *J* 12, 3.2 Hz, 4-H), 1.15 (2 H, qd, *J*

13, 3.2 Hz, axial 3,5-H), 1.62 (2 H, td, *J* 13.7, 3.4 Hz, axial 2,6-H), 1.76 (2 H, dd, *J* 13.2, 2.6 Hz, equatorial 3,5-H), 2.19 (2 H, dt, *J* 13.7, 1.5 Hz, equatorial 2,6-H), 2.63 (2 H, s, CH_2CN), 7.25 (5 H, m, phenyl); δ_C 22.50 (C-3), 26.10 (CH_2CN), 27.10 [$(CH_3)_3C$], 32.01 [$C(CH_3)_3$], 35.50 (C-2), 38.70 (C-1), 47.60 (C-4), 118.30 (*C*N), 125.01, 126.90, 128.80 (aromatic *C*H), 147.04 (aromatic *C*).

r-4-*t-Butyl*-c-1-(2-*trifluoroacetylaminoethyl*)-t-1-*phenylcyclohexane* (**29**).- Dry methanol (50 ml) was added to a flask containing nitrile **27** (500 mg, 1.96 mmol), followed by cobalt chloride (1.6 g). To this sodium borohydride (1.6 g) was added gradually over one hour with stirring. After 3 hours aqueous HCl (2 M, 10 ml) was added, and after a further hour the solvent was removed under reduced pressure. Ethyl acetate (100 ml) and ammonium hydroxide (2 M, 50 ml) were added to the residue. The aqueous phase was separated and extracted with ethyl acetate (2 × 50 ml). The organic layers were combined and washed with ammonium hydroxide (2 M, 50 ml) and then brine (2 × 50 ml). The ethyl acetate phase was cooled in an ice bath, and pyridine (5 ml) and trifluoroacetic anhydride (8 ml) were added. The mixture was allowed to warm to room temperature and left to stand for 4 hours. Water (50 ml) was added, and the organic layer was separated, washed with water (2 × 50 ml) and brine (2 × 50 ml), then dried over sodium sulphate. The solvent was removed under reduced pressure to give crude **29** (0.61 g). This was recrystallised from hexane to give pure *trifluoroacetamide* **29** as white needles (0.55 g, 78%), m.p. 150-150.5 °C (Found: C, 67.59; H, 7.81; N, 3.78. $C_{20}H_{28}F_6NO$ requires C, 67.58; H, 7.94; N, 3.94%); ν_{max} ($CHCl_3$) 3443, 2945, 2871, 1726 (C=O), 1605, 1546, 1212, 1172 (CF_3), 887, 646 cm^{-1}; δ_H (400 MHz) 0.89 (9 H, s, t-butyl), 1.00 (1 H, tt, *J* 12, 3 Hz, 4-H), 1.31 (2 H, br q, *J* 13 Hz, axial 3,5-H), 1.55 (2 H, td, *J* 13, 3 Hz, axial 2,6-H), 1.74 (2 H, br d, *J* 12 Hz, equatorial 3,5-H), 1.99 (2 H, t, *J* 7 Hz, CH_2CH_2NH), 2.16 (2 H, br d, *J* 12 Hz, equatorial 2,6-H), 3.07 (2 H, q, *J* 7 Hz, CH_2CH_2NH), 5.67 (1 H, br m, $CH_2NHCOCF_3$), 7.30 (5 H, m, phenyl); δ_C 22.66 (C-3), 27.48 [$(CH_3)_3C$], 31.55 [$C(CH_3)_3$], 32.33 (CH_2NH), 35.89 (C-2), 36.10 (CH_2CH_2NH), 38.36 (C-1), 47.67 (C-4), 115 (q, CF_3), 125.33, 126.18, 128.50 (aromatic *C*H), 148.99 (aromatic *C*), 157 (m, CF_3CONH) .

X-Ray Structure Determination of Compound **16**:[26] $C_{19}H_{24}N_2$, P-1, a = 8.331(1) Å, b = 17.829(2) Å, c = 18.643(2) Å, α = 71.82(1)°, β = 78.96(1)°, γ = 85.66(1)°, U = 2581.77 $Å^3$, μ = 0.33 cm^{-1}, F000 = 912.00, Z = 6, λ(Mo-K_α) = 0.7093 Å. Data was collected on an Enraf-Nonius CAD4F diffractometer using ω-2θ scans (2 < 2θ < 48°); No. unique data = 7995, total I > 3 σ I = 3070. R = 7.72%, R_ω = 5.45%, largest +ve peak = 0.16 e/$Å^3$, largest -ve peak = -0.09 e/$Å^3$. The structure was solved by direct methods, SHELX86,[27] and refined by full matrix least squares using SHELX76.[28] Data were corrected for Lorentz and polarization effects but not for absorption. Hydrogen atoms were included in calculated positions with fixed thermal parameters. The asymmetric unit of the crystal contained three crystallographically distinct but chemically identical molecules. The three molecules were in the chair conformation with the phenyl and t-butyl groups in equatorial positions. The carbons of the t-butyl groups and the carbon and nitrogen atoms of the $C(CN)_2$ groups were refined anisotropically. The atomic scattering factors for non-hydrogen and hydrogen atoms and the anomalous dispersion correction factors for non-hydrogen atoms were taken from the literature.[29] All calculations were performed on a VAX 8700 computer. The ORTEP programme was used to obtain the drawing.[30]

X-Ray Structure Determination of Compound **22**:[26] $C_{22}H_{30}O_4$, $P2_1/a$ Non Standard No. 14, a = 13.203(3) Å, b = 12.389(4) Å, c = 13.441(3) Å, β = 111.60°, U = 2044.18 $Å^3$, μ = 0.45 cm^{-1}, F000 = 776.00, Z

= 4, λ(Mo-K_α) = 0.7093 Å. Data was collected on an Enraf-Nonius CAD4F diffractometer using ω-2θ scans ($2 < 2\theta < 60^o$); No. unique data = 3488, total $I > 3\,\sigma\,I$ = 2247. R = 5.11%, R_ω = 5.92%, largest +ve peak = 0.16 e/Å^3, largest -ve peak = -0.10 e/Å^3. Other experimental details as for the determination of **16**, except that the asymmetric unit contained a single molecule and that all non-hydrogen atoms were refined anisotropically.

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