The assignment of the correct structures and conformational analysis of the isomeric *t*-5- and *t*-4-phenyl-*t*(*c*)-2-benzoyl-*r*-1-cyclohexanecarboxylic acids by NMR and FT-IR spectroscopy

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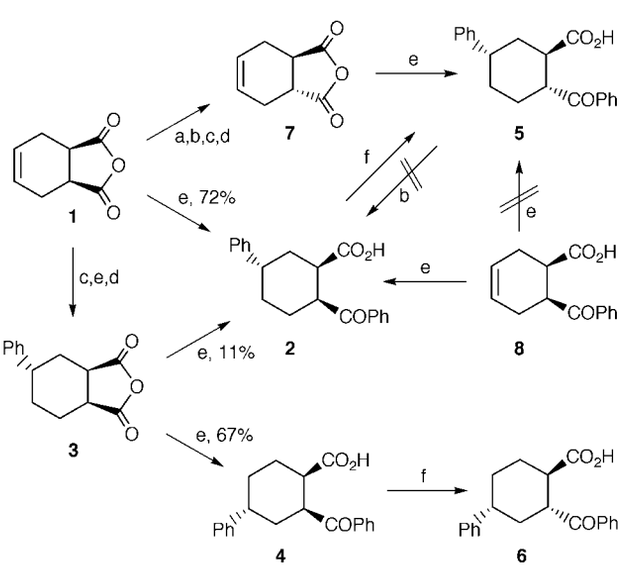
The $AlCl_3$ catalysed addition of benzene to *cis*-2-benzoylcyclohex-4-enecarboxylic acid results in the product, *t*-5-phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid (**2**), but not in its 2-*trans* epimer (**5**) as has been reported previously in the literature. The latter was obtained instead by treating **2** with NaOH in EtOH–H_2O. The structures and conformational assignment of **2**, its 4-*trans* phenyl positional isomer (**4**), and both their 2-*trans* benzoyl epimers (**5** and **6**, respectively, prepared by base-induced epimerisation) were elucidated by means of NMR spectroscopy. The postulated *trans*→*cis* transformation of the 2-*trans* isomer **5** to the product **2** does not in fact occur; indeed it is the reverse transformation that is viable. All of the compounds showed substantial intramolecular hydrogen-bonding in solution (*e.g.* in $CDCl_3$) by FT-IR measurements and, furthermore, a dynamic equilibrium between hydrogen-bonded and non hydrogen-bonded forms was observed by NMR for compound **2**.

Introduction

Both the literature data[1,2] and our own studies[3,4] indicate that the $AlCl_3$-catalysed reaction of *cis*-cyclohex-4-ene-1,2-dicarboxylic anhydride (**1**) with benzene results in *t*-5-phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid (**2**) (Scheme 1). However, the reaction of *t*-4-phenyl-*c*-1,2-cyclohexanedicarboxylic anhydride (**3**) with benzene yields mainly *t*-4-phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid[5a] (**4**) together with a minor amount of **2** (Scheme 1). Both **2** and **4** are of interest for the preparation of *cis*-condensed, saturated isoindolones,[4,6] however, for the preparation of the *trans*-condensed series, the isomeric *t*-5- and *t*-4-phenyl-*t*-2-benzoyl-*r*-1-cyclohexanecarboxylic acids (**5** and **6**, respectively) were required. Hence, the acids **2** and **4** have been isomerised by treatment with NaOH to the acids **5** and **6**, respectively; for the production of **5**, a one-pot, $AlCl_3$-catalysed, two-fold benzene addition (acylation) to the *trans*-anhydride **7** was also viable[7] (Scheme 1). Sugita and Tamura have earlier reported[5a] that the reaction of *c*-2-benzoyl-*r*-1-cyclohex-4-enecarboxylic acid[8] (**8**) with benzene afforded the *trans*-acid **5** in 11% yield. By treatment of what they believed to be **5** with sodium ethoxide, they presumed a *trans*→*cis* conversion to yield **2**; though these results are in contradiction to what we now report.



Scheme 1 Relational transformations between compounds **1**–**8**. Legend: a, MeOH–conc. H_2SO_4; b, EtONa–EtOH; c, H_2O–H_2SO_4; d, Ac_2O; e, benzene–$AlCl_3$; f, NaOH–H_2O–EtOH.

