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Enantioselective Synthesis of Functionalised Decalones by Robinson Annulation of Substituted Cyclohexanones, Derived from *R*-(−)-Carvone

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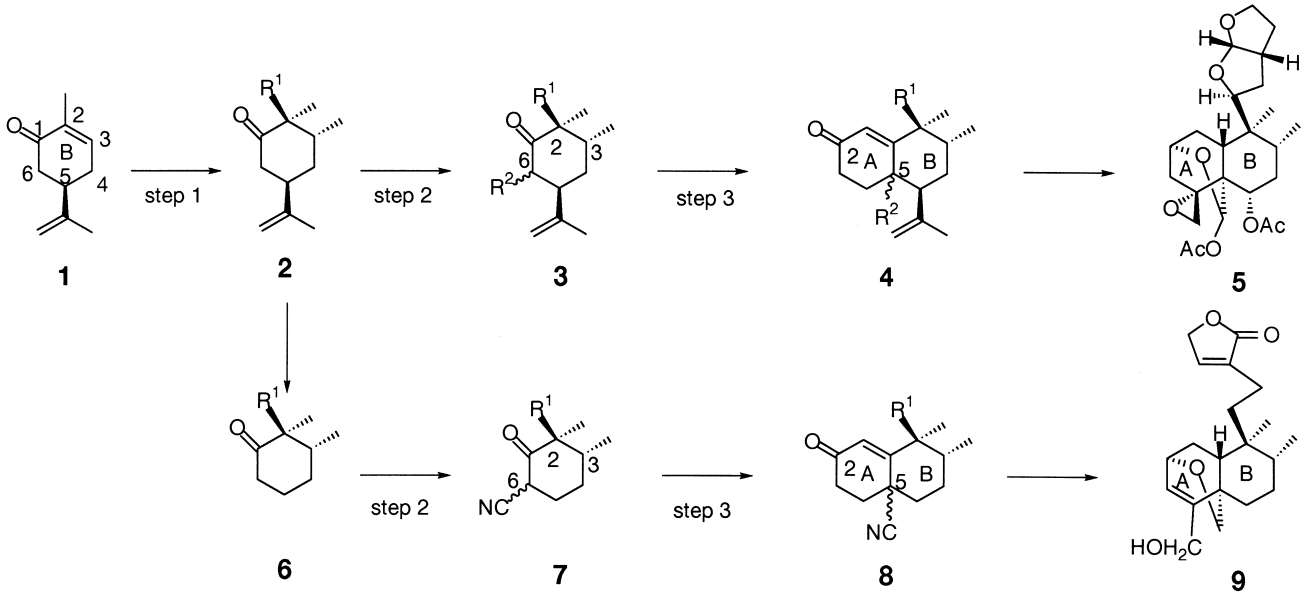
Abstract—The copper catalysed conjugate addition of methyl magnesium iodide to cyclohexenones and trapping of the enolate as its trimethylsilyl enol ether, followed by a trityl hexachloroantimonate ($TrSbCl_6$) catalysed Mukaiyama-reaction, was applied to *R*-(−)-carvone. This proved to be an efficient method for the preparation of C-2, C-3 functionalised chiral cyclohexanones. These compounds were converted into their α-cyano ketones, which were submitted to Robinson annulation reactions with methyl vinyl ketone. The scope and limitations of these annulations were investigated. A series of highly functionalised chiral decalones were obtained that can be used as starting compounds in the total syntheses of enantiomerically pure clerodanes.

Introduction

The copper catalysed conjugate addition of methyl magnesium iodide to enones leads to enolates that can be captured as their silyl enol ethers. A Lewis acid catalysed Mukaiyama reaction then allows the introduction of a second substituent. When these two reactions are applied to one of the enantiomers of carvone, highly functionalised chiral



Scheme 1.

Keywords: carvone; Mukaiyama reaction; α-cyano ketones; Robinson annulation.
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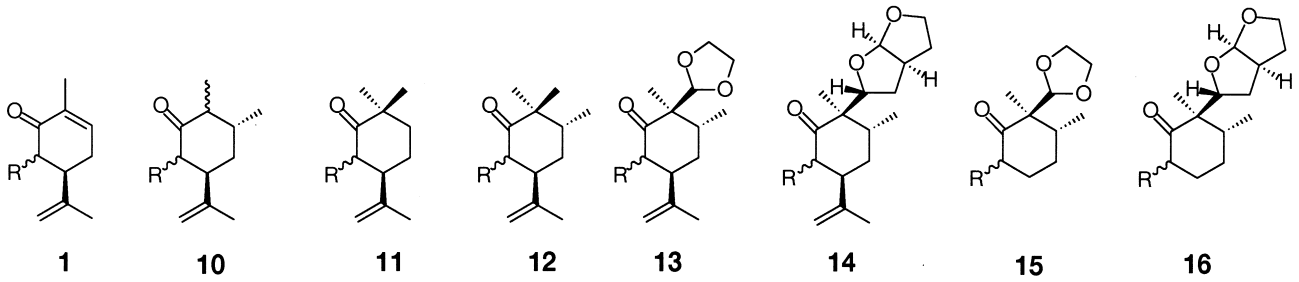


Figure 1. a, R=H; **b**, R=CHO; **c**, R=CN.

cyclohexanones are obtained that are excellent starting compounds for the total synthesis of enantiomerically pure natural products.[1,2] Carvone is especially useful in such total syntheses because the isopropenyl group first determines the stereochemistry of the cuprate conjugate addition and of the Mukaiyama reaction, and later on it can be transformed into an additional functional group at C-5, such as a hydroxyl group,[3] an acetate,[3] a double bond,[4] or a carbonyl group.[5]

Several examples of the copper catalysed conjugate addition of methyl magnesium iodide to carvone, followed by trapping of the enolate as its trimethylsilyl enol ether, followed by the introduction of a functionalised sidechain via a Mukaiyama reaction have been investigated, and the results of this research have been reported (step 1, Scheme 1).[6] This sequence of reactions leads to highly functionalised chiral cyclohexanones, which have been and can be used for the enantioselective total synthesis of clerodanes starting from carvone.

The next step in such a total synthesis is the introduction of an oxidised functional group at C-6 and the annulation of ring A (steps 2 and 3, Scheme 1). The Robinson annulation seemes particularly suitable to construct the decalin moiety in the synthesis of ring A bridged clerodanes like **5** and **9**, because it will provide for a carbonyl group at C-2, which after reduction could form one end of this bridge. For the construction of the other end of the bridge, a suitable functional group must be introduced at C-6 in the intermediate cyclohexanones **2** or **6**, which should end up as the functionalised substituent at C-5 in the clerodane as is indicated in the compounds **4** and **8** (Scheme 1). It would be nice if this functional group would facilitate the annulation reaction as well and a formyl group, an ester group or a cyano group should be considered to achieve that goal. In this way an enantioselective synthesis of this special type of ring A bridged clerodanes, which show a high activity as antifeedant,[7] may become feasible.

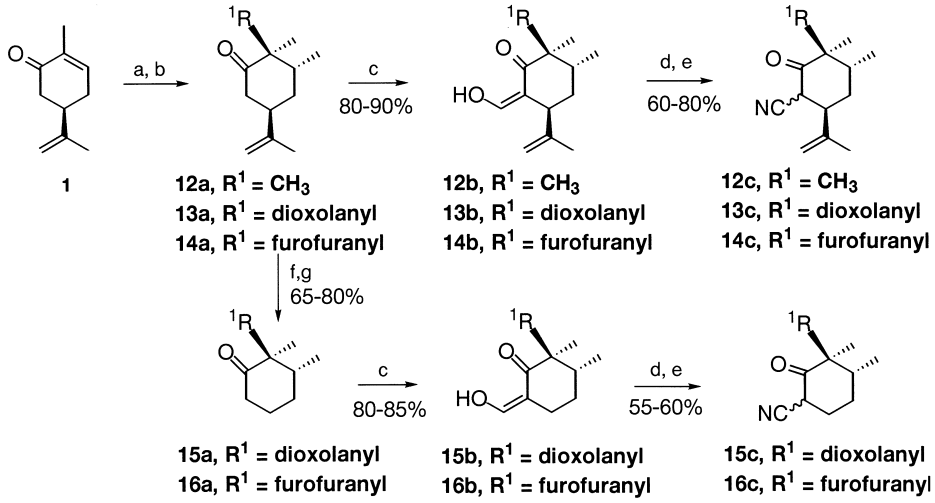
Therefore Robinson annulations of highly substituted carvone derived cyclohexanones were to give the annulated compounds in good yield and with the correct stereochemistry for the synthesis of clerodanes. A second goal is to gather more information about the scope, the limitations, and the stereochemistry of the Robinson annulation in heavily substituted cyclohexanones. A third goal is to extend and to demonstrate the reaction possibilities of carvone as a chiral starting material in the synthesis of natural products.

To achieve these goals, carvone (**1a**) and its substituted derivatives **10a–16a** were prepared, converted into their 6-formyl and 6-cyano derivatives (see Fig. 1), and submitted to Robinson annulation reactions with methyl vinyl ketone (MVK). The choice of compounds **10–16** with the formyl or cyano group at C-6 was done for the following reasons.

- (i) Compounds **1** and **10–14** show an increase in steric hindrance so that the influence of this factor on the annulation reaction with MVK (addition and ring closure) can be studied.
- (ii) Compounds **11** have the geminal methyl groups at C-2 that are present in many terpenoid natural products.
- (iii) Compounds **13** and **14** can provide for flexible intermediates in the synthesis of clerodanes.
- (iv) The reaction of compounds **1** and **10–14** will reveal the influence of the isopropenyl group on the stereochemistry of the annulation.
- (v) Compounds **15** and **16** will be studied to investigate the influence of the substituents at C-2 on the stereochemistry of the annulation reaction. Also in these cases suitable intermediates for the synthesis of clerodanes will be obtained.
- (vi) The formyl group was chosen as a substituent at C-6 because a formyl group is present in many ring A bridged clerodanes; at the same time it is an intermediate in the synthesis of the corresponding cyano compounds.
- (vii) The cyano group was chosen because it can be converted into a formyl group. Also, this group is known to activate the α hydrogen atoms so that an easy addition of the enolate to MVK may be expected, and it activates the carbonyl group for the subsequent ring closure reaction.[8] Both effects are effectuated with the least possible additional steric hindrance. For these reasons the cyano group has to be preferred over the ester group in this type of reaction and therefore the ester substituent was not included in these investigations.

Results and Discussion

Compounds **1b**,**c**, **10a–c**, **11a–c** and **12a–c** were prepared according to standard procedures. Compounds **13a–c**, and **14a–c** also could be obtained easily using standard conditions for the conjugate addition, followed by a Mukaiyama reaction for the introduction of the dioxolanyl group or the furofuranyl sidechain.[9] Formylation of these compounds generally proceeded in good yield and the conversion of



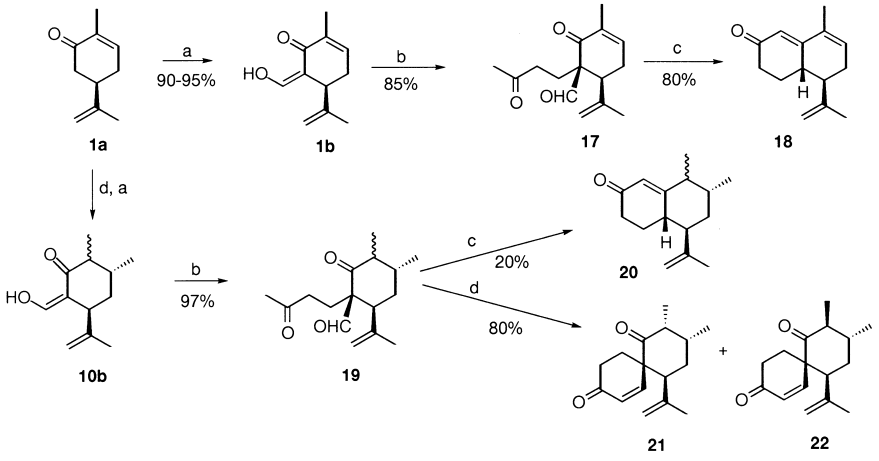
Scheme 2. (a) i, MeMgI, CuBr·Me_2S, TMSiCl, ii, Et_3N. (b) i, $TrSbCl_6$, −78°C, CH_2Cl_2, alkylating agent; ii, aqueous $NaHCO_3$. (c) NaH, HCOOEt. (d) H_2NOH, CH_3COONa. (e) $NaOCH_3$, CH_3OH. (f) i, O_3, CH_2Cl_2, MeOH; ii, $Cu(OAc)_2$, $FeSO_4$. (g) Pd/H_2.

the formyl compounds into the cyano compounds could be achieved via basic decomposition of the intermediate isoxazoles (see Scheme 2). In general the products were obtained in good yield as described in the general procedure in the experimental part.

For the introduction of the furofuranyl sidechain, *racemic* 2-methoxy-hexahydro-furo[2,3-*b*]furan was used, so in principle eight stereoisomers can be formed. In practice only two were obtained in a 1:1 mixture, which can be explained by an approach of the convex side of the hexahydro-furo[2,3-*b*]furanyl cation to that side of the silyl enol ether which is *cis* to the isopropenyl group and *trans* to the C-3 methyl group.[9] Compound **14a** can be separated from its diastereoisomer by crystallisation from di*iso*propyl ether, and the structure of **14a** was determined by X-ray crystallography.[10] The isopropenyl group was removed by ozonolysis of **13a** and **14a** followed by oxidation of the intermediate methoxy hydroperoxide by addition of $Cu(OAc)_2$ and $FeSO_4$[4] (see Scheme 2). In this way the enones were obtained, which could be reduced catalytically to the saturated ketones **15a** and **16a**. The formyl compounds **15b** and **16b** and the cyano ketones **15c** and **16c** were prepared as mentioned above.

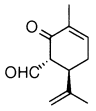
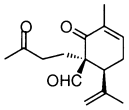
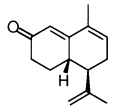
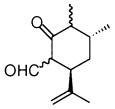
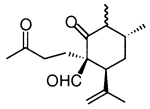
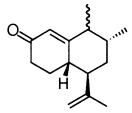
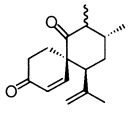
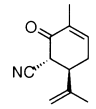
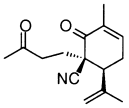
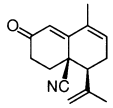
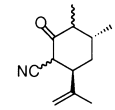
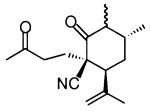
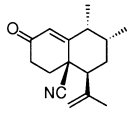
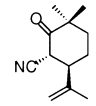
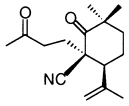
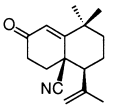
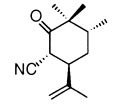
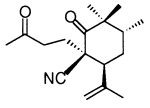
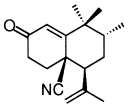
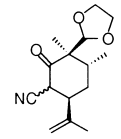
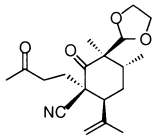
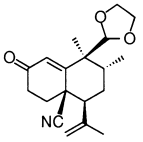
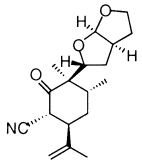
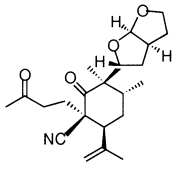
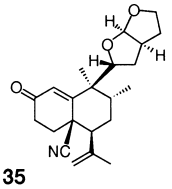
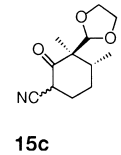
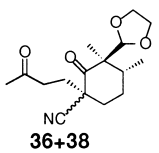
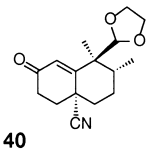
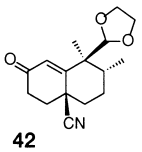
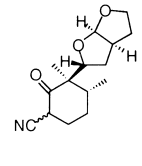
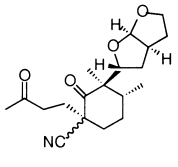
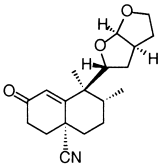
The formylation of carvone followed by Michael addition to methyl vinyl ketone proceeded without difficulties and in good yield. Further cyclisation of the adduct **17** went together with deformylation to give the bicyclic skeleton **18** in 40–78% yield.[11,12] However in the more hindered compound **10b** an alternative reaction possibility already appeared. In this case the formylation of **10** to **10b** and its base catalysed addition to MVK to give **19** proceeded normally, but in the base catalysed cyclisation reaction only a small amount of the 'normal' cyclisation product **20** was obtained together with products that resulted from retro Michael and deformylation reactions. Under Knoevenagel conditions a condensation with the less hindered aldehyde group was preferred, and the spiro compounds **21** and **22** were obtained as the main reaction product in a 2:7 ratio (Scheme 3). This behaviour has been observed regularly in steric congested situations[13,14] and must be considered as the preferred behaviour in these cases (vide infra). For these reasons the cyclisation reactions of the even more hindered formyl compounds **11b**–**16b** were not investigated further.

Instead it was decided to investigate the annulation reactions of the cyano ketones **1c** and **10c**–**16c**. The cyano



Scheme 3. (a) NaH, HCOOEt. (b) KOH, Et_3N, MVK, EtOAc. (c) KOH, MeOH, H_2O. (d) MeMgI, CuBr·Me_2S. (e) Pyrrolidine, AcOH, pH=7, THF.

Table 1. The entries 1, 3 and 5 have also been investigated for *S*-(+)-carvone (see Experimental). The Methods A–C and 1–6 are also described in the Experimental section

	starting compound	Method	adducts	yield	decalones		Method	yield	remarks
1	 **1b**	C	 **17**	85	 **18**		6	78	
2	 **10b**	C	 **19**	97	 **20**	 **21+22**	6	20	application of Method 5 gave an 80% yield of **21** and **22**
3	 **1c**	B		78	 **23**		1	85	
4	 **10c**	A	 **25**	88	 **26**		2 3	82 65	
5	 **11c**	A		94	 **24**		1	94	
6	 **12c**	A	 **27**	91	 **33**		1 4 3	0 84 73	the retro Michael reaction gave a 100% recovery of **12c**
7	 **13c**	A	 **28**	76	 **34**		4 3	41 25	48% recovery of **13c**
8	 **14c**	A	 **29**	95	 **35**		4	40	51% recovery of **14c**
9	 **15c**	A	 **36+38**	90	 **40**	 **42**	4	90	
10	 **16c**	A	 **37+39**	78	 **41**		4	90	

group is a good activator for Michael additions and after that it activates the carbonyl group for condensation in the cyclisation reaction. At the same time its own reactivity towards condensation is less than that of an aldehyde so that a 'normal' cyclisation to the decalin system may be expected as the main reaction. The results of these experiments are summarised in Table 1.

The cyano ketones can be roughly divided into two groups: compounds **1c**, **10c**, and **11c**, which react properly with MVK under basic conditions to give the annulated compounds in good yield, and compounds **12c**–**16c**, which react with difficulty with MVK to cyclised products using basic reaction conditions.

Some peculiar features were noticed in the reaction of **10c** with MVK; on TLC and GLC it was shown that the starting mixture of stereoisomers was converted into several stereoisomeric intermediates, but ultimately the reaction led to the most stable enantiomerically pure annulated product **26** (Scheme 4).