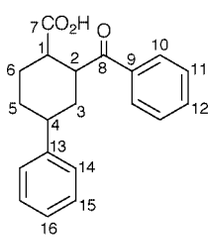


Fig. 1 The numbering system in use. The relative stereochemistry of the cyclohexane substituents (including hydrogens) is denoted as either *t* (*trans*) or *c* (*cis*) depending on their orientation with respect to the carboxylic acid group.

Since the melting points of the compounds that we have identified as **2** and **5** disagree with those in the literature,[3,5] and mindful of the ambiguous explanations for the formation of some of these compounds, there was clear confusion in the literature and we were thus motivated to reinvestigate these compounds and to firmly establish the correct structures of compounds **2**, **4**–**6** and to repeat some of the experiments[5] to clarify, for example, the supposed transformation of **8** to the *t*-2-benzoyl isomer **5**. Furthermore, we also possessed a desire to establish the nature of the solution-state conformations of these interesting and synthetically useful compounds. The correct transformations of compounds **1**–**8** are neatly summarised in Scheme 1 and the numbering system utilised is indicated in Fig. 1.

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Results and discussion

Synthesis and compound identification

Repeating the Friedel–Crafts reaction on **8**[5] provided a complex mixture which, according to HPLC analysis, contained 23% of unreacted **8** (R_t = 4.4 min), 61% of an unidentified product (R_t = 5.4 min), and only 14% of **2** (R_t = 17.3 min). Compound **5** (R_t = 23.5 min) was not detected at all in the mixture. After treatment of the reaction mixture with ethereal diazomethane, GC-MS analysis indicated that the main product was a chloro derivative ($M^{+\bullet}$ *m*/*z* 280 showing a characteristic Cl isotope pattern) and presumably it is *t*-5-chloro-*c*-2-benzoylcyclohexane-*r*-1-carboxylic acid though further investigation was not undertaken. Because of these results, we are pressed to state categorically that the $AlCl_3$-catalysed reaction of **8** with benzene results in the production of compound **2** and not **5**. Compound **2**, however, could readily be transformed into **5** by treatment with NaOH in EtOH–H_2O. Our measured melting point of **2** was 161.5–163 °C, which is far from the literature values of 179–181 °C,[5a] 182–183 °C,[5b] and 190 °C;[3] the melting point of **5** was measured as 189–190 °C, again in stark contrast to the literature values of 156–157 °C[5a] and 179–180 °C.[5b]

Furthermore, the presumed *trans*→*cis* conversion[5] (**5**→**2**) does not occur. (The *cis*→*trans* isomerisation has frequently been reported in the literature[9] and is known to occur in analogous compounds.[4,6]) However, the epimerisation **2**→**5** does partially occur autocatalytically upon heating in EtOH. Furthermore, neither the position of the IR *ν*OH and *ν*C=O bands[5] nor the reaction with bromine (which was presumed to be attributable to the presence of an *axial* benzoyl group) are sufficient for the characterisation of **5**; and finally, now that the melting points of the compounds have been correctly recorded, the depressed melting point of the mixture **2** + **5** cannot confirm the identity of **5**.[5a]

It is noteworthy that in the original synthesis of **8** by Fieser and Novello,[8] another compound that was presumed to be the *trans* isomer of **8** was also obtained although its structure was not confirmed. Herein lies a potential explanation for some of these inconsistencies in that from the *trans* isomer of **8**, the subsequent addition of benzene, together with the poor yield (11%) and an anomalous working-up procedure, may have possibly allowed workers to unwittingly isolate the side-product **5**,[5] thus accounting for these contradictory results.

Compound **4** was also prepared[5b,6] and it was found to be similarly epimerised to **6** by treatment with NaOH in EtOH–H_2O. All of the structures **2**, **4**–**6** were readily and unambiguously established by means of NMR spectroscopy (see below).