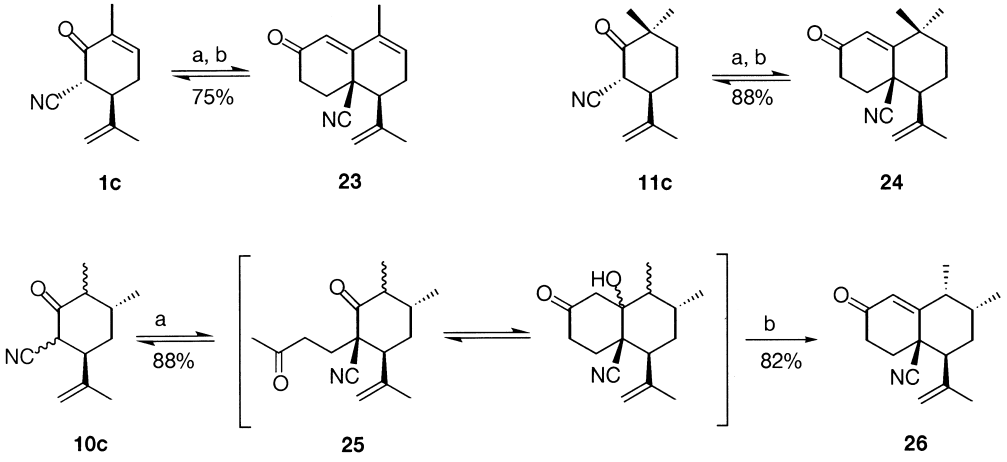
Problems began to appear when the steric hindrance increased to the level in compounds **12c**–**14c**. Here the Michael addition of MVK could still be realised using the standard basic conditions, but the ring closure of **27**, **28**, and **29** under basic conditions (0.6 equiv. NaOMe in benzene) did not occur, instead a retro Michael reaction took place to give back the starting cyano ketones **12c**–**14c**. However in practically all cases the ring closure of **27**, **28**, and **29** could be achieved using Knoevenagel conditions. Even in the most sterically crowded addition products ring closure under Knoevenagel conditions gave the cyclised enones **33**,[10] **34**, and **35**. In these reactions the intermediate hydroxy ketones **30**–**32** were not observed or could not be isolated, and the reaction proceeded smoothly to the enones. In the cyclisation of **28** and **29** the retro Michael reaction still proved to be a major side reaction, as under the more neutral Knoevenagel conditions.

In all these cases the stereochemistry of the Michael addition was determined by the isopropenyl group, directing the incoming MVK to the *trans* position. This means that in these addition products and in the cyclised products the cyano group and the substituent R^1 were in a *cis* position, which made these compounds unsuitable as intermediates for the total synthesis of clerodanes. This stereochemical result was not unexpected and these reactions were carried out in the first place to establish the scope of the annulation sequence.

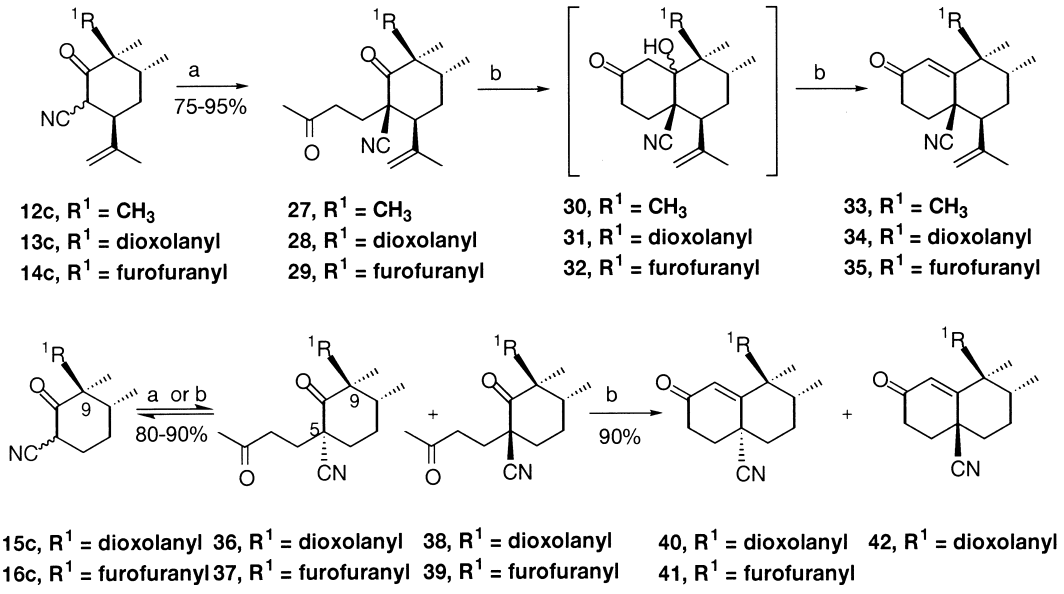
Nevertheless, one of the main goals of our research is the synthesis of ring A bridged clerodanes and therefore the annulation of the cyano ketones **15c** and **16c** was investigated also. In these compounds it was expected that the group R^1 at C-9 should be the determining factor for the stereochemistry at C-5. This large group should occupy the equatorial position in the starting cyano enolates so that the axial methyl group at C-9 should disfavour an approach of MVK from the α side. The 1,3 diaxial position of the methyl and cyano groups in the addition products **36** and **37** should not cause serious steric interaction, and the subsequent ring closure reaction also was expected to proceed via less hindered intermediates to the desired dehydrated products **40** and **41**.

In practice the outcome showed some modifications of these expectations. In both keto nitriles **15c** and **16c** a mixture of addition products **36**, **38** and **37**, **39** was obtained respectively.[15] These mixtures of adducts could be separated in the case of **36** and **38** and both isomers were subjected to Knoevenagel ring closure conditions. The isomer **36** gave a smooth reaction to what proved to be the dehydrated cyclised enone **40**. The other isomer **38** gave, after a much longer reaction time, the same cyclised reaction product **40** together with a small amount of its epimer **42** as a byproduct (Scheme 5).

The mixture of **37** and **39** could not be separated and the mixture was submitted to Knoevenagel cyclisation conditions to give the enone **41** as the only isolated product. The outcome of these two cyclisation reactions confirmed that under Knoevenagel conditions retro Michael reactions and re-additions can take place. Additional confirmation for this behaviour was obtained from an experiment in which an excess of *ethyl* vinyl ketone was added to the cyclisation reaction of compound **38** under Knoevenagel conditions. Together with the cyclised compounds **40** and **42**, a small amount of **43**, the ethyl vinyl ketone adduct of **15c**, could be isolated.



Scheme 4. (a) 0.2 equiv. $NaOCH_3$, MVK, C_6H_6. (b) 0.6 equiv. $NaOCH_3$, C_6H_6.



Scheme 5. (a) $NaOCH_3$, MVK, C_6H_6. (b) Pyrrolidine, CH_3COOH, MVK, $C_6H_5CH_3$.

For this reason also the addition–cyclisation–dehydration reaction of the cyano ketones with MVK under Knoevenagel conditions, which should lead to the desired most stable enones in a one-pot reaction, was tried out with the cyano ketones **10c**, **12c** and **13c**. It proved to be possible to obtain the enones **26**, **33** and **34** with the indicated stereochemistry, which was proven by X-ray diffraction for **33**. However, the reactions were slow and in practice the two step procedure via base catalysed Michael addition followed by cyclisation of the adducts under Knoevenagel conditions proved to be preferrable.

An explanation of these results can be found by application of the considerations of Nussbaumer[16] who states that cyclisation of the Michael adducts should take place via one of

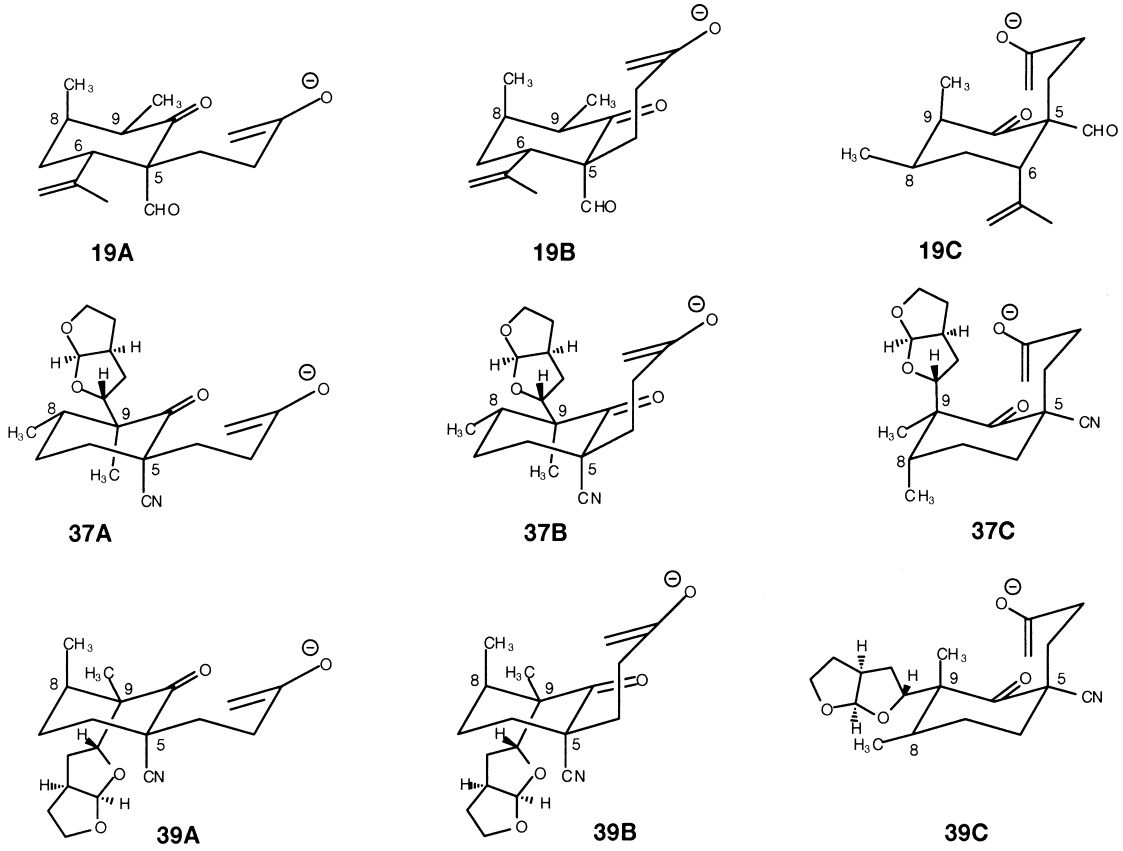


Figure 2.

the three types of chair-like transition states A, B and C of the intermediate enolates that are depicted in Fig. 2.

The *trans* equatorial pathway A leads to the thermodynamic and more stable *trans* decalin. This is normally the preferred pathway when there is no, or just a small, substituent at the angular position (C-5). Steric hindrance between an axial substituent at C-8 will cause the strongest interaction in the transition state that is depicted as path B, and this interaction usually will prevent ring closure along path B. The axial position of a large substituent at C-9 together with the axial position of the enolate sidechain is an unlikely conformation and will prevent cyclisation following path C. When all three transition states will have unfavourable steric interactions or when unlikely conformations are necessary, then ring closure does not take place and the retro Michael reaction prevails.

These considerations can also explain the results that are described in Scheme 3 for the cyclisation of compound **19**, which is depicted in the upper row of Fig. 2. The steric interaction between the aldehyde group and the enolate prevents cyclisation along path A, the steric hindrance between the axial methyl group at C-8 and the enolate prevents cyclisation along path B, and the axial positions of the isopropenyl group and the enolate that are necessary for cyclisation along path C, prevent that route. It is clear that cyclisation with the aldehyde group is an attractive alternative for cyclisation in compound **19** and this is what was observed.

In the cyano ketones this alternative cyclisation route is not available and in the less hindered cyano ketones **1c**, **10c** and **11c** a smooth base catalysed Robinson annulation to the decalins **23**, **24**, and **26** takes place in good yield (Scheme 4). When the steric crowding increases as in the cyano ketones **12c**–**14c**, cyclisation under basic conditions does not take place and the retro Michael reaction is observed as the only reaction. Nevertheless annulation can be achieved in a two-step sequence in which the Michael addition is performed under basic conditions at room temperature and the cyclisation is carried out in a separate reaction under Knoevenagel conditions at higher temperature. These more neutral Knoevenagel conditions do not favour the retro Michael reaction and the higher temperature allows to overcome the steric interactions for cyclisation, although in the sterically most crowded compounds the retro Michael reaction is still observed as a major side reaction.

In the Michael additions of the less crowded cyano ketones **15c** and **16c**, the isopropenyl group no longer determines the stereochemical course of the addition of MVK, and in both reactions mixtures of adducts are obtained. In Fig. 2 the transition states for the cyclisation of the two diastereomeric adducts **37** and **39** are depicted and it is clear that in isomer **37** a smooth cyclisation can take place via the relatively unhindered transition states **37A** or **37B** to give decalin **40**. In isomer **39** an easy cyclisation is not possible since in all transition states **39A**, **39B** and **39C** unfavourable steric interactions will operate. Instead a retro Michael reaction takes place, followed by re-addition to **37** and cyclisation to **40**. In the corresponding dioxolanyl substituted compounds **36** and **38** a similar reaction pattern can be observed, although in that case a small amount of the cyclised diastereoisomer **42** is also obtained (Scheme 5).

The conclusion that can be drawn from these experiments is that Robinson annulations *under basic conditions* suffer from steric hindrance that favour a cyclisation to spiro compounds in the formyl ketones and lead to retro Michael reactions in steric congested cyano ketones. The Robinson annulation of α-cyano ketones gives good results, also in steric congested situations, using base catalysed Michael addition followed by a separate cyclisation reaction under Knoevenagel conditions.

The stereochemistry of the annulation of 6-cyano-5-isopropenyl cyclohexanones occurs *trans* with respect to the isopropenyl group, which results in a *cis* position of the nitrile group and the major substituent at C-2. The stereochemistry of the annulation of 6-cyano-2-methyl-2-substituted cyclohexanones occurs mainly *cis* with respect to the substituent at C-2, which results in a *trans* position of the nitrile group and the major substituent at C-2. The equilibria that play a role under Knoevenagel annulation conditions ultimately lead to good yields of annulated products with a *trans* position of the nitrile group and the major substituent at C-2, which can be good chiral intermediates in the synthesis of ring A bridged clerodanes.

Experimental

General information and instrumentation

All reagents and solvents were used as received from commercial sources except toluene (dried by distillation from sodium and stored on sodium wire) and ether (distilled from sodium benzophenone ketyl and stored on sodium wire). GC analyses were performed with a Fisons GC 8000 apparatus provided with a 30 m DB-17 fused capillary column (internal diameter 0.25 mm, film thickness 0.25 μm) and a flame ionisation detector. Hydrogen was used as the carrier gas. Thin layer chromatography (TLC) was performed on precoated PET foil-backed plates (Fluka silica gel with fluorescent indicator 254 nm) and visualised by spraying with ceric molybdate or anisaldehyde or basic potassium permanganate stains. Column chromatography refers to flash chromatography performed on Fluka silica gel 60 with particle size 0.04–0.063 mm and eluents were routinely distilled prior to use. Light petroleum refers to the fraction with bp 40–60°C. Melting points were determined on a C. Reichert, Vienna, hot stage apparatus and are not corrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter for chloroform solutions and concentrations are specified in g/100 mL. ^{1}H and ^{13}C NMR spectra were, unless otherwise stated, recorded at 200 MHz and 50 MHz on a Bruker AC-E 200 spectrometer, respectively, using $CDCl_3$ as solvent. The chemical shift values are expressed in ppm (parts per million) relative to the residual $CHCl_3$ at 7.24 (^{1}H) and 77.00 (^{13}C) as internal standard. The multiplicity of the ^{1}H signals are expressed as: s=singlet, d=doublet, t=triplet, q=quartet, br s=broad singlet, m=multiplet. The multiplicity of the ^{13}C signals were determined with the DEPT technique, q=quartet, t=triplet, d=doublet, s=singlet. Infrared spectra were recorded on a

FT-IR, Biorad FTS 7 or on a Hitachi EPI-G3 spectrometer. MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. The ratios *m/z* and relative intensities (%) are indicated for significant peaks. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

General procedure for the preparation of the β keto nitriles

To a suspension of 900 mg (30 mmol) of a 80% suspension of NaH in mineral oil in 100 mL of dry ether was simultaneously added 30 mmol of the relevant ketone and 4.44 g (60 mmol) of ethyl formate at room temperature. After stirring overnight the reaction mixture was washed with three portions of 100 mL of an 1 M aqueous potassium hydroxide solution. The combined aqueous layers were acidified and extracted with three 100 mL-portions of ether. The ethereal extracts were washed with brine and dried over $MgSO_4$. Evaporation under reduced pressure gave the corresponding crude *hydroxymethylene ketone* in good yield and was used without further purification in the next reaction. An analytical sample was obtained by flash column chromatography on silica gel with light petroleum/ethyl acetate 96/4 as eluent.

A solution of 25 mmol of the relevant hydroxymethylene ketone in a mixture of 42 mL of chloroform and 18 mL of ethanol was treated with 3.99 g (57 mmol) of $NH_2OH{\cdot}HCl$ and 4.66 g (56 mmol) of anhydrous sodium acetate and stirring was continued for two days. The reaction mixture was diluted with 250 mL of ether and washed three times with 25 mL of brine, and dried on $MgSO_4$. Evaporation of the solvents sometimes gave the corresponding *isoxazole*, which was used in the next reaction without purification. An analytical sample was obtained by flash column chromatography on silica gel with light petroleum/ethyl acetate 95/5 as eluent. Otherwise a mixture of several products was obtained and not further analysed.

The residue was dissolved in 50 mL of ether and treated with 50 mL of a 1 M solution of sodium methanolate in methanol for 24 h. After concentration of the reaction mixture under reduced pressure the residue was dissolved in water and acidified with 4 M aqueous HCl and extracted with three 50 mL-portions of ether. The ethereal extracts were washed with brine and dried over $MgSO_4$. Evaporation of the solvents afforded the α-cyano ketones which were purified by crystallisation or by flash column chromatography on silica gel with ethyl acetate/light petroleum 30/70 as eluent.

(5*R*)-5-Isopropenyl-2-methyl-2-cyclohexenone [(−)-carvone] (1a) and (5*S*)-5-isopropenyl-2-methyl-2-cyclohexenone [(+)-carvone] were generous gifts from Quest International, $[\alpha]_D$=−59.5 (neat) and +55.7 (neat), respectively.

(5*S*)-6-Hydroxymethylene-5-isopropenyl-2-methyl-2-cyclohexenone (1b). This ketone was prepared as described starting with *R*-(−)-carvone in 88% yield as a colourless oil. $[\alpha]_D$=−9.73 (*c*=4.3); ^{1}H NMR δ 1.69 (s, 3H), 1.85 (s, 3H), 2.38–2.46 (m, 2H), 3.26 (t, *J*=7.2 Hz, 1H), 4.77 (q, *J*=0.8 Hz, 1H), 4.84 (q, *J*=1.6 Hz, 1H), 6.49 (ddd, *J*=1.4, 3.0, 4.4 Hz, 1H), 7.45 (br s, 1H), 14.50 (br s, 1H); ^{13}C NMR δ 15.4 (q), 19.6 (q), 29.1 (t), 41.8 (d), 109.7 (s), 113.7 (t), 134.6 (s), 141.2 (d), 145.6 (s), 169.2 (d), 189.3 (s); IR ν_{max} (liquid film) 3419, 3077, 2929, 2888, 1644, 1627, 1570, 1377, 1208, 1050, 898 cm^{-1}; MS *m/z* 178 (M^+, 70), 163 (21), 135 (25), 109 (100), 91 (30), 41 (14), 39 (20); HRMS: M^+, found 178.0991. $C_{11}H_{14}O_2$ requires 178.0994.

(4*S*)-4-Isopropenyl-7-methyl-4,5-dihydrobenzo[*d*]isoxazole. This compound was synthesised as its 4*R* stereoisomer in 92% yield as a light yellow oil. $[\alpha]_D$=+50.6 (*c*=1.9); ^{1}H NMR δ 1.67 (s, 3H), 1.99 (br s, 3H), 2.29–2.52 (m, 2H), 3.49 (t, *J*=9.5 Hz, 1H), 4.73 (s, 1H), 4.77 (s, 1H), 5.70 (br s, 1H), 7.95 (s, 1H); ^{13}C NMR δ 15.6 (q), 19.7 (q), 30.4 (t), 38.4 (d), 112.1 (t), 112.3 (s), 124.1 (s), 127.8 (d), 145.8 (s), 148.5 (d), 166.7 (s); IR ν_{max} (liquid film) 3078, 2972, 2941, 2919, 2876, 1718, 1646, 1473, 1437, 1376, 1345, 1249, 1201, 1066, 896 cm^{-1}; MS *m/z* 175 (M^+, 100), 160 (59), 146 (19), 134 (40), 133 (25), 105 (22), 91 (22), 79 (20), 77 (20); HRMS: M^+, found 175.0995. $C_{11}H_{13}NO$ requires 175.0997.

(1*R*,6*R*)-6-Isopropenyl-3-methyl-2-oxo-3-cyclohexenecarbonitrile (1c). The synthesis of this nitrile was performed without purification of the intermediates in 64% overall yield. Crystallisation was performed from hexane/*tert*-butyl methyl ether 4/1. Mp 81–83°C; $[\alpha]_D$=−13.8 (*c*=2.15); ^{1}H NMR δ 1.79 (s, 3H), 1.82 (s, 3H), 2.41–2.50 (m, 2H), 2.99 (ddd, *J*=5.8, 9.8, 13.0 Hz, 1H), 3.58 (d, *J*=13.0 Hz, 1H), 4.98 (d, *J*=0.7 Hz, 1H), 5.03 (br s, 1H), 6.79 (ddd, *J*=1.4, 3.0, 5.2 Hz, 1H); ^{13}C NMR δ 16.0 (q), 19.0 (q), 30.8 (t), 45.1 (d), 46.9 (d), 115.3 (t), 115.8 (s), 134.4 (s), 142.4 (s), 144.8 (d), 189.1 (s); IR ν_{max} (KBr) 3084, 2977, 2928, 2880, 2252, 1681, 1648, 1450, 1380, 1362, 1232, 1160, 1081, 911, 860 cm^{-1}; MS *m/z* 175 (M^+, 18), 147 (9), 135 (6), 132 (3), 83 (5), 82 (100), 77 (4), 54 (16), 53 (4), 39 (7); HRMS: M^+, found 175.0996. $C_{11}H_{13}NO$ requires 175.0997; Anal: found C, 75.26; H, 7.53; N, 7.88%. $C_{11}H_{13}NO$ requires C, 75.39; H, 7.47; N, 7.99%.

(5*R*)-6-Hydroxymethylene-5-isopropenyl-2-methyl-2-cyclohexenone. This compound was obtained as a colourless oil as described starting with *S*-(+)-carvone in 97% yield. $[\alpha]_D$=+7.6 (*c*=6.6); ^{1}H NMR δ 1.68 (s, 3H), 1.84 (t, *J*=1.6 Hz, 3H), 2.38–2.46 (m, 2H), 3.26 (t, *J*=7.2 Hz, 1H), 4.78 (s, 1H), 4.84 (s, 1H), 6.48 (ddd, *J*=1.4, 3.0, 4.4 Hz, 1H), 7.45 (br s, 1H), 14.50 (br s, 1H); ^{13}C NMR δ 15.4 (q), 19.6 (q), 29.1 (t), 41.8 (d), 109.7 (s), 113.7 (t), 134.6 (s), 141.2 (d), 145.6 (s), 169.2 (d), 189.3 (s); IR ν_{max} (liquid film) 3077, 2973, 2924, 2730, 1658, 1626, 1570, 1208 cm^{-1}; MS *m/z* 178 (M^+, 71), 163 (22), 149 (9), 145 (8), 137 (14), 135 (25), 109 (100), 107 (17), 91 (31), 77 (15), 41 (14), 39 (18); HRMS: M^+, found 178.0992. $C_{11}H_{14}O_2$ requires 178.0994.

(4*R*)-4-Isopropenyl-7-methyl-4,5-dihydrobenzo[*d*]isoxazole. This isoxazole was obtained in 92% yield as a light coloured oil of limited stability. $[\alpha]_D$=−53.5 (*c*=1.3); ^{1}H NMR δ 1.70 (s, 3H), 2.02 (br s, 3H), 2.32–2.52 (m, 2H), 3.53 (t, *J*=9.4 Hz, 1H), 4.76–4.81 (m, 1H), 5.71–5.77 (m, 1H), 7.98 (s, 1H); ^{13}C NMR δ 15.6 (q), 19.7 (q), 30.4 (t), 38.4 (d), 112.1 (t), 112.3 (s), 124.2 (s), 127.7 (d), 145.8 (s), 148.6 (d), 166.7 (s); IR ν_{max} (liquid film) 2985, 2980, 2940, 2873, 1725, 1642, 1590, 1472, 1433, 1378, 1344, 1220,

1160, 1070, 980, 938, 905 cm^{-1}; MS *m/z* 175 (M^+, 100), 160 (55), 146 (22), 134 (43), 133 (26), 105 (22), 91 (22), 79 (19), 77 (20); HRMS: M^+, found 175.1005. $C_{11}H_{13}NO$ requires 175.0997.

(1*S*,6*S*)-6-Isopropenyl-3-methyl-2-oxo-3-cyclohexenecarbonitrile. The nitrile was synthesised in 75% yield from *S*-(+)-carvone without purification of the intermediates. Crystallisation was performed from light petroleum/*tert*-butyl methyl ether 5/1. Mp 80–80.5°C; $[\alpha]_D$=+8.5 (*c*=1.78); ^1H NMR δ 1.77 (s, 3H), 1.78 (br s, 3H), 2.38–2.46 (m, 2H), 2.93 (ddd, *J*=6.3, 9.5, 13.1 Hz, 1H), 3.56 (d, *J*=13.1 Hz, 1H), 4.92 (d, *J*=0.8 Hz, 1H), 4.96 (q, *J*=1.4 Hz, 1H), 6.77 (ddd, *J*=1.4, 2.0, 5.0 Hz, 1H); ^{13}C NMR δ 15.7 (q), 18.7 (q), 30.5 (t), 44.8 (d), 46.7 (d), 114.8 (t), 115.6 (s), 133.9 (s), 142.2 (s), 144.9 (s), 188.9 (s); IR ν_{max} (KBr) 3075, 3000, 2966, 2918, 2245, 1683, 1642, 1450, 1437, 1383, 1365, 1210, 1180, 1082, 997, 908, 860 cm^{-1}; MS *m/z* 175 (M^+, 35), 160 (8), 133(6), 132 (6), 117 (16), 92 (13), 82 (100), 77 (31), 54 (64), 53 (21), 52 (25), 51 (16), 39 (19); HRMS: M^+, found 175.0998. $C_{11}H_{13}NO$ requires 175.0997; Anal: found C, 75.16; H, 7.53; N, 7.83%. $C_{11}H_{13}NO$ requires C, 75.39; H, 7.47; N, 7.99%.

(3*R*,5*R*)-5-Isopropenyl-2,3-dimethylcyclohexanone (10a). This ketone was synthesised from (*R*)-(−)-carvone as described before[2] in 85% yield and obtained as a 3:2 diastereoisomeric mixture according to GLC and NMR. An analytical sample was obtained after column chromatography on silica gel with light petroleum/ethyl acetate 9/1 as eluent.

Major isomer: ^1H NMR δ 0.79 (d, *J*=7.2 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 1.70 (s, 3H), 1.78–1.90 (m, 3H), 2.12–2.34 (m, 4H), 4.72 (br s, 1H), 4.73 (br s, 1H); ^{13}C NMR δ 11.7 (q), 13.7 (q), 20.3 (q), 36.0 (d), 37.5 (t), 40.8 (d), 46.4 (t), 48.1 (d), 109.5 (t), 147.4 (s), 212.6 (s); IR ν_{max} (liquid film) 3083, 2962, 2924, 2871, 1710, 1447, 1379, 986, 902 cm^{-1}; MS *m/z* 166 (M^+, 75), 151 (8), 123 (28), 109 (31), 97 (45), 96 (25), 95 (88), 83 (46), 69 (100), 55 (22), 41 (45); HRMS: M^+, found 166.1353. $C_{11}H_{18}O$ requires 166.1358.

Minor isomer: ^1H NMR δ 0.99 (d, *J*=6.2 Hz, 3H), 1.04 (d, *J*=6.6 Hz, 3H), 1.78–1.90 (m, 3H), 2.12–2.34 (m, 4H), 4.70 (br s, 1H), 4.79 (br s, 1H); ^{13}C NMR δ 11.2 (q), 12.8 (q), 21.6 (q), 34.7 (d), 34.9 (t), 40.5 (d), 43.8 (t), 51.3 (d), 111.4 (t), 147.3 (s), 212.7 (s); IR ν_{max} (liquid film) 3077, 2971, 2924, 2870, 1715, 1447, 1380, 1228, 1167, 986, 894 cm^{-1}; MS *m/z* 166 (M^+, 78), 151 (11), 123 (21), 109 (27), 97 (35), 96 (30), 95 (83), 83 (47), 69 (100) 55 (32), 41 (37); HRMS: M^+, found 166.1355. $C_{11}H_{18}O$ requires 166.1358.

(2*S*,3*R*,5*S*)-6-Hydroxymethylene-5-isopropenyl-2,3-dimethylcyclohexanone (10b). Obtained as usual as a colourless oil in 92% yield. $[\alpha]_D$=+12.6 (*c*=1.25); ^1H NMR δ 0.96 (d, *J*=6.2 Hz, 3H), 1.18 (d, *J*=7.0 Hz, 3H), 1.35–1.71 (m, 2H), 1.71–1.90 (buried m, 1H), 1.79 (br s, 3H), 2.26–2.43 (dq, *J*=5.2, 7.0 Hz, 1H), 3.09 (m, 1H), 4.52 (br s, 1H), 4.87 (br s, 1H), 8.70 (br s, 1H), 14.62 (br s, 1H); ^{13}C NMR δ 15.6 (q), 20.0 (q), 21.5 (q), 30.3 (d), 33.2 (t), 40.1 (d), 42.3 (d), 109.8 (s), 113.9 (t), 148.4 (s), 185.2 (s), 191.9 (d); IR ν_{max} (liquid film) 3079, 2969, 2933, 2876, 1732, 1642, 1590, 1453, 1361, 1332, 1181, 896 cm^{-1}; MS *m/z* 194 (M^+, 100), 179 (17), 153 (37), 152 (13), 151 (18), 120 (20), 110 (16), 55 (15), 43 (15), 41 (17); HRMS: M^+, found 194.1297. $C_{12}H_{18}O_2$ requires 194.1307.

(4*S*,6*R*,7*S*)-4-Isopropenyl-6,7-dimethyl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole. This compound was obtained in 88% yield as a rather unstable oil and therefore used without purification. ^1H NMR δ 1.02 (d, *J*=6.8 Hz, 3H), 1.29 (d, *J*=7.0 Hz, 3H), 1.56–1.83 (m, 3H), 1.75 (br s, 3H), 2.46 (dq, *J*=12.8, 6.8 Hz, 1H), 3.22 (dd, *J*=4.0, 5.4 Hz, 1H), 4.47 (br s, 1H), 4.82 (br s, 1H), 7.99 (s, 1H); ^{13}C NMR δ 16.9 (q), 18.9 (q), 21.3 (q), 33.1 (d), 34.3 (t), 35.8 (d), 37.0 (d), 112.6 (t), 146.9 (s), 149.8 (d), 154.5 (s), 171.5 (s).

(3*,4*R*,6*R*)-6-Isopropenyl-3,4-dimethyl-2-oxo-cyclohexanecarbonitrile (10c). This β keto nitrile was synthesised in the usual way but unfortunately it was isolated as an inseparable 1:2 mixture of diastereoisomers and used as such in the next reaction.

Major isomer: ^1H NMR (major peaks) δ 1.05 (d, *J*=6.4 Hz, 3H), 1.12 (d, *J*=7.0 Hz, 3H), 1.70 (s, 3H), 3.08 (m, 1H), 3.81 (d, *J*=5.8 Hz, 1H), 4.67 (s, 1H), 5.00 (s, 1H).

Minor isomer: ^1H NMR (major peaks) δ 0.99 (d, *J*=4.0 Hz, 3H), 1.00 (d, *J*=6.0 Hz, 3H), 1.70 (s, 3H), 2.87 (m, 1H), 3.66 (d, *J*=7.2 Hz, 1H), 4.75 (s, 1H), 4.90 (br s, 1H); IR ν_{max} (liquid film, diastereoisomeric mixture) 3087, 3075, 2972, 2935, 2880, 2250, 2206, 1722, 1650, 1647, 1452, 1377, 1197, 901 cm^{-1}; MS *m/z* 191 (M^+, 100), 176 (40), 135 (97), 134 (41), 97 (41), 95 (65), 70 (75), 69 (54), 55 (60), 41 (41); HRMS: M^+, found 191.1303. $C_{12}H_{17}NO$ requires 191.1310; (M^+-CH_3), found 176.1070. $C_{11}H_{14}NO$ requires 176.1075.

(5*R*)-5-Isopropenyl-2,2-dimethylcyclohexanone (11a). Treatment of the benzylimine of (*R*)-(−)-carvone with a catalytic amount of potassium *tert*-butoxide followed by *tert*-butyllithium gave a metalloenamine, which on methylation with methyl iodide afforded in 94% yield the above mentioned ketone as a yellow oil.[17] $[\alpha]_D$=+84.6 (*c*=8.6) [lit.[18]+91.2 ($CHCl_3$, *c*=11)]; ^1H NMR δ 1.07 (s, 3H), 1.16 (s, 3H), 1.53–1.83 (m, 4H), 1.77 (s, 3H), 2.29–2.41 (m, 2H), 2.54 (dd, *J*=13.1, 14.0 Hz, 1H), 4.73 (s, 1H), 4.77 (dd, *J*=1.4, 2.8 Hz, 1H); ^{13}C NMR δ 20.6 (q), 25.0 (q), 25.1 (q), 26.4 (t), 39.4 (t), 42.9 (t), 44.5 (s), 46.2 (d), 109.8 (d), 147.4 (s), 215.4 (s); IR ν_{max} (liquid film) 3060, 2988, 2962, 2930, 1702, 1637, 1452, 1380, 1149, 1101, 893 cm^{-1}; MS *m/z* 166 (M^+, 40), 151 (5), 123 (14), 110 (29), 109 (25), 107 (20), 95 (63), 82 (31), 81 (37), 69 (66), 68 (34), 67 (100), 55 (37), 41 (90), 39 (33); HRMS: M^+, found 166.1363. $C_{11}H_{18}O$ requires 166.1358.

(5*S*)-6-Hydroxymethylene-5-isopropenyl-2,2-dimethylcyclohexanone (11b). Formylation in the usual way gave this product in 88% yield and an analytical sample was obtained by column chromatography on silica gel with light petroleum/ethyl acetate 96/4 as eluent. $[\alpha]_D$=+19.7 (*c*=1.9); ^1H NMR δ 1.17 (s, 6H), 1.33–1.45 (m, 1H), 1.51 (dd, *J*=7.0, 11.7 Hz, 1H), 1.57–1.77 (m, 2H), 1.72 (s, 3H), 3.11 (dd, *J*=5.2, 5.6 Hz, 1H), 4.61 (br s, 1H), 4.90 (br s, 1H), 8.66 (s, 1H), 14.85 (br s, 1H); ^{13}C NMR δ 20.6 (q), 23.3 (t), 26.7 (q), 27.0 (q), 33.7 (t), 37.0 (s), 42.3 (d), 108.8 (s), 114.2

(t), 147.8 (s), 189.3 (s), 191.7 (d); IR ν_{max} (liquid film) 3079, 2965, 2939, 2864, 1642, 1590, 1454, 1348, 1189, 896 cm^{-1}; MS *m/z* 194 (M^+, 100), 179 (60), 153 (26), 151 (22), 138 (20), 123 (21), 120 (21), 110 (27), 95 (29), 93 (34), 69 (26), 43 (29), 41 (44), 39 (25); HRMS: M^+, found 194.1298. $C_{12}H_{18}O_2$ requires 194.1307.

(4*S*)-4-Isopropenyl-7,7-dimethyl-4,5,6,7-tetrahydrobenzo-[*d*]isoxazole. This product was prepared and used without purification in the next reaction due to its instability. ^1H NMR δ 1.26 (s, 3H), 1.28 (s, 3H), 1.52–1.84 (m, 4H), 1.67 (s, 3H), 3.22 (dd, *J*=5.8, 6.8 Hz, 1H), 4.63 (br s, 1H), 4.83 (br s, 1H), 7.91 (s, 1H); ^{13}C NMR δ 20.0 (q), 25.5 (t), 27.1 (q), 27.3 (q), 32.4 (s), 36.9 (t), 39.9 (d), 112.4 (t), 146.4 (s), 149.5 (d), 154.0 (s), 174.0 (s).

(1*R*,6*R*)-6-Isopropenyl-3,3-dimethyl-2-oxo-cyclohexane-carbonitrile (11c). Obtained in 71% overall yield without purification of intermediates after crystallisation from hexane/*tert*-butyl methyl ether 1/2. Mp 101–102°C; $[\alpha]_D$=+94.0 (*c*=1.15); ^1H NMR δ 1.12 (s, 3H), 1.20 (s, 3H), 1.44–1.97 (m, 4H), 1.78 (s, 3H), 2.58 (ddd, *J*=5.4, 10.4, 12.4 Hz, 1H), 3.78 (d, *J*=12.4 Hz, 1H), 4.92 (s, 1H), 4.98 (br s, 1H); ^{13}C NMR δ 19.1 (q), 24.4 (q), 25.1 (q), 26.4 (t), 39.0 (t), 44.8 (d), 44.8 (s), 51.5 (d), 114.1 (t), 115.8 (s), 143.2 (s), 204.3 (s); IR ν_{max} (KBr) 3069, 2992, 2962, 2941, 2875, 2248, 1720, 1644, 1455, 1397, 1374, 1210, 1088, 908 cm^{-1}; MS *m/z* 191 (M^+, 14), 176 (6), 163 (7), 162 (5), 148 (34), 135 (41), 120 (16), 108 (23), 107 (21), 95 (24), 94 (24), 93 (16), 84 (18), 69 (66), 55 (46), 41 (100), 39 (60); HRMS: M^+, found 191.1309. $C_{12}H_{17}NO$ requires 191.1310; Anal: found C, 75.41; H, 9.07; N 7.29%. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.96; N, 7.32%.

(5*S*)-5-Isopropenyl-2,2-dimethylcyclohexanone. This ketone was prepared as described for **11a** starting with the benzylimine of (*S*)-(+)-carvone. $[\alpha]_D$=−64.9 (*c*=3.1); ^1H NMR δ 1.10 (s, 3H), 1.16 (s, 3H), 1.53–1.83 (m, 4H), 1.77 (br s, 3H), 2.29–2.41 (m, 2H), 2.54 (dd, *J*=13.0, 14.0 Hz, 1H), 4.73 (s, 1H), 4.79 (dd, *J*=1.4, 2.6 Hz, 1H); ^{13}C NMR δ 20.5 (q), 25.0 (q), 25.1 (q), 26.3 (t), 39.4 (t), 43.0 (t), 44.5 (s), 46.3 (d), 109.8 (d), 147.4 (s), 215.4 (s); IR ν_{max} (liquid film) 3063, 2988, 2963, 2930, 1702, 1637, 1452, 1380, 1260, 1179, 1150, 1100, 891 cm^{-1}; MS *m/z* 166 (M^+, 44), 151 (3), 123 (20), 110 (33), 95 (63), 82 (32), 81 (38), 69 (66), 67 (100), 55 (37), 41 (91), 39 (38); HRMS: M^+, found 166.1361. $C_{11}H_{18}O$ requires 166.1358.