Hydrogen bonding investigation by FT-IR spectroscopy

The hydroxy protons of **4**–**6** were all predominantly intramolecularly hydrogen-bonded in $CDCl_3$ solution as evidenced by the presence of only one OH stretching band in the IR spectrum at *ca.* 3515 cm^{-1} (see Fig. 2), appropriate for the OH stretching band of an intramolecularly hydrogen-bonded OH group.[10] By the existence of two OH stretching bands (see Fig. 2) in the spectrum of **2** (0.01 M in $CDCl_3$), the presence of both intramolecularly hydrogen-bonded and non-hydrogen-bonded forms for **2** was clearly indicated. The wavenumber difference of 60 cm^{-1} between the two OH stretching bands in **2** is appropriate for the difference between non-hydrogen-bonded and intramolecularly hydrogen-bonded OH groups.[10]

To firmly establish the nature of the bands to be due to non-hydrogen-bonded and intramolecularly hydrogen-bonded OH groups and to exclude other potential causes for the presence of two OH stretching bands such as multiple conformers or Fermi resonance, **2** was also examined in CCl_4 solution. Dimerisation, which is usual for carboxylic acids even in dilute solutions, can be discounted as a cause for the presence of these two bands as it leads to a broad OH stretching band centred at *ca.* 3000 cm^{-1}.

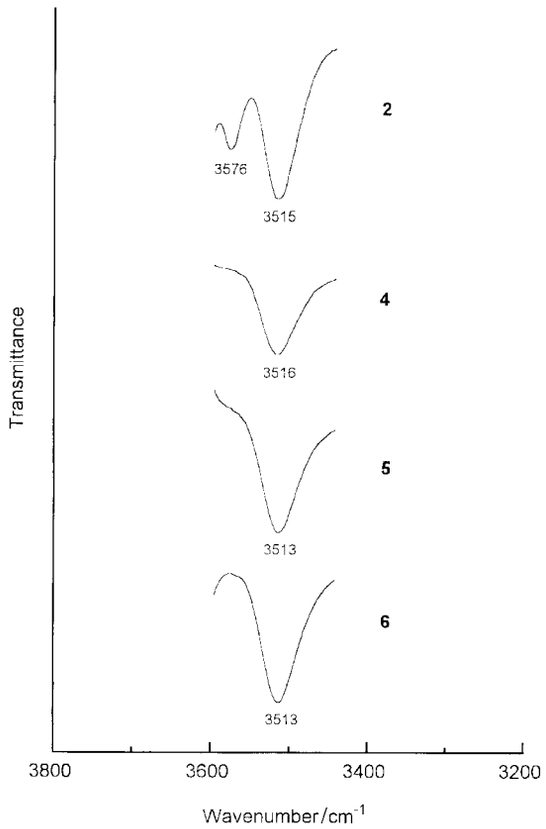


Fig. 2 The spectral region containing the non-hydrogen-bonded and intramolecularly hydrogen-bonded OH stretching bands of compounds **2**, **4**–**6** (0.01 M $CDCl_3$ solutions).

Direct evidence for identification of the high-frequency band as a vibration of a non-hydrogen-bonded OH, and indirect evidence for the low-frequency as a vibration of an intramolecularly hydrogen-bonded OH, was available by noting the intensity changes of these bands upon the addition of diethyl ether to a 0.005 M solution of **2** in CCl_4. The oxygen atom of diethyl ether, acting as a hydrogen acceptor, can form intermolecular hydrogen bonds with non-hydrogen-bonded hydroxy groups[10] and, in the case of the non-hydrogen-bonded hydroxy groups, increasing amounts of ether lead to a decrease in the intensity of their band (the higher frequency band), whilst for intramolecularly hydrogen-bonded hydroxy groups the intensity of their band (the lower frequency band) remains essentially unaffected.[10] As is evident from Fig. 3, the OH stretching bands of **2** behave in accordance with this notion, thus confirming the nature of these bands. Due to the sizeable concentration imbalance between the introduced ether and the solute, the new, intermolecularly hydrogen-bonded OH stretching band expected at lower frequencies was not readily discernable because of the possible overlap with other, more intense bands; even weak bands from the ether which can normally be ignored provided considerable interference in this respect. The intermolecularly hydrogen-bonded OH stretching band is also expected to be quite broad and weak in intensity, so much so that it is expected to be lost altogether in the baseline.

Structural elucidation and conformational analysis by NMR spectroscopy

The gross structural elucidations and assignments of the proton and carbon 1D spectra were readily accomplished using a conventional combination of DEPT, COSY, CHSHF (or HMQC), HMBC, and NOE difference experiments. From the gross chemical shift assignments of the protons, analysis of the proton vicinal coupling constants revealed the stereochemical structures and conformations of compounds **2**, **4**–**6** primarily