(5*R*)-6-Hydroxymethylene-5-isopropenyl-2,2-dimethyl-cyclohexanone. The preparation of this compound was in conformity with the above-mentioned method starting with the ketone derived from *S*-(+)-carvone and gave the hydroxymethylene compound in 85% yield as an oil. $[\alpha]_D$=−18.1 (*c*=2.81); ^1H NMR (Varian EM-390, 90 MHz) δ 1.23 (s, 6H), 1.35–1.90 (m, 4H), 1.76 (s, 3H), 3.16 (dd, *J*=4.0, 5.0 Hz, 1H), 4.63 (br s, 1H), 4.80 (br s, 1H), 8.70 (s, 1H), 14.95 (s, 1H); ^{13}C NMR δ 20.5 (q), 23.4 (t), 26.7 (q), 27.1 (q), 33.6 (t), 37.0 (s), 42.2 (d), 108.7 (s), 114.0 (t), 147.8 (s), 189.2 (s), 191.7 (d); IR ν_{max} (chloroform, Hitachi EPI-G3) 3080, 2965, 2940, 2865, 1640, 1590, 1455, 1350, 1190, 895 cm^{-1}; MS *m/z* 194 (M^+, 100), 179 (58), 153 (22), 151 (22), 138 (25), 123 (21), 120 (14), 110 (27), 95 (36), 93 (44), 69 (20), 43 (26), 41 (40), 39 (12); HRMS: M^+, found 194.1302. $C_{12}H_{18}O_2$ requires 194.1307.

(4*R*)-4-Isopropenyl-7,7-dimethyl-4,5,6,7-tetrahydrobenzo-[*d*]isoxazole. Obtained as a relatively unstable oil and used without purification in the next step. ^1H NMR (Varian EM-390, 90 MHz) δ 1.25 (s, 3H), 1.32 (s, 3H), 1.50–1.85 (m, 4H), 1.64 (br s, 3H), 3.23 (dd, *J*=6.0, 8.0 Hz, 1H), 4.70 (br s, 1H), 4.75 (br s, 1H), 7.90 (s, 1H).

(1*S*,6*S*)-6-Isopropenyl-3,3-dimethyl-2-oxo-cyclohexane-carbonitrile. This product was purified by column chromatography on silica gel followed by crystallisation from light petroleum/di-*iso*-propyl ether 1/2. The yield was 64% based on *S*-(+)-carvone. Mp 102–103°C; $[\alpha]_D$=−89.3 (*c*=2.11); ^1H NMR δ 1.09 (s, 3H), 1.18 (s, 3H), 1.58–1.86 (m, 4H), 1.77 (br s, 3H), 2.52 (ddd, *J*=5.3, 10.4, 12.6 Hz, 1H), 3.77 (d, *J*=12.6 Hz, 1H), 4.89 (s, 1H), 4.94 (br s, 1H); ^{13}C NMR δ 18.8 (q), 24.1 (q), 24.8 (q), 26.1 (t), 44.5 (d), 44.5 (s), 51.2 (d), 113.8 (t), 115.6 (s), 143.0 (s), 204.0 (s); IR ν_{max} (KBr, Hitachi EPI-G3) 3075, 2990, 2960, 2940, 2875, 2245, 1720, 1645, 1455, 1390, 1370, 1210, 1090, 905 cm^{-1}; MS *m/z* 191 (M^+, 19), 176 (15), 163 (15), 162 (15), 148 (31), 135 (43), 121 (16), 107 (33), 97 (18), 95 (18), 94 (30), 69 (93), 55 (70), 41 (100); HRMS: M^+, found 191.1307. $C_{12}H_{17}NO$ requires 191.1310; Anal: found C, 75.31; H, 9.06; N 7.22%. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.96; N, 7.32%.

(3*R*,5*R*)-Isopropenyl-2,2,3-trimethylcyclohexanone (12a). An 1,4 addition of methylmagnesium iodide to (*R*)-(−)-carvone catalysed by copper bromide dimethylsulfide complex[2] followed by quenching the intermediate enolate with methyl iodide gave ketone **12a** in 90% yield. $[\alpha]_D$=+14.8 (*c*=1.2); ^1H NMR δ 0.86 (d, *J*=7.0 Hz, 3H), 0.96 (s, 3H), 1.14 (s, 3H), 1.57–1.66 (m, 1H), 1.69 (s, 3H), 1.83–2.01 (m, 2H), 2.30–2.55 (m, 3H), 4.67 (br s, 1H), 4.74 (br s, 1H); ^{13}C NMR δ 16.2 (q), 21.1 (q), 21.2 (q), 25.4 (q), 33.0 (t), 39.4 (d), 40.6 (d), 42.1 (t), 48.2 (s), 110.4 (t), 147.4 (s), 216.2 (s); IR ν_{max} (liquid film) 3084, 2970, 2934, 2876, 1706, 1645, 1457, 1137, 892 cm^{-1}; MS *m/z* 180 (M^+, 66), 165 (8), 137 (15), 123 (17), 110 (36), 95 (54), 83 (100), 70 (48), 69 (41), 67 (29), 55 (25), 41 (22); HRMS: M^+, found 180.1516. $C_{12}H_{20}O$ requires 180.1514.

(3*R*,5*S*)-6-Hydroxymethylene-isopropenyl-2,2,3-trimethyl-cyclohexanone (12b). This compound was obtained in 79% yield as a colourless oil. $[\alpha]_D$=+25.9 (*c*=2.5); ^1H NMR δ 0.85 (d, *J*=4.8 Hz, 3H), 1.02 (s, 3H), 1.16 (s, 3H), 1.53–1.59 (m, 3H), 1.77 (br s, 3H), 3.04 (dd, *J*=3.6, 4.4 Hz, 1H), 4.52 (br s, 1H), 4.90 (br s, 1H), 8.71 (d, *J*=1.8 Hz, 1H), 14.71 (d, *J*=1.8 Hz, 1H); ^{13}C NMR δ 15.6 (q), 20.2 (q), 21.6 (q), 24.7 (q), 30.3 (t), 32.8 (d), 40.0 (s), 40.2 (d), 108.4 (s), 113.9 (t), 148.6 (s), 187.9 (s), 193.2 (d); IR ν_{max} (liquid film) 3079, 2970, 2937, 2877, 1633, 1586, 1455, 1347, 1335, 1177, 895 cm^{-1}; MS *m/z* 208 (M^+, 100), 193 (58), 167 (27), 138 (20), 123 (23), 120 (24), 110 (24), 107 (21), 95 (22), 43 (18), 41 (21); HRMS: M^+, found 208.1463. $C_{13}H_{20}O_2$ requires 208.1463.

(1*R*,4*R*,6*R*)-6-Isopropenyl-3,3,4-trimethyl-2-oxo-cyclo-hexanecarbonitrile (12c). Obtained as an oil after column chromatography with light petroleum/ethyl acetate 4/1 as

eluent in 61% yield, based on the corresponding ketone. ^{1}H NMR δ 0.88 (d, J=7.2 Hz, 3H), 1.08 (s, 3H), 1.25 (s, 3H), 1.59 (dt, J=10.6, 3.6 Hz, 1H), 1.76 (br s, 3H), 1.95 (m, 1H), 2.09 (ddd, J=4.3, 12.2, 14.0 Hz, 1H), 2.77 (td, J=12.2, 4.3 Hz, 1H), 3.82 (d, J=12.2 Hz, 1H), 4.89 (s, 1H), 4.93 (s, 1H); ^{13}C NMR δ 16.1 (q), 19.5 (q), 22.0 (q), 26.0 (q), 33.0 (t), 40.4 (d), 44.1 (d), 45.8 (d), 48.4 (s), 113.9 (t), 116.1 (s), 143.3 (s), 204.9 (s); IR ν_{max} (liquid film) 3079, 2973, 2940, 2881, 2250, 1717, 1647, 1460, 1385, 1336, 1301, 1094, 900 cm^{-1}; MS m/z 205 (M^+, 28), 190 (5), 177 (43), 162 (28), 148 (10), 135 (56), 120 (12), 84 (100), 83 (67), 69 (84), 55 (26), 41 (43), 39 (22); HRMS: M^+, found 205.1463. $C_{13}H_{19}NO$ requires 205.1467.

(2*R*,3*R*,5*R*)-2-(1,3-Dioxolan-2-yl)-5-isopropenyl-2,3-dimethylcyclohexanone (13a). This ketone was obtained as a colourless oil as described before.[6] $[\alpha]_D$=+15.6 (c=1.3); ^{1}H NMR δ 0.87 (d, J=7.2 Hz, 3H), 0.93 (s, 3H), 1.51–1.73 (m, 1H), 1.70 (s, 3H), 2.07–2.19 (m, 1H), 2.22–2.57 (m, 4H), 3.76–3.99 (m, 4H), 4.73 (s, 1H), 4.75 (br s, 1H), 5.32 (s, 1H); ^{13}C NMR δ 12.6 (q), 16.6 (q), 20.5 (q), 33.4 (t), 36.2 (d), 40.8 (d), 44.6 (t), 56.3 (s), 65.1 (t), 65.5 (t), 105.0 (d), 109.8 (t), 147.5 (s), 211.5 (s); IR ν_{max} (liquid film) 3079, 2960, 2940, 2890, 1712, 1653, 1457, 1388, 1089, 990, 960, 890 cm^{-1}; MS m/z 238 (M^+, 3), 195 (1), 165 (0.5), 74 (3), 73 (100), 69 (1), 67 (1), 55 (2), 45 (5), 41 (2); HRMS: M^+, found 238.1564. $C_{14}H_{22}O_3$ requires 238.1569.

(2*R*,3*R*,5*S*)-2-(1,3-Dioxolan-2-yl)-6-hydroxymethylene-5-isopropenyl-2,3-dimethylcyclohexanone (13b). The synthesis of this compound was accomplished in 86% yield in the usual way. $[\alpha]_D$=+94.4 (c=1.5); ^{1}H NMR δ 0.98 (d, J=6.9 Hz, 3H), 1.21 (s, 3H), 1.46–1.73 (m, 2H), 1.79 (s, 3H), 2.11 (ddd, J=3.5, 6.9, 10.3 Hz, 1H), 3.07 (t, J=4.8 Hz, 1H), 3.80–3.99 (m, 4H), 4.76 (br s, 1H), 4.93 (br s, 1H), 5.18 (s, 1H), 8.75 (br s, 1H), 14.77 (br s, 1H); ^{13}C NMR δ 15.4 (q), 17.2 (q), 21.4 (q), 26.5 (d), 31.4 (t), 40.0 (d), 47.0 (s), 65.0 (t), 65.2 (t), 108.0 (d), 110.8 (s), 114.3 (t), 147.6 (s), 185.1 (s), 192.2 (d); IR ν_{max} (liquid film) 3400, 3095, 2933, 2875, 1653, 1588, 1340, 1193, 1104, 899 cm^{-1}; MS m/z 266 (M^+, 3), 183 (12), 149 (10), 77 (5), 74 (3), 73 (100), 45 (6), 43 (6); HRMS: M^+, found 266.1520. $C_{15}H_{22}O_4$ requires 266.1518.

(4*S*,6*R*,7*S*)-7-(1,3-Dioxolan-2-yl)-4-isopropenyl-6,7-dimethyl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole. Obtained as a rather unstable colourless oil in 83% yield after chromatographic purification on silica gel with ethyl acetate/light petroleum 1/19. ^{1}H NMR δ 0.96 (d, J=7.0 Hz, 3H), 1.26 (s, 3H), 1.60–1.71 (m, 1H), 1.74 (s, 3H), 1.80–1.91 (m, 1H), 2.28–2.36 (m, 1H), 3.24 (t, J=6.0 Hz, 1H), 3.75–4.05 (m, 4H), 4.64 (s, 1H), 4.86 (s, 1H), 5.04 (s, 1H), 7.99 (s, 1H); MS m/z 263 (M^+, 13), 248 (1), 220 (2), 194 (5), 73 (100), 45 (6); HRMS: M^+, found 263.1518. $C_{15}H_{21}NO_3$ requires 263.1521. Anal: found C, 68.26; H, 8.16; N, 4.86%. $C_{15}H_{21}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%.

(1*,3*R*,4*R*,6*R*)-3-(1,3-Dioxolan-2-yl)-6-isopropenyl-3,4-dimethyl-2-oxo-cyclohexanecarbonitrile (13c).** Synthesised in 70% yield by treatment with sodium methoxide of the corresponding isoxazole and obtained as an oil. Purification proved to be very troublesome and the product was obtained as a 3:2 mixture of stereoisomers, according to NMR. This mixture was used in the next reaction. After repeated crystallisations from hexane/*tert*-butyl methyl ether 1/4 the major isomer was isolated analytically pure.

Major isomer: mp 127–128°C; $[\alpha]_D$=+80.7 (c=1.05); ^{1}H NMR δ 0.92 (d, J=7.2 Hz, 3H), 1.06 (s, 3H), 1.38–1.66 (m, 1H), 1.79 (br s, 3H), 2.02–2.41 (m, 2H), 2.85 (dd, J=4.9, 6.8 Hz, 1H), 3.82–3.98 (m, 4H), 4.00–4.08 (m, 1H), 4.89 (br s, 1H), 4.96 (s, 1H), 4.98 (t, J=1.4 Hz, 1H); ^{13}C NMR δ 14.8 (q), 16.6 (q), 18.8 (q), 33.2 (t), 35.0 (d), 45.7 (d), 46.4 (d), 55.7 (s), 64.9 (t), 65.4 (t), 105.7 (d), 113.9 (t), 115.9 (s), 143.4 (s), 201.3 (s); IR ν_{max} (liquid film) 3083, 2965, 2898, 2211, 1723, 1666, 1454, 1380, 1091, 1026, 946, 900 cm^{-1}.

Minor isomer: ^{1}H NMR δ 0.86 (d, J=6.8 Hz, 3H), 1.16 (s, 3H), 1.38–1.66 (m, 1H), 1.77 (s, 3H), 2.02–2.41 (m, 2H), 2.78 (dd, J=4.9, 11.7 Hz, 1H), 3.82–3.98 (m, 4H), 4.00–4.10 (m, 1H), 4.84 (br s, 1H), 4.96 (s, 1H), 4.98 (t, J=1.4 Hz, 1H); ^{13}C NMR δ 14.4 (q), 15.2 (q), 21.9 (q), 28.1 (d), 29.8 (t), 41.5 (d), 45.6 (d), 55.7 (s), 64.7 (t), 65.2 (t), 107.3 (d), 113.8 (t), 118.5 (s), 144.6 (t), 201.3 (s); IR ν_{max} (liquid film, diastereoisomeric mixture) 3086, 2966, 2897, 2248, 2211, 1725, 1667, 1454, 1380, 1092, 946 cm^{-1}; MS m/z 263 (M^+, 2), 262 (2), 248 (1), 127 (1), 74 (3), 73 (100), 69 (1), 55 (2), 45 (6), 43 (2), 41 (2); HRMS: M^+, found 263.1519. $C_{15}H_{21}NO_3$ requires 263.1521. Anal: found C, 68.56; H, 8.11; N, 5.12%. $C_{15}H_{21}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%.

(2*R*,3*R*,5*R*)-2-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-5-isopropenyl-2,3-dimethylcyclohexanone (14a). Prepared in 35% yield as described before as a white solid.[6] Mp 120–121°C; $[\alpha]_D$=+65.7 (c=2.1); ^{1}H NMR δ 0.89 (s, 3H), 0.89 (d, J=7.0 Hz, 3H), 1.52 (m, 1H), 1.69 (s, 3H), 1.70 (m, 2H), 2.16–2.29 (m, 4H), 2.33 (m, 1H), 2.55 (m, 1H), 2.71 (d, J=12.6 Hz, 1H), 2.82 (m, 1H), 3.87 (m, 2H), 4.63 (dd, J=6.2, 9.6 Hz, 1H), 4.75 (m, 2H), 5.66 (d, J=5.0 Hz, 1H); ^{13}C NMR δ 13.4 (q), 16.7 (q), 20.4 (q), 32.6 (t), 33.0 (t), 33.1 (t), 36.8 (d), 40.4 (d), 41.9 (d), 43.3 (t), 54.3 (s), 68.0 (t), 82.6 (t), 109.0 (d), 147.4 (s), 213.4 (s); IR ν_{max} (KBr) 3073, 2981, 2960, 2884, 1703, 1643, 1458, 1383, 1327, 1219, 1094, 1018, 928, 891 cm^{-1}; MS m/z 278 (M^+, 2), 167 (7), 166 (36), 123 (27), 114 (6), 113 (100), 95 (6), 83 (7), 70 (5), 69 (51), 67 (9), 55 (10), 43 (4), 41 (8); HRMS: M^+, found 278.1884. $C_{17}H_{26}O_3$ requires 278.1882; Anal: found C, 73.44; H, 9.31%. $C_{17}H_{26}O_3$ requires C, 73.34; H, 9.34%.

(2*R*,3*R*,5*S*)-2-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-6-hydroxymethylene-5-isopropenyl-2,3-dimethylcyclohexanone (14b). Prepared in 95% yield as a light yellowish oil, which was sufficiently pure to use in the next reaction. $[\alpha]_D$=+46.7 (c=3.9); ^{1}H NMR δ 0.92 (d, J=6.8 Hz, 3H), 1.14 (s, 3H), 1.49–1.73 (m, 4H), 1.76 (br s, 3H), 1.89 (dd, J=3.4, 6.8 Hz, 1H), 1.94–2.05 (m, 1H), 2.26 (ddd, J=9.6, 12.8, 19.4 Hz, 1H), 2.80 (m, 1H), 2.97 (m, 1H), 3.85 (ddd, J=4.0, 6.0, 8.0 Hz, 2H), 4.37 (dd, J=6.2, 9.8 Hz, 1H), 4.59 (s, 1H), 4.91 (s, 1H), 5.59 (d, J=5.0 Hz, 1H), 8.66 (d, J=2.0 Hz, 1H), 14.79 (d, J=2.0 Hz, 1H); ^{13}C NMR 16.9 (q), 17.2 (q), 21.6 (q), 27.9 (d), 30.9 (t), 32.6 (t), 33.6 (t), 40.1 (d), 42.2 (d), 46.0 (s), 68.0 (t), 84.7 (d), 109.0 (d), 110.6 (s), 114.4 (t), 148.1 (s), 186.5 (s), 192.6 (d); IR ν_{max} (liquid film) 3080, 2962, 2875, 1640, 1588, 1455, 1337,

1249, 1183, 1101, 1014, 901 cm^{-1}; MS *m/z* 306 (M^+, 5), 208 (5), 195 (13), 194 (100), 179 (7), 161 (9), 152 (8), 151 (6), 137 (6), 113 (65), 67 (5), 55 (5); HRMS: M^+, found 306.1832. $C_{18}H_{26}O_4$ requires 306.1831.

(1*S*,3*R*,4*R*,6*R*)-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-6-isopropenyl-3,4-dimethyl-2-oxo-cyclohexanecarbonitrile (14c). This keto nitrile was obtained in 84% yield based on the corresponding ketone as a white solid after crystallisation from hexane/*tert*-butyl methyl ether 1/2. Mp 135°C; $[\alpha]_D$=+127.7 (*c*=1.25); ^{1}H NMR δ 0.89 (d, *J*=7.0 Hz, 3H), 0.90 (s, 3H), 1.52 (dt, *J*=14.4, 7.2 Hz, 1H), 1.65–2.00 (buried m, 3H), 1.77 (s, 3H), 2.10 (ddd, *J*=3.8, 8.2, 12.6 Hz, 2H), 2.37 (dd, *J*=2.6, 6.8 Hz, 1H), 2.77 (ddd, *J*=3.5, 6.5, 8.8 Hz, 2H), 3.85 (dd, *J*=5.2, 8.4 Hz, 2H), 4.05 (d, *J*=12.2 Hz, 1H), 4.25 (dd, *J*=5.8, 10.1 Hz, 1H), 4.91 (br s, 2H), 5.62 (d, *J*=5.1 Hz, 1H); ^{13}C NMR δ 14.6 (q), 16.5 (q), 18.8 (q), 32.5 (t), 32.6 (t), 33.9 (t), 36.3 (d), 41.7 (d), 45.2 (d), 45.9 (d), 54.3 (s), 68.6 (t), 83.3 (d), 109.1 (d), 113.8 (t), 116.4 (s), 143.6 (s), 204.1 (s); IR ν_{max} (KBr) 3082, 2973, 2876, 2209, 1721, 1653, 1457, 1387, 1101, 1011 cm^{-1}; MS *m/z* 303 (M^+, 0.4), 175 (0.3), 167 (4), 114 (6), 113 (100), 83 (7), 69 (48), 67 (8), 55 (11), 41 (9); HRMS: M^+, found 303.1831. $C_{18}H_{25}NO_3$ requires 303.1834. Anal: found C, 71.33; H, 8.33; N, 4.41%. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62%.

(2*R*,3*R*)-2-(1,3-Dioxolan-2-yl)-2,3-dimethyl-5-cyclohexenone. A stream of an ozone/oxygene mixture was bubbled through a solution of 1.0 g (4.2 mmol) of **13a** in 25 mL of methanol and 25 mL of dichloromethane at −78°C until a blue colour appeared. The excess of ozone was expelled by a stream of nitrogen and 1.25 g (4.4 mmol) of $FeSO_4{\cdot}7H_2O$ and 1.68 g (8.4 mmol) of $Cu(OAc)_2{\cdot}2H_2O$ were added and the temperature was raised overnight to room temperature. The solvents were evaporated and the residue was dissolved in 25 mL of aqueous 4 M HCl and extracted with three 100-mL portions of ether. The combined extracts were washed with 50 mL of aqueous 2 M NaOH and with brine, dried on magnesium sulfate, filtered, and evaporated to give 0.56 g (67%) of the enone after purification on silica gel with light petroleum/ethyl acetate 3/1 as eluent. $[\alpha]_D$=−110.6 (*c*=1.4); ^{1}H NMR δ 0.90 (d, *J*=7.0 Hz, 3H), 0.96 (s, 3H), 1.97–2.12 (m, 1H), 2.34–2.40 (m, 1H), 2.47–2.60 (m, 1H), 3.70–3.89 (m, 4H), 5.10 (s, 1H), 5.87 (dt, *J*=10.0, 2.0 Hz, 1H), 6.74 (dt, *J*=10.0, 4.0 Hz, 1H); ^{13}C NMR δ 12.6 (q), 16.4 (q), 31.8 (t), 33.4 (d), 52.4 (s), 65.0 (t), 65.2 (t), 105.3 (d), 128.8 (d), 147.7 (d), 201.1 (s); IR ν_{max} (liquid film) 3032, 2961, 2884, 1682, 1457, 1388, 1212, 1106, 1089, 991 cm^{-1}; MS *m/z* 196 (M^+, 2), 181 (2), 127 (3), 123 (9), 109 (4), 83 (3), 73 (100), 68 (7), 55 (4), 45 (9); HRMS: M^+, found 196.1102. $C_{11}H_{16}O_3$ requires 196.1099.

(2*R*,3*R*)-2-(1,3-Dioxolan-2-yl)-2,3-dimethylcyclohexanone (15a). A solution of 196 mg (1 mmol) of the above-mentioned enone in 15 mL of ethyl acetate was stirred under hydrogen in the presence of 15 mg of 10% Pd on charcoal for 4 h. The reaction mixture was filtered and evaporated to give 186 mg (95%) of a colourless oil which was purified by column chromatography on silica gel with light petroleum/ethyl acetate 96/4 as eluent. $[\alpha]_D$=−8.11 (*c*=1.41); ^{1}H NMR δ 0.84 (d, *J*=7.0 Hz, 3H), 0.93 (s, 3H), 1.42–1.50 (m, 1H), 1.74–1.80 (m, 2H), 1.85–1.94 (m, 1H), 2.19–2.38 (m, 3H), 3.73–3.89 (m, 4H), 5.26 (s, 1H); ^{13}C NMR δ 12.9 (q), 16.3 (q), 23.0 (t), 28.6 (t), 36.6 (d), 39.4 (t), 56.1 (s), 65.1 (t), 65.1 (t), 105.4 (d), 212.6 (s); IR ν_{max} (liquid film) 2947, 2879, 1709, 1461, 1392, 1309, 1246, 1208, 1162, 1123, 1060, 1034, 963, 949, 1089, 949 cm^{-1}; MS *m/z* 198 (M^+, 4), 183 (1), 155 (2), 142 (1), 127 (2), 111 (3), 74 (3), 73 (100), 55 (4), 45 (8), 41 (3); HRMS: M^+, found 198.1256. $C_{11}H_{18}O_3$ requires 198.1256.

(2*R*,3*R*)-2-(1,3-Dioxolan-2-yl)-6-hydroxymethylene-2,3-dimethylcyclohexanone (15b). This yellow oil was synthesised in 85% yield in the usual way as described. $[\alpha]_D$=+117.4 (*c*=1.3); ^{1}H NMR δ 0.75 (d, *J*=6.9 Hz, 3H), 0.95 (s, 3H), 1.07–1.23 (m, 1H), 1.41–1.50 (m, 1H), 1.78–1.89 (m, 1H), 2.04 (dd, *J*=4.9, 7.6 Hz, 2H), 3.55–3.63 (m, 2H), 3.65–3.75 (m, 2H), 4.88 (s, 1H), 8.41 (br s, 1H), 14.36 (br s, 1H); ^{13}C NMR δ 15.7 (q), 17.2 (q), 22.1 (t), 27.9 (t), 30.4 (d), 47.4 (s), 64.7 (t), 65.1 (t), 107.8 (d), 109.0 (s), 186.8 (s), 187.6 (d); IR ν_{max} (liquid film) 2973, 2933, 2883, 1635, 1590, 1462, 1392, 1330, 1212, 1188, 1143, 1105, 1050, 997, 950 cm^{-1}; MS *m/z* 226 (M^+, 2), 149 (4), 127 (8), 83 (5), 73 (100), 69 (5), 55 (7), 45 (10), 43 (8), 41 (5); HRMS: M^+, found 226.1204. $C_{12}H_{18}O_4$ requires 226.1205.

(3*R*,4*R*)-3-(1,3-Dioxolan-2-yl)-3,4-dimethyl-2-oxo-cyclohexanecarbonitrile (15c). According to NMR a 3:2 mixture of stereoisomers was obtained in 60% yield based on ketone **15a** without purification of the intermediates.

Major isomer: ^{1}H NMR δ 0.87 (d, *J*=7.2 Hz, 3H), 0.99 (s, 3H), 1.43–2.35 (m, 5H), 3.80–4.08 (m, 5H), 4.99 (s, 1H); ^{13}C NMR δ 14.3 (q), 16.1 (q), 26.9 (t), 27.3 (t), 36.2 (d), 41.6 (d), 56.5 (s), 64.9 (t), 65.4 (t), 105.4 (d), 117.0 (s), 201.9 (s).

Minor isomer: ^{1}H NMR δ 0.89 (d, *J*=6.8 Hz, 3H), 1.13 (s, 3H), 1.43–2.35 (m, 5H), 3.80–4.08 (m, 5H), 5.28 (s, 1H); ^{13}C NMR δ(14.9 (q), 15.3 (q), 24.4 (t), 26.1 (t), 33.2 (d), 40.6 (d), 54.6 (s), 64.7 (t), 65.1 (t), 107.3 (d), 118.7 (s), 202.3 (s); IR ν_{max} (liquid film, diastereoisomeric mixture) 3293, 2945,2894, 2250, 2206, 1720, 1664, 1459, 1400, 1299, 1160, 1113, 1092, 1026, 990, 944 cm^{-1}.

(2*R*,3*R*)-2-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-2,3-dimethyl-5-cyclohexenone. This enone was prepared as described for the dioxolanyl-derivative (vide supra) in 82% yield. After purification by column chromatography on silica gel with light petroleum/ethyl acetate 3/1 as eluent a colourless oil was obtained. $[\alpha]_D$=−75.4 (*c*=2.0); ^{1}H NMR δ 0.97 (d, *J*=7.2 Hz, 3H), 1.00 (s, 3H), 1.63–1.74 (m, 2H), 2.03–2.31 (m, 4H), 2.50 (ddd, *J*=2.2, 4.6, 20.8 Hz, 1H), 2.86 (m, 1H), 3.84 (ddd, *J*=1.4, 6.0, 6.6 Hz, 2H), 4.42 (dd, *J*=6.4, 9.8 Hz, 1H), 5.62 (d, *J*=5.0 Hz, 1H), 5.88 (ddd, *J*=2.0, 4.0, 10.0 Hz, 1H), 6.75 (ddd, *J*=4.0, 8.0, 10.0 Hz, 1H); ^{13}C NMR δ 13.8 (q), 16.0 (q), 31.9 (t), 32.7 (t), 33.5 (t), 35.1 (d), 42.2 (d), 50.7 (s), 67.9 (t), 82.5 (d), 109.1 (d), 129.0 (d), 146.9 (d), 202.6 (s); IR ν_{max} (liquid film) 3041, 2974, 2906, 2883, 1678, 1464, 1381, 1214, 1101, 1023, 929 cm^{-1}; MS *m/z* 236 (M^+, 5), 166 (33), 124 (87), 113 (84), 109 (56), 95 (35), 85 (32), 83 (73), 69 (100), 67 (32), 55 (34); HRMS: M^+, found 236.1416. $C_{14}H_{20}O_3$ requires 236.1412.

(2*R*,3*R*)-2-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-2,3-dimethylcyclohexanone (16a). This substituted cyclohexanone was obtained as described before in 99% yield as a colourless oil after purification by column chromatography on silica gel with light petroleum/ethyl acetate 3/2 as eluent. $[\alpha]_D$=+33.4 (*c*=2.05); ^{1}H NMR δ 0.87 (d, *J*=7.0 Hz, 3H), 0.90 (s, 3H), 1.40–1.45 (m, 1H), 1.64–1.86 (m, 5H), 1.96–2.17 (m, 3H), 2.28–2.31 (m, 1H), 2.51–2.55 (m, 1H), 2.82–2.85 (m, 1H), 3.86 (ddd, *J*=4.2, 8.6, 9.8 Hz, 2H), 4.51 (dd, *J*=6.4, 9.6 Hz, 1H), 5.62 (d, *J*=5.0 Hz, 1H); ^{13}C NMR δ 13.9 (q), 15.9 (q), 22.9 (t), 28.4 (t), 32.8 (t), 33.2 (t), 37.7 (d), 38.8 (t), 42.2 (d), 54.6 (s), 68.0 (t), 82.5 (d), 109.1 (d), 214.5 (s); IR ν_{max} (liquid film) 2948, 2882, 1708, 1458, 1396, 1369, 1304, 1095, 1015, 958, 928 cm^{-1}; MS *m*/*z* 238 (M^+, 2), 166 (11), 113 (18), 95 (13), 85 (60), 83 (100), 69 (27), 67 (11), 55 (12), 47 (19), 41 (12); HRMS: M^+, found 238.1568. $C_{14}H_{22}O_3$ requires 238.1569.

(2*R*,3*R*)-2-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-6-hydroxymethylene-2,3-dimethyl-cyclohexanone (16b). This product was synthesised as described in the general procedure. After purification by column chromatography on silica gel with light petroleum/ethyl acetate 19/1 as eluent a colourless oil was obtained in 83% yield. $[\alpha]_D$=+81.6 (*c*=2.0); ^{1}H NMR δ 0.97 (d, *J*=6.8 Hz, 3H), 1.14 (s, 3H), 1.30–1.46 (m, 1H), 1.60–1.74 (m, 3H), 1.92–2.14 (m, 2H), 2.27–2.36 (m, 2H), 2.48 (dd, *J*=9.6, 12.8 Hz, 1H), 2.84–2.89 (m, 1H), 3.88 (ddd, *J*=4.0, 8.8, 9.6 Hz, 2H), 4.35 (dd, *J*=6.2, 9.6 Hz, 1H), 5.65 (d, *J*=5.0 Hz, 1H), 8.63 (s, 1H), 14.35 (s, 1H); ^{13}C NMR δ 16.8 (q), 17.1 (q), 23.0 (t), 28.1 (t), 32.7 (t), 33.6 (d), 33.7 (t), 42.2 (d), 46.8 (s), 68.0 (t), 84.6 (d), 109.2 (d), 109.4 (s), 187.9 (d), 189.1 (s); IR ν_{max} (liquid film) 2960, 2881, 1714, 1631, 1591, 1457, 1330, 1183, 1101, 1015, 922 cm^{-1}; MS *m*/*z* 266 (M^+, 1), 154 (37), 139 (14), 113 (100), 83 (10), 70 (6), 69 (63), 67 (10), 55 (20), 43 (13), 41 (13); HRMS: M^+, found 266.1514. $C_{15}H_{22}O_4$ requires 266.1518.

(6,7)-7-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-6,7-dimethyl-4,5,6,7-tetrahydrobenzo[*d*]isoxazole. This product was isolated in 73% yield as a light yellow solid after column chromatography on silica gel with ethyl acetate/light petroleum 1/7. Mp 115–116°C; ^{1}H NMR δ 0.94, (d, *J*=6.9 Hz, 3H), 1.04 (s, 3H), 1.37–1.52 (m, 1H), 1.62–1.75 (m, 2H), 1.98–2.09 (m, 1H), 2.21–2.30 (m, 1H), 2.30–2.40 (m, 2H), 2.58 (dt, *J*=19.2, 9.6 Hz, 1H), 2.84–2.89 (m, 1H), 3.81 (ddd, *J*=4.2, 5.4, 8.6 Hz, 2H), 4.31 (dd, *J*=6.3, 9.8 Hz, 1H), 5.43 (d, *J*=5.0 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR δ 15.7 (q), 17.2 (q), 28.5 (t), 32.6 (t), 34.3 (t), 35.0 (d), 42.1 (d), 42.7 (s), 68.1 (t), 82.7 (d), 109.1 (d), 113.8 (s), 149.2 (d), 171.6 (s); MS *m*/*z* 263 (M^+, 6), 180 (6), 152 (9), 151 (89), 136 (10), 123 (8), 114 (6), 113 (100), 69 (54), 67 (7), 55 (7); HRMS: M^+, found 263.1521. $C_{15}H_{21}NO_3$ requires 263.1521; Anal: found C, 68.09; H, 8.16; N, 5.37%. $C_{18}H_{25}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%.

(1*S*,3*R*,4*R*)-3-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-3,4-dimethyl-2-oxo-cyclohexanecarbonitrile (16c). This nitrile was obtained in 77% yield after a 4-day treatment with sodium methanolate in ether of the intermediate oxim or benzo[*d*]isoxazole and was purified by crystallisation from *tert*-butyl methyl ether at −20°C. Mp 118–119°C; $[\alpha]_D$=+144.1 (*c*=0.8); ^{1}H NMR δ 0.92 (d, *J*=6.6 Hz, 3H), 0.92 (s, 3H), 1.40–1.51 (ddq, *J*=7.2, 13.4, 6.6 Hz, 1H), 1.64–1.76 (m, 2H), 1.91 (t, *J*=9.6 Hz, 1H), 1.97–2.21 (m, 3H), 2.33–2.42 (m, 2H), 2.82 (m, 1H), 3.88 (dd, *J*=5.4, 8.2 Hz, 2H), 4.08 (dd, *J*=7.6, 11.4 Hz, 1H), 4.31 (dd, 5.8, 10.2 Hz, 1H), 5.63 (d, 5.0 Hz, 1H); ^{13}C NMR δ 14.1 (q), 16.0 (q), 26.3 (t), 26.7 (t), 32.4 (t), 33.6 (t), 37.1 (d), 40.9 (d), 41.7 (d), 54.9 (s), 68.4 (t), 82.7 (d), 109.0 (d), 117.4 (s), 204.4 (s); IR ν_{max} (CCl_4) 2964, 2878, 2252, 1726, 1458, 1389, 1270, 1214, 1181, 1144, 1099, 1065, 1013, 933 cm^{-1}; MS *m*/*z* 263 (M^+, 1), 167 (5), 114 (5), 113 (100), 83 (7), 70 (7), 69 (40), 67 (6), 55 (9), 43 (4), 41 (6); HRMS: M^+, found 263.1523. $C_{15}H_{21}NO_3$ requires 263.1521; Anal: found C, 68.33; H, 8.22; N, 5.27%. $C_{18}H_{25}NO_3$ requires C, 68.41; H, 8.04; N, 5.32%.

Michael addition of methyl vinyl ketone to β keto nitriles and β keto aldehydes

Method A. A solution of 10 mmol of the appropriate β keto nitrile and 12.5 mmol of methyl vinyl ketone in 50 mL of benzene was treated under nitrogen with 2 mmol of sodium methanolate (2 mL of an 1 M solution in methanol) until no starting material was detected by GC or TLC. The reaction mixture was acidified with 1 M hydrochloric acid in water to pH=1. The benzene layer was diluted with 50 mL of ether, washed with 50 mL of brine, dried, and evaporated to afford the corresponding diketone.

Method B. A solution of 2 mmol of substrate and 250 mg (3.6 mmol) of methyl vinyl ketone in 10 mL of THF was treated with 60 mg (0.6 mmol) of triethylamine at room temperature for three days. The reaction mixture was poured into water and acidified to pH=2 with aqueous 1 M HCl and extracted three times with ether. The combined extracts were washed with brine, dried on magnesium sulfate, filtered, and evaporated to afford the corresponding diketone.

Method C. A stirred solution of 10 mmol of substrate and 1.50 g (14.8 mmol) of triethylamine in 25 mL of ethyl acetate was treated with 1.05 g (15 mmol) of methyl vinyl ketone followed by three pellets of potassium hydroxide. Temperature and reaction time are indicated for the individual compounds. The reaction mixture was poured into water and acidified to pH=2 with aqueous 1 M HCl and extracted three times with ether. The combined extracts were washed with brine, dried on magnesium sufate, filtered, and evaporated to afford the corresponding diketone.

(1*S*,6*S*)-6-Isopropenyl-3-methyl-2-oxo-1-(3-oxo-butyl)-3-cyclohexenecarbaldehyde (17). This yellow oily compound was obtained via Method C in 87% yield after 3.5 h at 0°C and used without purification for the next reaction. $[\alpha]_D$=−68.6 (*c*=4.5); ^{1}H NMR δ 1.63 (s, 3H), 1.77 (t, *J*=1.6 Hz, 3H), 2.07 (s, 3H), 2.03–2.43 (m, 5H), 2.70–2.79 (m, 1H), 2.81–2.84 (m, 1H), 4.62 (s, 1H), 4.79 (t, *J*=1.3 Hz, 1H), 6.85 (t, *J*=1.6 Hz, 1H), 9.84 (s, 1H); ^{13}C NMR δ 15.6 (q), 22.3 (q), 25.9 (t), 28.4 (t), 29.7 (q), 37.8 (t), 49.2 (d), 60.1 (s), 115.1 (t), 134.5 (s), 142.8 (d), 143.7 (s), 198.4 (s), 202.6 (d), 207.2 (s); IR ν_{max} (tetra) 3087, 2977, 2929, 2851, 1727, 1669, 1659, 1435,1360, 1295, 1165,

1074, 1040, 904, 854, 839 cm^{-1}; MS *m/z* 248 (M^+, 11), 230 (7), 220 (22), 205 (7), 187 (9), 177 (8), 163 (17), 162 (37), 161 (20), 149 (51), 147 (32), 135 (13), 121 (82), 109 (13), 107 (10), 105 (13), 91 (22), 82 (100), 77 (16), 55 (13), 43 (50), 41 (17), 39 (15); HRMS: M^+, found 248.1416. $C_{15}H_{20}O_3$ requires 248.1416.