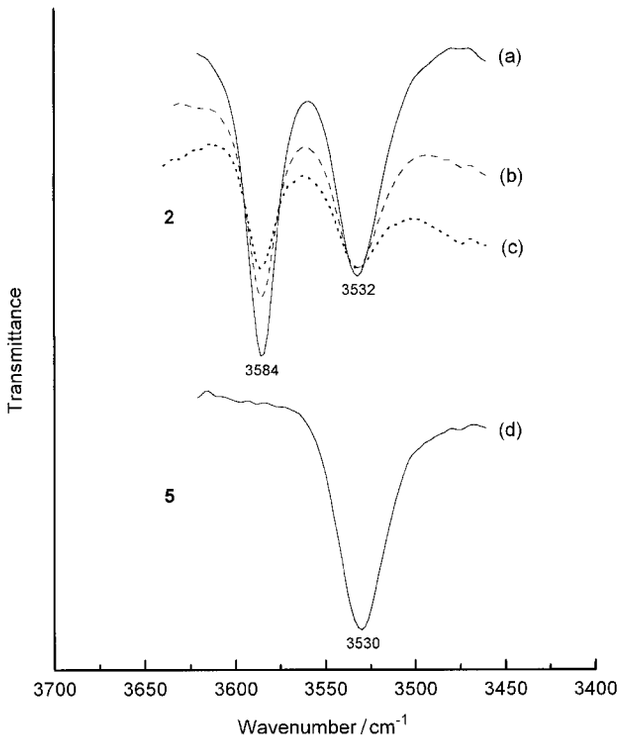
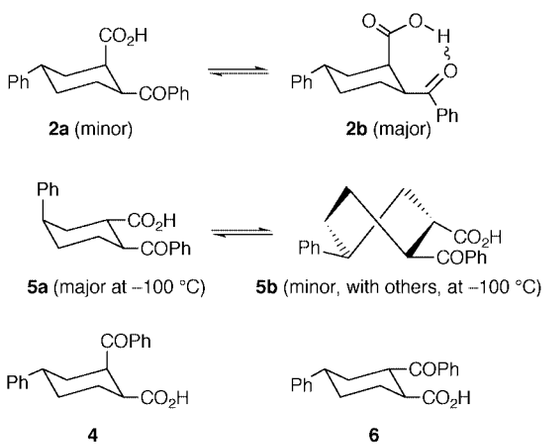


Fig. 3 Intensity changes of the OH stretching bands of **2** (0.005 M in CCl_4) upon the addition of diethyl ether; (a) no ether, (b) 8 drops of ether, (c) 15 drops of ether. The spectrum of **5** (0.005 M in CCl_4) is included for comparison (d).

due to the availability and abundance of a sufficient number of spectroscopically disperse protons. In particular, due to each of the methine protons being partnered by at least one geminal methylene group, an immediate and independent indication of an axial orientation of each methine proton was thus facilitated by the presence of *trans* diaxial coupling, or not by the lack thereof.

Chair conformations (see Scheme 2, hydrogen-bonding not



Scheme 2 The conformational equilibria for compounds **2** and **5** and the preferred conformations for compounds **4** and **6**, all in $CDCl_3$ solution. For clarity, the hydrogen bonding which is present in **4**, **5a**, **5b** and **6** is not shown.

shown for simplicity) with both the carboxy and phenyl groups equatorial and the benzoyl group axial for **4**, and with all groups equatorial for **6**, provide for vicinal proton coupling constants in accord with those measured. The spectra of both **4** and **6** showed no evidence for exchange-broadening at ambient temperature in $CDCl_3$ solution and none was forthcoming on lowering the temperature down to −60 °C. Disruption of the intramolecular hydrogen-bonding by the use of d_6-DMSO as the solvent (substantiated by the relative ease of saturation transfer to the carboxylic acid proton upon irradiation of the residual water signal) did not result in significant changes to the observed coupling constants, indicating little change in the nature of the cyclohexane ring conformation on changing from $CDCl_3$ to d_6-DMSO solution for these two compounds. This implies that the preferred conformers in $CDCl_3$ solution do not predominate as a result of hydrogen bonding, but that steric constraints and other considerations also favour these same conformations.

The principle difference between **4** and **6** is that the benzoyl group at C2 is simply changed from an equatorial to an axial orientation and the significant carbon chemical shift differences between the two compounds reflect this change—relative to **6**, C2 is shifted upfield by 4 ppm in **4** and both C4 and C6, as a result of steric compression effects, are shifted upfield by 5 ppm.