(1*R*,6*R*)-6-Isopropenyl-3-methyl-2-oxo-1-(3-oxo-butyl)-3-cyclohexenecarbaldehyde. This bright yellow oily compound was obtained via Method C in 88% yield after 3 h at 0°C. Purification was performed by column chromatography on silica gel with ethyl acetate/light petroleum 1/2. ^1H NMR δ 1.64 (br s, 3H), 1.79 (t, *J*=1.6 Hz, 3H), 2.07 (s, 3H), 2.03–2.43 (m, 5H), 2.70–2.79 (m, 1H), 2.81 (d, *J*=1.8 Hz, 1H), 4.61 (s, 1H), 4.79 (t, *J*=1.3 Hz, 1H), 6.64 (t, *J*=1.6 Hz, 1H), 9.82 (s, 1H); ^{13}C NMR δ 15.6 (q), 22.3 (q), 26.0 (t), 28.3 (t), 29.7 (q), 37.7 (t), 49.1 (d), 60.0 (s), 115.1 (t), 134.5 (s), 142.7 (d), 143.7 (s), 198.4 (s), 202.8 (d), 207.8; IR ν_{max} (tetra) 3086, 2979, 2930, 2850, 1726, 1666, 1659, 1435,1360, 1296, 1166, 1070, 1040, 904, 854, 839 cm^{-1}; MS *m/z* 248 (M^+, 11), 220 (22), 162 (37), 161 (20), 149 (49), 147 (32), 121 (76), 91 (22), 82 (100), 77 (13), 43 (50); HRMS: M^+, found 248.1416. $C_{15}H_{20}O_3$ requires 248.1416.

(1*S*,3*S*,4*R*,6*S*)-6-Isopropenyl-3,4-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbaldehyde (19). The synthesis of this product via Method C was performed in 18 h at room temperature. After purification by column chromatography on silica gel with ethyl acetate/light petroleum 1/4 as eluent a 19:1 mixture of two diastereoisomers was obtained in 97% yield as a light coloured oil, which solidified in the refrigator. Recrystallisation from di*iso*propyl ether gave colourless crystals. Mp 40–42°C; $[\alpha]_D$=−24.8 (*c*=3.4); ^1H NMR δ 0.97 (d, *J*=5.8 Hz, 3H), 0.98 (d, *J*=6.4 Hz, 3H), 1.57 (br s, 3H), 1.60–1.85 (m, 3H), 1.96 (s, 3H), 1.93–2.24 (m, 5H), 2.56 (m, 1H), 4.29 (s, 1H), 4.78 (br s, 1H), 10.16 (s, 1H); ^{13}C NMR δ 11.5 (q), 20.6 (q), 24.5 (q), 29.2 (t), 29.9 (q), 32.6 (t), 34.3 (d), 37.8 (t), 48.2 (d), 50.9 (d), 60.1 (s), 113.9 (t), 144.8 (s), 205.0 (s), 206.8 (s), 214.4 (s); IR ν_{max} (tetra) 3083, 2975, 2934, 2875, 1723, 1715, 1694, 1648, 1455, 1374, 1285, 1217, 1169, 1094, 1024, 976, 947, 900 cm^{-1}; MS *m/z* 264 (M^+, 2), 236 (100), 221 (7), 193 (43), 178 (22), 165 (33), 163 (31), 135 (19), 121 (18), 109 (20), 95 (18), 55 (18), 43 (49), 41 (19); HRMS: M^+, found 264.1718. $C_{16}H_{24}O_3$ requires 264.1725; (M^+−CO), found 236.1775. $C_{15}H_{24}O_2$ requires 236.1776.

(1*S*,6*S*)-6-Isopropenyl-3-methyl-2-oxo-1-(3-oxo-butyl)-3-cyclohexenecarbonitrile. This *R*-(−)-carvone-derived product was obtained via Method B in 78% yield as a white solid on standing in the refrigerator. Mp 72–74°C; $[\alpha]_D$=−37.3 (*c*=3.2); ^1H NMR δ 1.81 (s, 3H), 1.82 (s, 3H), 2.02–2.13 (m, 2H), 2.15 (s, 3H), 2.52–2.60 (m, 1H), 2.66–2.87 (m, 4H), 4.92 (s, 1H), 4.97 (t, *J*=1.4 Hz, 1H), 6.75 (br s, 1H); ^{13}C NMR δ 16.4 (q), 20.5 (q), 26.4 (t), 29.5 (t), 30.0 (d), 39.5 (t), 49.9 (s), 50,2 (d), 116,7 (t), 117.9 (s), 133.4 (s), 142.8 (s), 144.3 (d), 191.8 (s), 206.8 (s); IR ν_{max} (tetra) 3082, 3028, 2983, 2923, 2231, 1721, 1690, 1648, 1436, 1360, 1285, 1165, 908 cm^{-1}; MS *m/z* 245 (M^+, 6), 203 (7), 202 (11), 188 (7), 187 (7), 175 (17), 174 (49), 160 (7), 135 (16), 82 (100), 54 (6), 43 (6); HRMS: M^+, found 245.1412. $C_{15}H_{19}NO_2$ requires 245.1416.

(1*R*,6*R*)-6-Isopropenyl-3-methyl-2-oxo-1-(3-oxo-butyl)-3-cyclohexenecarbonitrile. Synthesis of this *S*-(+)-carvone-derived product was performed by Method B and the residue was purified by column chromatography on silica gel with ethyl acetate/light petroleum 1/4 to give a 95% yield of an oil with solidified on standing in the refrigerator. Mp 78°C; $[\alpha]_D$=+33.0 (*c*=2.4); ^1H NMR δ 1.79 (br s, 6H), 2.00–2.11 (m, 2H), 2.13 (s, 3H), 2.52–2.57 (m, 1H), 2.63–2.83 (m, 4H), 4.90 (s, 1H), 4.95 (br s, 1H), 6.73 (br s, 1H); ^{13}C NMR δ 16.3 (q), 20.5 (q), 26.4 (t), 29.5 (t), 30.0 (d), 39.5 (t), 50.0 (s), 50.1 (d), 116.7 (t), 117.9 (s), 133.3 (s), 142.8 (s), 144.4 (d), 191.8 (s), 206.7 (s); IR ν_{max} (tetra) 3083, 3027, 2983, 2923, 2232, 1721, 1690, 1642, 1436, 1360, 1285, 1165, 1045, 908 cm^{-1}; MS *m/z* 245 (M^+, 2), 203 (3), 202 (5), 175 (8), 174 (4), 160 (3), 131 (3), 83 (5), 82 (100), 54 (10), 43 (8); HRMS: M^+, found 245.1413. $C_{15}H_{19}NO_2$ requires 245.1416; Anal: found C, 73.23; H, 7.88; N, 5.73%. $C_{15}H_{19}NO_2$ requires C, 73.44; H, 7.81; N, 5.71%.

(1*S*,3*S*,4*R*,6*S*)-6-Isopropenyl-3,4-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile (25). Obtained after 1.5 h in 88% yield via Method A and purified by column chromatography on silica gel with light petroleum/ethyl acetate 4/1 as eluent. $[\alpha]_D$=+50.3 (*c*=1.4); ^1H NMR δ 1.00 (d, *J*=5.8 Hz, 3H), 1.01 (d, *J*=6.4 Hz, 3H), 1.71–1.85 (buried m, 3H), 1.75 (br s, 3H), 2.02–2.26 (m, 2H), 2.11 (s, 3H), 2.39–2.53 (m, 2H), 2.64–2.73 (m, 2H), 4.58 (s, 1H), 5.00 (q, *J*=0.6 Hz, 1H); ^{13}C NMR δ 12.1 (q), 20.4 (q), 23.6 (q), 30.1 (q), 30.6 (t), 31.9 (t), 34.4 (d), 38.7 (t), 47.1 (d), 50.2 (d), 55.6 (s), 114.9 (t), 118.9 (s), 143.5 (s), 206.2 (s), 206.4 (s); IR ν_{max} (KBr) 3089, 2973, 2933, 2876, 2240, 1714, 1454, 1374, 1171, 901 cm^{-1}; MS *m/z* 261 (M^+, 71), 246 (32), 233 (12), 218 (64), 204 (77), 191 (45), 190 (47), 176 (43), 148 (41), 146 (60), 122 (42), 121 (100), 106 (20), 95 (12), 79 (15), 77 (12), 55 (17), 43 (36), 41 (11); HRMS: M^+, found 261.1725. $C_{16}H_{23}NO_2$ requires 261.1729.

(1*S*,6*S*)-6-Isopropenyl-3,3-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile. Obtained in 94% yield as a viscous oil via Method A after a reaction time of 3 h. ^1H NMR δ 1.05 (s, 3H), 1.18 (s, 3H), 1.40–1.75 (m, 3H), 1.84 (br s, 3H), 1.89–1.98 (m, 2H), 2.09 (s, 3H), 2.16–2.33 (m, 2H), 2.54–2.84 (m, 2H), 4.86 (s, 1H), 4.92 (q, *J*= 1.4 Hz, 1H); ^{13}C NMR δ 21.0 (q), 25.3 (t), 27.1 (q), 27.3 (t), 27.4 (q), 30.0 (q), 39.4 (t), 40.0 (t), 47.1 (s), 51.1 (s), 54.6 (d), 116.1 (t), 119.2 (s), 143.0 (s), 205.8 (s), 206.9 (s).

(1*S*,4*R*,6*S*)-6-Isopropenyl-3,3,4-trimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile (27). This product was obtained in 91% yield via Method A after 2 h and purified by column chromatography on silica gel with light petroleum/ethyl acetate 5/1. ^1H NMR δ 0.88 (d, *J*=6.8 Hz, 3H), 1.00 (s, 3H), 1.05–1.26 (m, 1H), 1.37 (s, 3H), 1.57–1.68 (m, 1H), 1.86 (t, *J*=0.6 Hz, 3H), 2.01 (dd, *J*=7.4, 8.6 Hz, 2H), 2.13 (s, 3H), 2.16–2.30 (m, 1H), 2.35–2.43 (m, 1H), 2.61–2.76 (m, 2H), 4.82 (s, 1H), 4.98 (s, 1H); ^{13}C NMR δ 16.0 (q), 21.2 (q), 22.7 (q), 27.1 (q), 27.9 (t), 30.0 (q), 31.4 (t), 37.4 (d), 39.7 (t), 48.5 (d), 49.7 (s), 50.8 (s), 116.1 (t), 119.2 (s), 142.9 (s), 206.9 (s), 207.1 (s); IR ν_{max} (KBr) 3080, 2972, 2939, 2880, 2227, 1716, 1462, 1374, 1168, 1020, 906 cm^{-1}; MS *m/z* 275 (M^+, 40), 260 (4), 247 (19), 232 (28), 205 (38), 190 (24), 177 (47), 165 (23), 162 (15), 146 (53), 121 (100),

84 (70), 69 (41), 55 (27), 43 (31), 41 (18); HRMS: M^+, found 275.1880. $C_{17}H_{25}NO_2$ requires 275.1885.

(1*S*,3*R*,4*R*,6*S*)-3-(1,3-Dioxolan-2-yl)-6-isopropenyl-3,4-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile (28). Obtained via Method A in 76% yield as a very viscous oil after a reaction time of three days. Purification was performed by column chromatography on silica gel with ethyl acetate/light petroleum 3/7 as eluent. ^{1}H NMR δ 0.85 (d, J=7.2 Hz, 3H), 0.98 (s, 3H), 1.53 (dd, J=3.6, 10.2 Hz, 1H), 1.85 (br s, 3H), 1.92 (dd, J=7.2, 8.4 Hz, 2H), 2.10 (s, 3H), 2.28–2.36 (m, 1H), 2.49–2.58 (m, 3H), 2.62–2.82 (m, 1H), 3.80–3.91 (m, 3H), 3.96–3.98 (m, 1H), 4.91 (s, 1H), 4.95 (br s, 1H), 5.68 (s, 1H); ^{13}C NMR δ 13.7 (q), 16.3 (q), 20.9 (q), 27.2 (t), 29.9 (q), 32.3 (t), 34.2 (t), 39.8 (t), 48.8 (d), 51.9 (s), 58.3 (s), 64.8 (t), 65.5 (t), 103.9 (d), 116.4 (t), 118.2 (s), 142.3 (s), 201.7 (s), 206.9 (s); IR ν_{max} (liquid film) 3080, 2948, 2892, 2230, 1721, 1716, 1449, 1373, 1243, 1162, 1113, 1033, 992, 938 cm^{-1}; MS *m*/*z* 333 (M^+, 1), 263 (3), 248 (3), 176 (2), 148 (4), 135 (7), 121 (10), 105 (9), 74 (38), 73 (100), 67 (18), 55 (30), 45 (92), 43 (12), 41 (28); HRMS: M^+, found 333.1941. $C_{19}H_{27}NO_4$ requires 333.1940.

(1*S*,3*R*,4*R*,6*S*)-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-6-isopropenyl-3,4-dimethyl-2-oxo-1(3-oxo-butyl)-cyclohexanecarbonitrile (29). Obtained via Method A after 19 days as white crystals in 95% yield after column chromatography with ethyl acetate/light petroleum 3/7 as eluent. Mp 82–82.5°C; $[\alpha]_D$=−15.8 (c=1.49); ^{1}H NMR δ 0.91 (d, J=7.0 Hz, 3H), 0.99 (s, 3H), 1.54 (ddd, J=2.8, 6.2, 9.6 Hz, 1H), 1.80 (ddd, J=1.6, 5.8, 7.8 Hz, 2H), 1.93 (br s, 3H), 1.97–2.11 (m, 3H), 2.16 (s, 3H), 2.33–2.53 (m, 3H), 2.67–2.88 (m, 3H), 3.86–4.08 (m, 2H), 4.96 (s, 1H), 4.97–5.03 (m, 1H), 5.03 (br s, 1H), 5.04 (br s, 1H), 5.71 (d, J=5.0 Hz, 1H); ^{13}C NMR δ 15.4 (q), 16.4 (q), 21.0 (q), 27.8 (t), 30.1 (q), 32.2 (t), 32.6 (t), 33.7 (t), 34.3 (d), 40.0 (t), 42.2 (d), 48.8 (d), 51.3 (s), 56.0 (s), 68.0 (t), 81.7 (d), 109.2 (d), 116.5 (t), 118.7 (s), 142.5 (s), 204.1 (s), 207.2 (s); IR ν_{max} (KBr) 3080, 2975, 2873, 2212, 1721, 1713, 1457, 1387, 1101, 1011, 998 cm^{-1}; MS *m*/*z* 373 (M^+, 0.7), 260 (6), 167 (15), 114 (7), 113 (100), 83 (8), 73 (9), 69 (30), 55 (9), 43 (9), 41 (6); HRMS: M^+, found 373.2246. $C_{22}H_{31}NO_4$ requires 373.2253.

(1*R*,3*R*,4*R*)-3-(1,3-Dioxolan-2-yl)-3,4-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile (36) and (1*S*,3*R*,4*R*)-3-(1,3-Dioxolan-2-yl)-3,4-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile (38). This product was synthesised in 90% yield as a 5:4 mixture of stereoisomers via Method A after stirring for 8 h at room temperature. The individual isomers were obtained after column chromatography with ethyl acetate/light petroleum 3/7 as eluent. The MS spectrum of the major (less polar) isomer was superimposable with the one obtained from the annelated product 40, vide infra.

*Major (less polar) isomer (**36**):* $[\alpha]_D$=−95.4 (c=1.3); ^{1}H NMR δ 0.82 d, J=7.1 Hz, 3H), 0.95 (s, 3H), 1.45–1.54 (m, 1H), 1.68–1.88 (m, 2H), 2.08 (s, 3H), 2.04–2.20 (m, 2H), 2.22–2.48 (m, 2H), 2.50–2.82 (m, 2H), 3.80–3.88 (m, 3H), 3.90–4.00 (m, 1H), 5.58 (s, 1H); ^{13}C NMR δ 13.8 (q), 16.1 (q), 25.5 (t), 29.4 (t), 29.8 (q), 33.6 (t), 35.9 (d), 39.2 (t), 47.8 (s), 58.2 (s), 64.9 (t), 65.4 (t), 104.0 (d), 119.1 (s), 202.6 (s), 206.6 (s); IR ν_{max} (liquid film) 2939, 2885, 2231, 1718, 1716, 1448, 1369, 1229, 1144, 1099 cm^{-1}; MS *m*/*z* 275 [$(M-18)^+$, 0.4], 274 (0.3), 215 (0.2), 188 (0.7), 187 (0.4), 174 (0.6), 160 (0.6), 159 (0.5), 140 (0.7), 138 (0.7), 117 (0.6), 116 (0.9), 115 (0.7), 105 (0.6), 104 (0.5), 103 (0.5), 91 (1.3), 77 (1.0), 74 (3.0), 73 (100), 55 (2.0), 45 (9.5), 43 (1.5), 41 (1.2); HRMS: $(M-18)^+$, found 275.1514. $C_{16}H_{21}NO_3$ requires 275.1521.

*Minor (more polar) isomer (**38**):* $[\alpha]_D$=+47.6 (c=1.3); ^{1}H NMR δ 0.95 d, J=6.8 Hz, 3H), 1.23 (s, 3H), 1.62–1.84 (m, 4H), 2.06 (s, 3H), 2.07–2.20 (m, 3H), 2.48–2.62 (m, 2H), 3.67–3.83 (m, 4H), 5.10 (s, 1H); ^{13}C NMR δ 15.9 (q), 16.9 (q), 27.0 (t), 29.0 (t), 29.7 (q), 34.2 (d), 34.4 (t), 38.7 (t), 47.8 (s), 56.1 (s), 64.5 (t), 65.1 (t), 106.3 (d), 119.6 (s), 204.3 (s), 206.3 (s); IR ν_{max} (liquid film) 2940, 2883, 2231, 1716, 1448, 1369, 1228, 1140, 1099 cm^{-1}; MS *m*/*z* 293 (M^+, 1.1), 278 (0.3), 265 (0.2), 250 (0.2), 235 (0.4), 222 (0.8), 208 (0.7), 151 (1.6), 127 (1.5), 74 (3.1), 73 (100), 69 (1.4), 55 (3.8), 45 (8.1), 43 (6.6), 41 (2.4); HRMS: M^+, found 293.1622. $C_{16}H_{23}NO_4$ requires 293.1627.

(1*R*,3*R*,4*R*)-3-(1,3-Dioxolan-2-yl)-3,4-dimethyl-2-oxo-1-(3-oxo-pentyl)-cyclohexanecarbonitrile (43) and (1*S*,3*R*,4*R*)-3-(1,3-Dioxolan-2-yl)-3,4-dimethyl-2-oxo-1-(3-oxo-pentyl)-cyclohexanecarbonitrile (44). This product was synthesised in 87% yield as a 5:4 mixture of stereoisomers via Method A after stirring 8 h at room temperature. The individual isomers were obtained after column chromatography with ethyl acetate/light petroleum 1/5 as eluent.

*Minor (less polar) isomer (**43**):* $[\alpha]_D$=−87.0 (c=1.3); ^{1}H NMR δ 0.86 (d, J=7.1 Hz, 3H), 0.99 (s, 3H), 1.01, (t, J=7.3 Hz, 3H), 1.50–1.59 (m, 1H), 1.74–1.93 (m, 2H), 2.09–2.24 (m, 2H), 2.35 (q, J=7.3 Hz, 2H), 2.35–2.47 (m, 2H), 2.55–2.63 (m, 2H), 3.81–3.90 (m, 3H), 3.96–4.00 (m, 1H), 5.61 (s, 1H); ^{13}C NMR δ 7.8 (q), 14.0 (q), 16.3 (q), 25.7 (t), 29.7 (t), 33.9 (t), 36.0 (t), 36.1 (d), 38.1 (t), 48.4 (s), 58.4 (s), 65.1 (t), 65.6 (t), 104.2 (d), 119.4 (s), 202.9 (s), 209.6 (s); IR ν_{max} (liquid film) 2979, 2941, 2884, 2231, 1717, 1461, 1393, 1375, 1261, 1201, 1138, 1113, 1032, 988 cm^{-1}.

*Major (more polar) isomer (**44**):* $[\alpha]_D$=+26.8 (c=1.3); ^{1}H NMR δ 0.95 (d, J=6.8 Hz, 3H), 0.96 (t, J=7.1 Hz, 3H), 1.24, (s, 3H), 1.65–1.82 (m, 3H), 2.09–2.21 (m, 3H), 2.35–2.47 (m, 1H), 2.41 (q, J=7.3 Hz, 2H), 2.55–2.73 (m, 2H), 3.70–3.90 (m, 4H), 5.56 (s, 1H); ^{13}C NMR δ 7.6 (q), 16.0 (q), 16.9 (q), 27.1 (t), 29.1 (t), 34.3 (d), 34.5 (t), 35.7 (t), 47.9 (s), 56.2 (s), 64.6 (t), 65.2 (t), 106.4 (d), 119.7 (s), 202.4 (s), 209.3 (s); IR ν_{max} (liquid film) 2978, 2941, 2884, 2231, 1717, 1461, 1392, 1375, 1201, 1138, 1113, 1032, 988 cm^{-1}; MS *m*/*z* 307 (M^+, 0.8), 168 (6), 151 (2), 139 (12), 127 (5), 74 (3), 73 (100), 69 (1), 57 (18), 55 (8), 45 (5), 43 (5), 41 (2); HRMS: M^+, found 307.1777. $C_{16}H_{23}NO_4$ requires 307.1784.

(1*,3*R*,4*R*)-[(2*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-2-yl]-3,4-dimethyl-2-oxo-1-(3-oxo-butyl)-cyclohexanecarbonitrile (37) and (39). This product was synthesised following Method A in 78% yield after 18-h reaction

time. After column chromatography with ethyl acetate/light petroleum 3/7 as eluent there was obtained according to ^{1}H NMR and GLC an inseparable 6/5 mixture of diastereoisomers.

*Major isomer (**37**):* ^{1}H NMR (selected peaks) δ 0.99 (d, J=6.8 Hz, 3H), 1.19 (s, 3H), 1.70–1.90 (m, 6H), 2.08–2.30 (m, 5H), 2.14 (s, 3H), 2.58–2.76 (m, 3H), 3.81–3.95 (m, 2H), 4.24 (dd, J=7.2, 9.0 Hz, 1H), 5.63 (d, J=5.0 Hz, 1H); ^{13}C NMR δ 15.8 (q), 16.5 (q), 26.7 (t), 29.6 (t), 29.9 (q), 32.8 (t), 33.5 (t), 33.7 (t), 36.9 (d), 39.1 (t), 42.4 (d), 48.4 (s), 55.6 (s), 67.7 (t), 82.5 (d), 109.4 (d), 119.9 (s), 204.9 (s), 206.8 (s).

*Minor isomer (**39**):* ^{1}H NMR (selected peaks) δ 0.88 (d, J=6.8 Hz, 3H), 0.95 (s, 3H), 1.70–1.90 (m, 6H), 2.08–2.30 (m, 5H), 2.14 (s, 3H), 2.58–2.76 (m, 3H), 3.81–3.95 (m, 2H), 4.92 (dd, J=5.8, 9.8 Hz, 1H), 5.71 (d, J=4.9 Hz, 1H); ^{13}C NMR δ 15.1 (q), 16.1 (q), 25.6 (t), 29.9 (q), 29.9 (t), 32.6 (t), 33.9 (t), 35.2 (t), 37.1 (d), 39.5 (t), 42.2 (d), 47.7 (s), 52.2 (s), 68.0 (t), 81.9 (d), 109.2 (d), 120.0 (s), 204.7 (s), 206.8 (s).

IR ν_{max} (tetra, diastereoisomeric mixture) 2973, 2963, 2873, 2236, 1725, 1717, 1451, 1371, 1169, 1109, 1024, 941 cm^{-1}; MS m/z 333 (M^+, 0.9), 221 (4), 167 (17), 151 (4), 139 (8), 138 (6), 113 (100), 83 (8), 71 (6), 69 (41), 57 (6), 55 (11), 43 (13), 41 (6); HRMS: M^+, found 233.1938. $C_{19}H_{27}NO_4$ requires 333.1940.

General procedure for the Robinson annelation

Method 1. A stirred solution of 1 mmol of the appropriate β keto nitrile and 1.2 mmol of methyl vinyl ketone in 10 mL of benzene was treated at room temperature with 0.2 mmol of sodium methanolate (0.2 mL of an 1 M solution in methanol) until all starting material had disappeared and another 0.6 mmol of sodium methanolate was added and stirred for the indicated time. The reaction mixture was diluted with 50 mL of ether and 5 mL of water and acidified with 2 mL of an aqueous 1 M solution of hydrochloric acid. The organic layer was separated and washed with brine, dried over magnesium sulfate, filtered, and evaporated to give the dehydrated, annelated product.

Method 2. A stirred solution of 1 mmol of the appropriate β keto nitrile and 1.2 mmol of methyl vinyl ketone in 10 mL of benzene was treated at room temperature with 0.2 mmol of sodium methanolate (0.2 mL of a 1 M solution in methanol) until all starting material had disappeared and then 0.6 mmol of sodium methanolate (0.6 mL of a 1 M solution in methanol) was added and stirred for the indicated time. The reaction mixture was diluted with 50 mL of ether and 5 mL of water and acidified with 2 mL of an aqueous 1 M solution of hydrochloric acid. The organic layer was separated and washed with brine, dried over magnesium sulfate, filtered, and evaporated to give the annelated β hydroxy ketone. This ketone was dissolved in toluene and refluxed for 1 h in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was washed with brine, dried on magnesium sulfate, and evaporated to give the corresponding dehydrated, annelated product.

Method 3. A stirred solution of 1 mmol of the β keto nitrile under investigation in 15 mL of dry toluene was treated with 5 mL of a 0.2 M solution of pyrrolidine in THF, adjusted with acetic acid at pH=5.2, and 1.2 mmol of methyl vinyl ketone. The reaction mixture was refluxed for 3 h, cooled, diluted with 100 mL of ether, washed with 25 mL of a 4 M aqueous NaOH solution and with brine, dried, and evaporated to give the corresponding annelated product.

Method 4. A solution of 5 mL of a 0.2 M solution of pyrrolidine in THF, adjusted with acetic acid at pH=5.2, in 25 mL of dry toluene was heated at reflux temperature. A solution of 0.5 mmol of the (3-oxo-butyl)-derivative in 10 mL of dry toluene was added and refluxed for another 30 min. The reaction mixture was cooled, diluted with 50 mL of ether, washed with 25 mL of an aqueous 1 M solution of NaOH and with brine, dried, and evaporated to afford the annelated product.

Method 5. A solution of 0.69 mL (8.33 mmol) of pyrrolidine in 10 mL of THF was neutralised with acetic acid (pH=7.0) and 7.6 mmol of the appropriate substrate was added and refluxed for the indicated time. The reaction mixture was cooled, diluted with 50 mL of ether and 25 mL of water and extracted three times with ether. The combined extracts were washed with brine, dried, and evaporated to afford the annelated product.

Method 6. A solution of 10 mmol of the (3-oxo-butyl)-substituted ketone in 25 mL of methanol was treated with 10 mL of a 45% aqueous solution of KOH at the indicated temperature. After the indicated time water was added and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated to afford the annelated product.

(4a*R*,5*R*)-5-Isopropenyl-8-methyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (18). This crystalline product was obtained via Method 6 by stirring for 1 h at 0°C in 78% yield. The crude product was purified by distillation under reduced pressure (Kugelrohr, 0.02 mmHg, oven temperature 170°C). Mp 70–71°C; ^{1}H NMR δ 1.42–1.56 (m, 1H), 1.70 (s, 3H), 1.84 (br s, 3H), 1.98–2.49 (m, 7H), 4.82 (m, 2H), 5.95 (br s, 1H), 6.14 (m, 1H); ^{13}C NMR δ 18.1 (q), 19.3 (q), 27.7 (t), 31.8 (t), 37.8 (t), 38.0 (d), 48.7 (d), 113.5 (t), 122.0 (d), 131.7 (s), 136.7 (d), 145.8 (s), 159.1 (s), 200.8 (s); IR ν_{max} (tetra) 3072, 2992, 2925, 2873, 1660, 1583, 1440, 1346, 1316, 1264, 1210, 910, 890 cm^{-1}; MS m/z 202 (M^+, 32), 160 (65), 145 (40), 132 (100), 131 (75), 118 (55), 117 (96), 115 (36), 105 (46), 91 (81), 79 (33), 65 (34), 51 (33), 41 (46), 39 (43); HRMS: M^+, found 202.1355. $C_{14}H_{18}O$ requires 202.1358.

(4a*S*,5*S*)-5-Isopropenyl-8-methyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one. This product was obtained in 75% yield via Method 6 by stirring for 18 h at room temperature. Purification was performed by column chromatography with ethyl acetate/light petroleum 1/9 as eluent. Mp 77–80°C; ^{1}H NMR δ 1.39 (dddd, J=5.0, 11.5, 15.0, 16.5 Hz, 1H), 1.63 (t, J=1.0 Hz, 3H), 1.76 (q, J=1.6 Hz, 3H), 2.09–2.41 (m, 7H), 4.75 (s, 1H), 4.76 (t, J=1.6 Hz, 1H), 5.87 (d, J=1.2 Hz, 1H), 6.08 (m, 1H); ^{13}C NMR δ 17.8 (q), 19.0 (q), 27.4 (t), 31.5 (t), 37.5 (t), 37.7 (d), 48.4 (d), 113.2 (t), 121.7

(d), 131.4 (s), 136.4 (d), 145.5 (s), 158.7 (s), 200.3 (s); IR ν_{max} (KBr) 3069, 2991, 2931, 2876, 1669, 1643, 1596, 1443, 1350, 1270, 919, 898 cm^{-1}; MS *m/z* 202 (M^+, 24), 160 (78), 145 (42), 132 (100), 131 (80), 118 (66), 117 (91), 115 (39), 105 (46), 91 (81), 79 (33), 77 (54), 65 (34), 53 (34), 51 (37), 41 (68), 39 (44); HRMS: M^+, found 202.1356. $C_{14}H_{18}O$ requires 202.1358; Anal: found C, 83.42; H, 8.99%. $C_{14}H_{18}O$ requires C, 83.12; H, 8.97%.

(2*R*,3*S*,5*S*,6*S*)-5-Isopropenyl-2,3-dimethyl-spiro[5.5]undec-7-ene-1,9-dione (21) and (2*S*,3*S*,5*S*,6*S*)-5-Isopropenyl-2,3-dimethyl-spiro[5.5]undec-7-ene-1,9-dione (22). A 4/1 mixture of diastereoisomers was obtained via Method 5 in 80% yield after column chromatography with ethyl acetate/light petroleum 1/4 as eluent. This diastereoisomeric mixture was separated by column chromatography with ethyl acetate/light petroleum 1/19.

*Minor isomer (**21**)* (isopropenyl substituent in an equatorial position): mp 140–141°C; $[\alpha]_D$=+69.2 (*c*=0.46); ^{1}H NMR (400 MHz, C_6D_6) δ 0.70 (d, *J*=7.2 Hz, 3H), 0.97 (d, *J*=6.6 Hz, 3H), 1.23 (ddd, *J*=14.1, 3.5, 2.2 Hz, 1H), 1.51 (br s, 3H), 1.89 (m, 2H), 2.01 (ddd, *J*=13.9, 13.9, 4.8 Hz, 1H), 2.22 (m, 1H), 2.33 (dd, *J*=16.6, 3.5 Hz, 1H), 2.43 (m, 2H), 3.14 (ddd, *J*=17.3, 14.1, 5.5 Hz, 1H), 4.64 (s, 1H), 4.78 (br s, 1H), 6.00 (d, *J*=10.4 Hz, 1H), 6.59 (dd, *J*=10.4, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.6 (q), 13.7 (q), 21.8 (q), 29.1 (t), 34.4 (t), 35.8 (t), 36.9 (d), 46.2 (d), 51.7 (d), 55.1 (s), 115.0 (t), 130.5 (d), 144.7 (s), 146.4 (d), 197.5 (s), 207.6 (s); MS *m/z* 246 (M^+, 8), 231 (4), 218 (3), 204 (8), 188 (8), 175 (11), 173 (12), 162 (19), 161 (17), 152 (18), 147 (19), 133 (41), 123 (21), 120 (25), 119 (26), 106 (75), 105 (100), 95 (43), 92 (39), 91 (92), 77 (38), 65 (21), 55 (36), 41 (40), 39 (25); Anal: found C, 78.74; H, 9.24%. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%.

*Major isomer (**22**)* (isopropenyl substituent in an axial position): mp 97–98°C; $[\alpha]_D$=+0.6 (*c*=3.9); ^{1}H NMR (400 MHz, C_6D_6) δ 0.83 (d, *J*=6.4 Hz, 3H), 1.13 (d, *J*=6.4 Hz, 3H), 1.28–1.97 (m, 6H), 1.50 (s, 3H), 2.25 (m, 2H), 2.39 (m, 1H), 4.57 (s, 1H), 4.86 (s, 1H), 6.17 (d, *J*=10.6 Hz, 1H), 7.19 (d, *J*=10.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 12.6, (q), 20.9 (q), 24.9 (q), 32.2 (t), 33.4 (t), 33.6 (t), 35.4 (d), 47.1 (d), 50.1 (d), 51.6 (s), 114.2 (t), 130.3 (d), 144.8 (s), 151.7 (d), 196.5 (s), 212.2 (s); MS *m/z* 246 (M^+, 9), 231 (5), 218 (3), 213 (4), 204 (12),190 (9), 175 (14), 173 (14), 162 (41), 161 (23), 152 (23), 147 (24), 133 (39), 120 (26), 119 (30), 106 (76), 105 (100), 95 (77), 92 (36), 91 (92), 79 (33), 77 (40), 69 (16), 67 (26), 65 (24), 55 (41), 41 (48), 39 (28); Anal: found C, 78.58; H, 9.29%. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%.

(4a*S*,5*R*,7*R*,8*)-5-Isopropenyl-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (20).** This product was obtained via Method 6 after 12 h at room temperature in 20% yield. After purification by column chromatography on silica gel with light petroleum/ethyl acetate 80/20 as eluent a 7/3 inseparable diastereoisomeric mixture was obtained.

Major isomer: ^{1}H NMR δ 0.73 (d, *J*=7.1 Hz, 3H), 1.00 (d, *J*=7.3 Hz, 3H), 1.46 (br s, 3H), 1.00–2.50 (m, 10H), 4.56 (m, 2H), 5.61 (br s, 1H); ^{13}C NMR δ 18.4 (q), 19.9 (q), 21.2 (q), 26.6 (t), 31.9 (t), 34.7 (d), 35.5 (d), 36.4 (t), 45.2 (d), 47.0 (d), 112.3 (t), 126.5 (d), 146.6 (s), 169.9 (s), 200.0 (s).

Minor isomer: ^{1}H NMR δ 0.55 (d, *J*=7.1 Hz, 3H), 0.82 (d, *J*=6.8 Hz, 3H), 1.48 (br s, 3H), 1.00–2.50 (m, 10H), 4.56 (m, 2H), 5.66 (d, *J*=2.0 Hz, 1H); ^{13}C NMR δ 13.1 (q), 15.4 (q), 18.3 (q), 26.0 (t), 34.7 (d), 35.6 (t), 38.7 (t), 40.6 (d), 42.0 (d), 47.2 (d), 112.4 (t), 124.1 (d), 146.5 (s), 168.1 (s), 199.9 (s).

(4a*R*,5*S*)-4a-Cyano-5-isopropenyl-8-methyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one (23). This crystalline product was prepared via Method 1 in 79% yield after a reaction time of 2 h. Mp 106–108°C; $[\alpha]_D$=−156.5 (*c*=2.25); ^{1}H NMR δ 1.87 (ddd, *J*=4.6, 14.2, 16.0 Hz, 1H), 1.89 (s, 3H), 1.90 (s, 3H), 2.27–2.42 (m, 3H), 2.62–2.84 (m, 3H), 5.00 (s, 1H), 5.02 (t, *J*=1.6 Hz, 1H), 6.02 (s, 1H), 6.27 (d, *J*=5.6 Hz, 1H); ^{13}C NMR δ 19.6 (q), 20.5 (q), 30.1 (t), 31.5 (t), 34.7 (t), 39.1 (s), 50.5 (d), 116.7 (t), 118.8 (s), 123.4 (d), 130.2 (s), 137.1 (d), 142.5 (s), 152.5 (s), 197.5 (s); IR ν_{max} (KBr) 3074, 2963, 2921, 2226, 1677, 1625, 1588, 1444, 1307, 1265, 1238, 1174, 1054, 922, 887 cm^{-1}; MS *m/z* 227 (M^+, 100), 212 (36), 210 (10), 199 (41), 185 (31), 184 (30), 172 (74), 170 (69), 156 (30), 143 (43), 130 (29), 118 (20), 115 (22), 91 (18), 77 (25), 55 (12), 43 (16), 41 (14), 39 (14); HRMS: M^+, found 227.1305. $C_{15}H_{17}NO$ requires 227.1310; Anal: found C, 79.05; H, 7.56; N, 6.19%. $C_{15}H_{17}NO$ requires C, 79.25; H, 7.53; N, 6.16%.

(4a*S*,5*R*)-4a-Cyano-5-isopropenyl-8-methyl-4,4a,5,6-tetrahydronaphthalen-2(3*H*)-one. This crystalline product was obtained via Method 1 in 85% yield after stirring the reaction mixture for 2 h. Mp 114–115°C; $[\alpha]_D$=+156.7 (*c*=1.1); ^{1}H NMR δ 1.85 (ddd, *J*=4.6, 14.2, 15.6 Hz, 1H), 1.87 (s, 3H), 1.88 (s, 3H), 2.27–2.41 (m, 3H), 2.61–2.83 (m, 3H), 5.00 (s, 1H), 5.01 (br s, 1H), 6.06 (s, 1H), 6.28 (d, *J*=5.6 Hz, 1H); ^{13}C NMR δ 19.5 (q), 20.5 (q), 30.1 (t), 31.4 (t), 34.7 (t), 39.1 (s), 50.5 (d), 116.6 (t), 118.8 (s), 123.3 (d), 130.2 (s), 137.1 (d), 142.5 (s), 152.4 (s), 197.4 (s); IR ν_{max} (KBr, Hitachi EPI-G3) 3070, 2990, 2925, 2225, 1660, 1650, 1580, 1440, 1350, 1315, 1270, 1210, 910, 890 cm^{-1}; MS *m/z* 227 (M^+, 100), 212 (50), 210 (21), 199 (59), 186 (16), 185 (35), 184 (51), 172 (82), 170 (91), 158 (31), 143 (75), 130 (60), 115 (55), 91 (45), 77 (62), 51 (38), 41 (51), 39 (67); HRMS: M^+, found 227.1306. $C_{15}H_{17}NO$ requires 227.1310. Anal: found C, 78.95; H, 7.56; N, 5.99%. $C_{15}H_{17}NO$ requires C, 79.25; H, 7.53; N, 6.16%.