The spectra of compound **2** showed clear indications of exchange-broadening at ambient temperature; somewhat disconcertingly, the exchange phenomenon appeared to be particularly sensitive to the concentration, so much so that even the "same" sample[11] run on different occasions displayed inconsistencies in the extent of exchange-broadening—this is generally against the grain of what is normally experienced with conformational equilibria involving simple bond rotations. However, rotational isomerism of the benzoyl and carboxylic groups together with intramolecular hydrogen-bond formation provided a more rational explanation for the observed behaviour and extraction of the coupling constants from the resolved spectra acquired at −60 °C revealed that this dynamic phenomenon was an equilibrium between two conformers of the same chair conformation—one with intramolecular hydrogen bonding (**2b**) and the other without (**2a**), together with some slight distortion of the cyclohexane ring between the two forms. The ratio of the hydrogen-bonded form **2b**, known to be the major form from FT-IR measurements, to the non-hydrogen-bonded form **2a** was approximately 10 : 1 under these conditions (213–303 K). Furthermore, examination of **2** in d_6-DMSO at 30 °C revealed that the non-hydrogen-bonded form (again indicated by the facile transfer of saturation from the residual water to the carboxylic acid proton) possessed similar coupling constants to the major conformer **2b** in $CDCl_3$ solution at −60 °C. (This uneventful result helps to confirm that the equilibrium is indeed between a non-hydrogen- and a hydrogen-bonded form and is not the result of a gross conformational change in the cyclohexane ring and which consequently implies that the hydrogen bonding is responsible *per se*, for the slight ring deformation that is apparent.) The two forms are shown in Scheme 2, the only significant difference being the rotational state of the benzoyl group which allows the formation of an intramolecular hydrogen bond in **2b** but not in **2a**.

This seemingly inexplicable behaviour of **2**, in contrast to that of **4** where a hydrogen-bonded form is fully favoured (**2** and **4** are simply related by the interchange of the benzoyl and carboxylic groups whilst maintaining the same cyclohexane ring conformation), was examined further by theoretical PM3 calculations. The strong predominance of an intramolecularly hydrogen-bonded form for **4** is supported by the PM3 calculations which indicate that the rotamer, in which the orientation of the benzoyl group allows intramolecular hydrogen bonding to the carboxylic group, is clearly favoured—even without taking into account the stabilising effect of this bond which of course directs the equilibrium towards an even more biased state. The calculations for **2** predict that a benzoyl rotamer which does not permit hydrogen bonding (*i.e.* **2a**) is in fact more favoured over one which permits hydrogen bonding (*i.e.* **2b**); in practice the stabilising effect of the hydrogen bonding can make the latter pre-

dominant and is mediated of course by solvent effects (*cf.* the relative concentrations of **2a** and **2b** by FT-IR in CCl_4 and $CDCl_3$ solutions, see Figs. 2 and 3). Nevertheless, a discernible equilibrium is predicted by the PM3 calculations which can only be enhanced by hydrogen bond stabilisation.

The NMR spectra of compound **5** showed no evidence for exchange-broadening at ambient temperature, but upon lowering the temperature dynamic effects readily become evident and at very low temperatures, −100 °C in d_6-acetone, the superimposed spectra of two interconverting conformers (ratio 4:1) were revealed. However, despite the fact that the signals had not sufficiently sharpened at the lower limit of the solvent range, the major conformer was clearly identifiable as a chair conformer (**5a**) by the examination of its spectra but in contrast the minor signals were not readily recognisable as any one particular conformer and they likely represent an equilibrium of still rapidly interconverting conformers which we will denote as **5b**. There are possibly up to three accessible twist–boat conformers in which all the substituents are either isoclinal or pseudoequatorial and which can thus contribute to **5b**. Based on the preference of other cyclohexane systems with bulky *trans vicinal* groups for adopting a chair conformation in which both groups are diaxial,[12] such a conformation for **5** (*i.e.* contribution to **5b**) though, cannot immediately be ruled out on steric grounds. However, intramolecular hydrogen bonding is evident for both conformers **5a** and **5b** by FT-IR spectroscopy and this effectively rules out the presence of a chair conformation in which the carboxylic and benzoyl groups are diaxial thus precluding hydrogen bonding. This equilibrium of the chair conformer **5a** and the twist–boat conformers **5b** is depicted in Scheme 2, again for simplicity the hydrogen bonding present in both conformers is not shown.

Quite evidently, an increase in temperature is also accompanied by a strong shift in the equilibrium towards the twist–boat conformers **5b**, as evidenced by the time-averaged spectra obtained at room temperature not being in agreement with the weight-averaged spectra calculated from the spectra obtained at low temperature, *e.g.* with respect to the proton–proton coupling constants. How biased the equilibrium is towards the twist–boat conformers **5b** at room temperature, unfortunately, is difficult to discern as the model coupling constants for the twist–boat conformers are not available. Furthermore, given the cm^{-1} consistency (see Fig. 2) of the hydrogen-bonded OH stretching band for all four compounds, **2**, **4**–**6**, no indication is available by FT-IR of the number of conformers present (*NB* the chair conformer **5a** and all three accessible twist–boat conformers **5b** can incorporate intramolecular hydrogen bonding). This equilibrium shift, though, is easily rationalised because the twist–boat conformers **5b** are greatly favoured by the entropy term[13] ($\Delta S_{CT} + R \ln 3$, *i.e.* an increase of temperature). At 173 K the contribution of the twist–boat conformers **5b** is approximately 20% (experimental), corresponding to a $\Delta G°$ of +0.46 kcal mol^{-1}. Taking into account the increased stability of the twist–boat conformers **5b** by a further entropy term, (3.2 + 2.2)0.125 = 0.68 kcal mol^{-1}, it is clear that the twist–boat conformers **5b** can indeed become favoured at room temperature (*ca.* 60%, calculated).

Disruption of the intramolecular hydrogen-bonding in **5** by the use of d_6-DMSO as the solvent, thus removing this stabilising effect and also introducing an additional steric factor, allowed the equilibrium position to be primarily determined by the steric hindrance of the substituents. The result was that a substantial shift in the conformational equilibrium was clearly effected as evidenced by the notable changes in the vicinal coupling constants of the methine protons, although the shift did not result in a recognisably biased equilibrium. By comparison, compounds **2**, **4**, and **6** maintain the same cyclohexane ring conformation in DMSO as they do in other solvents, as indicated by the vicinal coupling constants for the methine protons remaining essentially independent of the solvent.

Experimental

General

HPLC analysis was performed on a Waters 600 chromatograph equipped with a Waters 486 tuneable absorbance detector using a NovaPak C_{18} 150 × 3.9 mm ID column (Waters) with aqueous 0.1% trifluoroacetic acid (pH ~2) and MeOH (40:60) as eluent (flow rate 0.8 ml min^{-1}, detection at 254 nm). GC-MS analysis utilised a Finnigan GCQ mass spectrometer equipped with a HP-5 column utilising helium as the carrier gas with a constant velocity of 30 cm s^{-1} and injector temperature of 300 °C. For FT-IR measurements, either a Perkin–Elmer Paragon 1000 PC FT Mattson (for KBr disks) or a Galaxy 6020 FTIR (for solutions) spectrometer was utilised. Solution spectra were measured in a variable path length cell (set to 4 mm) equipped with KBr windows. The geometries of the compounds with respect to both the cyclohexane ring conformation and various rotamers of the substituents were optimised and their heats of formation calculated by a semi-empirical PM3[14] method on a personal computer using HyperChem software.[15] Default value settings were used in all calculations and solvent effects were not included.

NMR spectra were acquired on a JEOL Lambda 400 series spectrometer equipped with either a 5 mm normal configuration CH probe or a 5 mm inverse HX probe operating at 399.78 MHz for ^1H and 100.54 MHz for ^{13}C. The spectra were run at ambient temperature in the solvents indicated and both ^1H and ^{13}C were referenced internally to the solvent; for $CHCl_3$, ^{13}C at 77.00 ppm and ^1H at 7.26 ppm. 1D proton spectra were acquired with single-pulse excitation, 45° flip angle, and spectral widths of 7 kHz (digital resolution 0.11 Hz pt^{-1}). NOE difference measurements were acquired on samples flushed with dry, nitrogen gas and using saturation times of 6–8 s. Spectral widths were the same as for the normal proton spectra, but with the resolution reduced to 0.9 Hz pt^{-1}; 1 Hz of exponential weighting was usually applied prior to Fourier transformation. 1D carbon spectra were acquired with single-pulse excitation, 45° flip angle, spectral widths of 20 kHz (digital resolution 0.5 Hz pt^{-1}), and with 1 Hz of exponential weighting applied prior to Fourier transformation. DEPT spectra (90 and 135°) were acquired under similar conditions. COSY (double-quantum filtered), CHSHF (with partial homonuclear decoupling in f1), HMQC, and HMBC experiments were acquired with spectral widths appropriately optimised from the 1D spectra. HMQC and HMBC sequences both incorporated a pre-emptive BIRD sequence, the delay for which was optimised by minimisation of the incoming FID (*ca.* 0.6 s). Both HMQC and HMBC experiments utilised a $^1J_{HC}$ coupling of 145 Hz whilst the HMBC correlations were optimised for a long-range $^nJ_{HC}$ coupling of 5 Hz.