(4a*S*,5*S*,7*R*,8*R*,8a*S*)-4a-Cyano-8a-hydroxy-5-isopropenyl-7,8-dimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1*H*)-one. This product was synthesised via Method 2 after 2 h in 88% yield without dehydration and purified by column chromatography with ethyl acetate/light petroleum 1/4 as eluent. Mp 185–188°C; $[\alpha]_D$=+2.8 (*c*=1.5); ^{1}H NMR δ 0.96 (d, *J*=7.0 Hz, 3H), 1.02 (d, *J*=7.4 Hz, 3H), 1.52 (dt, *J*=13.2, 3.0 Hz, 1H), 1.84 (t, *J*=0.6 Hz, 3H), 2.00–2.27 (m, 7H), 2.42–2.80 (m, 4H), 4.92 (br s, 1H), 5.02 (br s, 1H); ^{13}C NMR δ 12.8 (q), 14.8 (q), 21.3 (q), 29.5 (t), 33.6 (d), 36.0 (t), 38.4 (t), 41.0 (d), 47.5 (s), 50.0 (t), 79.0 (s), 114.9 (t), 122.0 (s), 144.4 (s), 209.2 (s); IR ν_{max} (KBr) 3435, 3068, 2985, 2970, 2895, 2229, 1710, 1474, 1384, 1179, 973, 907 cm^{-1}; MS *m/z* 261 (M^+, 21), 246 (4), 243 (20),

228(10), 202 (12), 201 (45), 186 (12), 172 (13), 149 (12), 123 (19), 95 (50), 83 (24), 69 (31), 55 (44), 43 (100), 41 (34); HRMS: M^+, found 261.1725. $C_{16}H_{23}NO_2$ requires 261.1729; Anal: found C, 73.71; H, 8.79; N, 5.51%. $C_{16}H_{23}NO_2$ requires C, 73.52; H, 8.87; N, 5.36%.

(4a*R*,5*S*,7*R*,8*R*)-4a-Cyano-5-isopropenyl-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (26). This product was synthesised via Method 2 in 82% yield after a reaction time of 16 h. Purification was performed by column chromatography with ethyl acetate/light petroleum 1/4 as eluent. Mp 84–86°C; $[\alpha]_D=-154.7$ ($c=2.0$); ^{1}H NMR δ 0.73 (d, $J=7.0$ Hz, 3H), 1.03 (d, $J=6.6$ Hz, 3H), 1.51–1.57 (m, 1H), 1.82 (s, 3H), 2.07–2.50 (m, 6H), 2.83 (ddq, $J=2.0$, 6.6, 8.8 Hz, 1H), 4.92 (s, 1H), 4.93 (t, $J=1.4$ Hz, 1H), 5.85 (d, $J=2.0$ Hz, 1H); ^{13}C NMR δ 12.9 (q), 15.5 (q), 20.8 (q), 31.8 (t), 33.9 (t), 34.2 (d), 36.0 (t), 39.0 (d), 42.0 (s), 48.8 (d), 116.0 (t), 120.0 (s), 126.4 (d), 142.9 (s), 159.8 (s), 196.5 (s); IR ν_{max} (KBr) 3076, 2969, 2931, 2229, 1682, 1455, 1385, 1289, 1266, 1226, 903 cm^{-1}; MS *m/z* 243 (M^+, 48), 228 (35), 201 (80), 186 (30), 172 (32), 158 (21), 145 (20), 144 (17), 130 (17), 118 (15), 95 (100), 91 (27), 77 (24), 55 (50), 43 (22), 41 (44), 39 (21); HRMS: M^+, found 243.1614. $C_{16}H_{21}NO$ requires 243.1623; Anal: found C, 78.81; H, 8.83; N, 5.49%. $C_{16}H_{21}NO$ requires C, 78.97; H, 8.70; N, 5.76%.

(4a*R*,5*S*)-4a-Cyano-5-isopropenyl-8,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (24). Obtained via Method 1 as white crystals in 94% yield after crystallisation from hexane/*tert*-butyl methyl ether 95/5. The reaction was performed in 48 h. Mp 93–94°C; $[\alpha]_D=-11.4$ ($c=2.5$); ^{1}H NMR δ 1.15 (s, 3H), 1.36 (s, 3H), 1.64–1.79 (m, 4H), 1.87 (br s, 3H), 1.97–2.13 (m, 2H), 2.33–2.70 (m, 3H), 4.91 (s, 1H), 4.94 (q, $J=1.6$ Hz, 1H), 6.07 (s, 1H); ^{13}C NMR δ 21.1 (q), 25.2 (t), 29.6 (s), 29.9 (q), 30.2 (q), 34.0 (t), 34.2 (t), 37.8 (s), 39.5 (t), 55.2 (d), 116.1 (t), 120.2 (s), 126.2 (d), 143.2 (s), 164.9 (s), 197.7 (s); IR ν_{max} (KBr) 3073, 2969, 2930, 2229, 1682, 1450, 1384, 1346, 1289, 1226, 1126, 903 cm^{-1}; MS *m/z* 243 (M^+, 41), 228 (22), 201 (100), 187 (17), 186 (35), 172 (28), 145 (24), 130 (15), 91 (14), 81 (51), 55 (18), 41 (25), 39 (11); HRMS: M^+, found 243.1620. $C_{16}H_{21}NO$ requires 243.1623; Anal: found C, 78.91; H, 8.73; N, 5.71%. $C_{16}H_{21}NO$ requires C, 78.97; H, 8.70; N, 5.76%.

(4a*R*,5*R*,8a*R*)-4a-Cyano-8a-hydroxy-5-isopropenyl-8,8-dimethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2(1*H*)-one. This from S(+)-carvone-derived cyclised but not dehydrated product was obtained via Method 1 after 16 h. Purification was achieved by column chromatography with ethyl acetate/light petroleum 1/4 as eluent to give white crystals in 66% yield. Mp 193–194°C; ^{1}H NMR δ 0.93 (s, 3H), 1.31 (s, 3H), 1.37 (dt, $J=13.1$, 3.1 Hz, 1H), 1.54 (dq, $J=13.4$, 3.2 Hz, 1H), 1.75 (dt, $J=3.3$, 13.3 Hz, 1H), 1.87 (s, 3H), 2.00 (dt, $J=3.2$, 13.0 Hz, 1H), 2.05–2.30 (m, 2H), 2.36–2.47 (m, 3H), 2.54–2.78 (m, 2H), 2.96 (d, $J=14.5$ Hz, 1H), 4.94 (s, 1H), 4.95 (s, 1H); ^{13}C NMR δ 21.5 (q), 24.0 (q), 25.4 (t), 25.7 (q), 32.0 (t), 35.8 (t), 37.9 (t), 39.1 (s), 44.2 (s), 46.3 (t), 47.1 (d), 79.4 (s), 115.0 (t), 122.9 (s), 143.9 (s), 209.0 (s); IR ν_{max} (KBr, Hitachi EPI-G3) 3590, 3475, 3050, 2950, 2925, 2850, 2210, 1705, 1635, 1440, 1390, 1370, 1340, 1300, 1205, 1125, 1060, 950, 905 cm^{-1}; MS *m/z* 261 (M^+, 68), 246 (5), 243 (6), 233 (6), 218 (9), 217 (12), 192 (18), 190 (11), 177 (32), 176 (100), 134 (14), 123 (7), 121 (7), 95 (9), 93 (11), 55 (19), 43 (21), 41 (26); HRMS: M^+, found 261.1723. $C_{16}H_{23}NO_2$ requires 261.1729; Anal: found C, 73.71; H, 8.76; N, 5.51%. $C_{16}H_{21}NO$ requires C, 73.52; H, 8.87; N, 5.36%.

(4a*S*,5*R*)-4a-Cyano-5-isopropenyl-8,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one. Obtained after 48 h as white crystals in 74% yield after column chromatography on silica gel with ethyl acetate/light petroleum 1/4 as eluent. Mp 89–94°C; $[\alpha]_D=+9.7$ ($c=3.0$); ^{1}H NMR δ 1.17 (s, 3H), 1.38 (s, 3H), 1.40–1.82 (m, 4H), 1.88 (br s, 3H), 1.99–2.13 (m, 2H), 2.35–2.67 (m, 3H), 4.94 (s, 1H), 4.95 (q, $J=1.6$ Hz, 1H), 6.10 (s, 1H); ^{13}C NMR δ 20.8 (q), 25.0 (t), 29.7 (q), 30.0 (s), 30.2 (q), 34.0 (t), 34.2 (t), 37.6 (s), 39.3 (t), 55.0 (d), 115.9 (t), 120.0 (s), 126.0 (d), 143.0 (s), 164.7 (s), 197.3 (s); MS *m/z* 243 (M^+, 39), 228 (32), 201 (100), 187 (19), 186 (45), 172 (33), 145 (28), 130 (15), 91 (14), 81 (50), 55 (18), 41 (25), 39 (11); HRMS: M^+, found 243.1613. $C_{16}H_{21}NO$ requires 243.1623; Anal: found C, 78.71; H, 8.79; N, 5.61%. $C_{16}H_{21}NO$ requires C, 78.97; H, 8.70; N, 5.76%.

(4a*R*,5*S*,7*R*)-4a-Cyano-5-isopropenyl-7,8,8-trimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (33). This product was obtained as white crystals via Method 3 in 84% yield after purification by column chromatography with ethyl acetate/light petroleum 1/9 as eluent. Mp 119–121°C; $[\alpha]_D=-171.2$ ($c=3.5$); ^{1}H NMR δ 0.88 (d, $J=7.0$ Hz, 3H), 1.11 (s, 3H), 1.45 (s, 3H), 1.46 (dt, $J=13.6$, 3.6 Hz, 1H), 1.75–1.95 (m, 1H), 1.88 (s, 3H), 2.28 (dd, $J=3.2$, 13.2, 1H), 2.40–2.68 (m, 5H), 4.97 (s, 1H), 5.01 (t, $J=1.4$ Hz, 1H), 6.10 (s, 1H); ^{13}C NMR δ 16.4 (q), 20.9 (q), 27.2 (q), 31.0 (q), 32.1 (t), 34.2 (t), 34.6 (t), 38.2 (d), 38.9 (s), 41.2 (s), 48.1 (d), 116.5 (t), 120.4 (s), 127.8 (d), 143.0 (s), 164.2 (s), 197.4 (s); IR ν_{max} (KBr) 3074, 2971, 2949, 2875, 2222, 1682, 1600, 1455, 1380, 1304, 1271, 1185, 1093, 915 cm^{-1}; MS *m/z* 257 (M^+, 33), 242 (18), 216 (15), 215 (100), 214 (13), 200 (20), 186 (12), 173 (11), 172 (41), 158 (9), 95 (14), 41 (9); HRMS: M^+, found 257.1772. $C_{17}H_{23}NO$ requires 257.1780; Anal: found C, 79.33; H, 9.33; N, 5.31%. $C_{17}H_{23}NO$ requires C, 79.33; H, 9.01; N, 5.44%.

(4a*R*,5*S*,7*R*,8*S*)-4a-Cyano-8-(1,3-dioxolan-2-yl)-5-isopropenyl-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (34). Obtained via Method 4 in 41% yield after purification with column chromatography on silica gel with ethyl acetate/light petroleum 3/7 as eluent. From the basic water layer β keto nitrile **13c** was isolated in 48% yield. $[\alpha]_D=-145.2$ ($c=1.2$); ^{1}H NMR δ 0.90 (d, $J=7.0$ Hz, 3H), 1.02 (s, 3H), 1.45 (dt, $J=13.8$, 6.0 Hz, 1H), 1.83–1.91 (m, 1H), 1.91 (s, 3H), 2.26–2.71 (m, 6H), 3.81–3.91 (m, 3H), 3.91–4.00 (m, 1H), 4.96 (s, 1H), 5.02 (t, $J=1.4$ Hz, 1H), 5.55 (s, 1H), 6.15 (s, 1H); ^{13}C NMR δ 16.4 (q), 17.1 (q), 21.1 (q), 31.8 (t), 33.6 (d), 34.4 (t), 35.0 (t), 39.6 (s), 47.8 (d), 48.7 (s), 65.2 (t), 65.8 (t), 103.8 (d), 116.6 (t), 119.7 (s), 131.4 (d), 143.0 (s), 157.9 (s), 197.1 (s); IR ν_{max} (KBr) 3075, 2987, 2958, 2227, 1682, 1609, 1454, 1384, 1268, 1232, 1166, 1113, 1080, 1065, 988, 889 cm^{-1}; MS *m/z* 315 (M^+, 3), 87 (2), 85 (9), 83 (14), 74 (3), 73 (100), 69 (2), 47 (2), 45 (4); HRMS: M^+, found 315.1834. $C_{19}H_{25}NO_3$ requires 315.1834.

(4a*R*,5*S*,7*R*,8*S*)-4a-Cyano-8-[(2*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-2-yl]-5-isopropenyl-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (35). Obtained via Method 4 in 40% yield as light yellow crystals. The corresponding β keto nitrile **14c** was recovered from the basic water layer in 56% yield. Mp 201–202°C; $[\alpha]_D$=−55.3 (*c*=0.97); ^{1}H NMR δ 0.85 (d, *J*=7.0 Hz, 3H), 0.95 (s, 3H), 1.38 (dt, *J*=13.8, 5.8 Hz, 1H), 1.68–1.89 (m, 4H), 1.90 (s, 3H), 1.97–2.28 (m, 2H), 2.30–2.50 (m, 4H), 2.64–2.79 (m, 2H), 3.79–4.00 (m, 2H), 4.86 (dd, *J*=5.8, 10.2 Hz, 1H), 4.95 (s, 1H), 5.00 (t, *J*=1.4 Hz, 1H), 5.66 (d, *J*=5.0 Hz, 1H), 6.03 (s, 1H); ^{13}C NMR δ 16.8 (q), 18.2 (q), 21.3 (q), 32.0 (t), 32.8 (t), 34.1 (t), 34.5 (t), 35.2 (d), 35.5 (t), 39.1 (s), 42.2 (d), 47.1 (s), 47.7 (d), 68.0 (t), 81.4 (d), 108.8 (d), 116.7 (t), 120.0 (s), 131.3 (d), 143.0 (s), 158.9 (s), 197.2 (s); IR ν_{max} (tetra) 3074, 2976, 2955, 2867, 2230, 1682, 1610, 1457, 1378, 1315, 1268, 1109, 1018, 994, 909 cm^{-1}; MS *m/z* 355 (M^+, 0.1), 244 (6), 243 (36), 228 (4), 176 (6), 175 (9), 114 (6), 113 (100), 69 (42), 67 (5), 55 (7); HRMS: M^+, found 355.2134. $C_{22}H_{29}NO_3$ requires 355.2147; $[M-C_6H_8O_2+H^+]+$, found 243.1625. $C_{16}H_{21}NO$ requires 243.1627. Anal: found C, 74.53; H, 8.33; N, 3.61%. $C_{22}H_{29}NO_3$ requires C, 74.33; H, 8.22; N, 3.94%.

(4a*R*,7*R*,8*S*)-4a-Cyano-8-(1,3-dioxolan-2-yl)-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (40) and (4a*S*,7*R*,8*S*)-4a-Cyano-8-(1,3-dioxolan-2-yl)-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (42). Starting from **36** a 5/1 mixture of annelated products was obtained in 88% yield via Method 4 after 90 min. Purification by column chromatography on silica gel with ethyl acetate/light petroleum 1/4 as eluent afforded the pure annelated products.

A reaction for 90 min under the conditions of Method 4 afforded in 92% yield only the annelated product **40**, starting from **38**.

*Major isomer (**40**):* $[\alpha]_D$=+156.4 (*c*=1.1); ^{1}H NMR δ 1.03 (d, *J*=6.3 Hz, 3H), 1.36 (s, 3H), 1.46–2.72 (m, 9H), 3.80–4.05 (m, 4H), 4.92 (s, 1H), 6.44 (s, 1H); ^{13}C NMR δ 17.4 (q), 19.0 (q), 27.8 (t), 34.1 (t), 34.8 (d), 35.9 (t), 36.9 (t), 37.0 (s), 45.9 (s), 64.5 (t), 64.7 (t), 107.3 (d), 121.4 (s), 129.2 (d), 159.5 (s), 197.6 (s); IR ν_{max} (liquid film) 2936, 2888, 2229, 1681, 1601, 1458, 1415, 1380, 1342, 1320, 1265, 1211, 1170, 1093, 1030, 992, 958 cm^{-1}; MS *m/z* 275 (M^+, 0.5), 274 (0.3), 215 (0.2), 188 (0.7), 187 (0.4), 174 (0.6), 160 (0.6), 159 (0.5), 140 (0.7), 138 (0.9), 117 (0.6), 116 (0.7), 115 (0.7), 105 (0.6), 104 (0.5), 103 (0.5), 91 (1.6), 77 (1.2), 74 (3.0), 73 (100), 55 (1.9), 45 (9.5), 41 (1.3); HRMS: M^+, found 275.1514. $C_{16}H_{21}NO_3$ requires 275.1521, $(M-H)^+$, found 274.1440. $C_{16}H_{20}NO_3$ requires 274.1443.

*Minor isomer (**42**):* $[\alpha]_D$=−102.1 (*c*=0.6); ^{1}H NMR δ 0.88 (d, *J*=7.1 Hz, 3H), 1.04 (s, 3H), 1.55–2.79 (m, 9H), 3.83–4.02 (m, 4H), 5.52 (s, 1H), 6.15 (s, 1H); ^{13}C NMR δ 15.9 (q), 16.9 (q), 25.3 (t), 32.7 (t), 34.0 (d), 34.8 (t), 36.3 (s), 36.9 (t), 48.7 (s), 65.2 (t), 65.7 (t), 103.7 (d), 121.0 (s), 131.4 (d), 157.4 (s), 197.2 (s); IR ν_{max} (liquid film) 2947, 2922, 2884, 2228, 1675, 1618, 1606, 1560, 1455, 1397, 1313, 1279, 1206, 1075, 1069, 1029, 990, 909 cm^{-1}; MS *m/z* 275 (M^+, 1.1), 274 (0.5), 260 (0.2), 188 (1.1), 187 (0.6), 175 (0.5), 159 (0.9), 133 (0.9), 117 (1.4), 116 (1.5), 115 (2.2), 91 (2.0), 74 (3.0), 73 (100), 59 (2.9), 55 (2.1), 45 (6.6); HRMS: M^+, found 275.1517. $C_{16}H_{21}NO_3$ requires 275.1521.

(4a*R*,5*S*,7*R*,8*S*)-4a-Cyano-8-[(2*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-2-yl]-7,8-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (41). This crystalline product was obtained in 91% yield via Method 4 after purification by column chromatography on silica gel with ethyl acetate/light petroleum 1/4 as eluent. Mp 121–123°C; $[\alpha]_D$=+143.0 (*c*=0.7); ^{1}H NMR δ 1.08 (d, *J*=6.0 Hz, 3H), 1.39 (s, 3H), 1.53 (dt, *J*=13.8, 4.6 Hz, 1H), 1.69–1.84 (m, 4H), 1.89–1.93 (m, 1H), 1.97–2.20 (m, 3H), 2.26–2.40 (m, 2H), 2.55–2.73 (m, 2H), 2.77–3.00 (m, 1H), 3.88–3.96 (m, 2H), 4.47 (dd, *J*=7.0, 10.1 Hz, 1H), 5.73 (d, *J*=5.0 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR δ 17.9 (q), 21.0 (q), 28.2 (t), 33.1(t), 33.7 (t), 34.0 (t), 35.3 (d), 36.2 (t), 37.0 (s), 37.4 (t), 42.0 (d), 46.0 (s), 68.2 (t), 84.2 (d), 108.9 (d), 121.3 (s), 128.5 (d), 161.2 (s), 197.4 (s); IR ν_{max} (tetra) 2971, 2955, 2869, 2230, 1682, 1610, 1453, 1374, 1316, 1109, 1018, 912 cm^{-1}; MS *m/z* 315 (M^+, 0.5), 203 (15), 188 (5), 167 (6), 114 (6), 113 (100), 83 (7), 69 (50), 67 (7), 57 (6), 55 (14), 43 (10), 41 (9); HRMS: M^+, found 315.1833. $C_{19}H_{25}NO_3$ requires 315.1834; Anal: found C, 72.33; H, 8.23; N, 4.41%. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 7.99; N, 4.44%.

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