The ^1H and ^{13}C NMR data of the compounds **2**, **4**–**6** in various solvents and at various temperatures are recorded below. The compounds **2**, **4**–**6** have been prepared previously,[2–7] however the following transformations for **5** and **6** are worth noting.

***t*-5-Phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid 2.** ^{13}C NMR ($(CD_3)_2CO$, 27 °C) δ 202.19 (C8), 174.21 (C7), 147.42 (C13), 138.31 (C9), 132.86 (C12), 129.30 (C11), 129.25 (C15), 128.88 (C10), 127.63 (C14), 126.93 (C16), 47.60 (C2), 42.92 (C1), 40.18 (C5), 36.23 (C6), 33.87 (C4), 25.40 (C3). ^1H NMR ($(CD_3)_2CO$, 27 °C) δ 7.92 (2 H, m, H10), 7.57 (1 H, m, H12), 7.50 (2 H, m, H11), 7.30 (4 H, m, H14, H15), 7.19 (1 H, m, H16), 3.63 (1 H, ddd, $J_{1e} = J_{3e} = 4.1$, $J_{3a} = 11.7$ Hz, H2a), 3.36 (1 H, ddd, $J_{2a} = 4.1$, $J_{6a} = 3.8$, $J_{6e} = 3.3$ Hz, H1e), 2.93 (1 H, dddd, $J_{4a} = 12.7$, $J_{4e} = 3.5$, $J_{6a} = 12.4$, $J_{6e} = 3.6$ Hz, H5a), 2.28 (1 H, m, $J_{1e} = 3.3$, $J_{4e} = 1.9$, $J_{5a} = 3.6$, $J_{6a} = -13.4$ Hz, H6e), 2.16 (1 H, dddd, $J_{2a} = 11.7$, $J_{3e} = -13.1$, $J_{4a} = 12.9$, $J_{4e} = 3.5$ Hz, H3a), 2.10 (1 H, m, $J_{1e} = 3.8$, $J_{5a} = 12.4$, $J_{6e} = -13.4$ Hz, H6a), 2.07 (1 H, m, $J_{2a} = 4.1$, $J_{3a} = -13.1$, $J_{4a} = 4.0$ Hz, H3e), 2.00 (1 H, m,

J_{3a} = 3.5, J_{4a} = −12.8, J_{5a} = 3.5, J_{6e} = 1.9 Hz, H4e), 1.75 (1 H, dddd, J_{3a} = 12.9, J_{3e} = 4.0, J_{4e} = −12.8, J_{5a} = 12.7 Hz, H4a). ^{13}C NMR ($CD_3)_2CO$, −60 °C) δ (major) 202.44 (C8), 175.11 (C7), 147.38 (C13), 137.72 (C9), 133.07 (C12), 129.39 (C11), 129.32 (C15), 128.98 (C10), 127.67 (C14), 127.05 (C16), 46.98 (C2), 42.95 (C1), 40.38 (C5), 35.86 (C6), 33.93 (C4), 25.20 (C3). ^{13}C NMR (($CD_3)_2CO$, −60 °C) δ (minor) 202.4 (C8), 178.24 (C7), 147.06 (C13), 140.16 (C9), 129.29 (C15), 127.60 (C14), 127.11 (C16), 45.48 (C2), 41.44 (C1), 41.26 (C5), 31.27 (C4), 31.10 (C6), 27.44 (C3). ^{1}H NMR (($CD_3)_2CO$, −60 °C) δ (major) 7.99 (2 H, m, H10), 7.65 (1 H, m, H12), 7.57 (2 H, m, H11), 7.35 (4 H, m, H14, H15), 7.25 (1 H, m, H16), 3.73 (1 H, m, J_{1e} = 4, J_{3e} = 5.5, J_{3a} = 10 Hz, H2a), 3.42 (1 H, m, J_{2a} = 4, J_{6a} = 4.6 Hz, H1e), 2.86 (1 H, dddd, J_{4a} = 12.3, J_{4e} = 3.4, J_{6a} = 12.6, J_{6e} = 3.4 Hz, H5a), 2.25 (1 H, m, J_{5a} = 3.4, J_{6a} = −12.7 Hz, H6e), 2.13 (1 H, m, J_{1e} = 4.6, J_{5a} = 12.6, J_{6e} = −12.7 Hz, H6a), 2.09 (1 H, m, J_{2a} = 10 Hz, H3a), 2.09 (1 H, m, J_{2a} = 5.5 Hz, H3e), 1.97 (1 H, m, J_{4a} = −11.2, J_{5a} = 3.4 Hz, H4e), 1.79 (1 H, m, J_{4e} = −11.2, J_{5a} = 12.3 Hz, H4a). ^{1}H NMR (($CD_3)_2CO$, −60 °C) δ (minor) 3.60 (1 H, m, J_{2a} = 6.2, J_{6a} = 6.2 Hz, H1e), 2.77 (1 H, ddd, J_{1e} = 6.2, J_{3a} = 13.0, J_{3e} = 5.8 Hz, H2a), 2.36 (1 H, dddd, J_{4a} = 12.7, J_{4e} = 3.2, J_{6a} = 12.8, J_{6e} = 3.2 Hz, H5a), 2.29 (1 H, m, J_{5a} = 3.2, J_{6a} = −12.8, H6e), 1.88 (1 H, m, J_{1e} = 6.2, J_{5a} = 12.8 Hz, J_{6e} = −12.8, H6a), 1.60 (1 H, m, J_{3a} = 3.1, J_{4a} = −12.9, J_{5a} = 3.2 Hz, H4e), 1.41 (1 H, dddd, J_{3a} = 13.2, J_{3e} = 2.3, J_{4e} = −12.9, J_{5a} = 12.7 Hz, H4a), 1.12 (1 H, m, J_{2a} = 5.8, J_{3a} = −13.7, J_{4a} = 2.3 Hz, H3e), 0.83 (1 H, dddd, J_{2a} = 13.0, J_{3e} = −13.7, J_{4a} = 13.2, J_{4e} = 3.1 Hz, H3a).

***t*-4-Phenyl-*c*-2-benzoyl-*r*-1-cyclohexanecarboxylic acid 4.** ^{13}C NMR ($CDCl_3$, 27 °C) δ 202.39 (C8), 179.42 (C7), 145.78 (C13), 136.37 (C9), 132.79 (C12), 128.62 (C11), 128.41 (C15), 128.28 (C10), 126.67 (C14), 126.28 (C16), 43.11 (C2), 42.86 (C1), 38.63 (C4), 35.75 (C3), 33.36 (C5), 24.38 (C6). ^{1}H NMR ($CDCl_3$, 27 °C) δ 7.90 (2 H, m, H10), 7.52 (1 H, m, H12), 7.43 (2 H, m, H11), 7.23 (2 H, m, H15), 7.14 (1 H, m, H16), 7.06 (2 H, m, H14), 4.30 (1 H, ddd, J_{1a} = 4.3, J_{3a} = 5.5, J_{3e} = 2.3 Hz, H2e), 2.67 (1 H, ddd, J_{2e} = 4.3, J_{6a} = 13.0, J_{6e} = 4.1 Hz, H1a), 2.47 (1 H, dddd, J_{1a} = 13.0, J_{5a} = 13.2, J_{5e} = 3.7, J_{6e} = −13.5 Hz, H6a), 2.46 (1 H, dddd, J_{3a} = 13.1, J_{3e} = 2.9, J_{5a} = 12.9, J_{5e} = 3.3 Hz, H4a), 2.27 (1 H, dddd, J_{2e} = 2.3, J_{3a} = −13.4, J_{4a} = 2.9, J_{5e} = 2.4 Hz, H3e), 2.23 (1 H, dddd, J_{1a} = 4.1, J_{5a} = 3.8, J_{5e} = 3.6, J_{6a} = −13.5 Hz, H6e), 2.04 (1 H, ddddd, J_{3e} = 2.4, J_{4a} = 3.3, J_{5a} = −12.9, J_{6a} = 3.7, J_{6e} = 3.6 Hz, H5e), 1.98 (1 H, ddd, J_{2e} = 5.5, J_{3e} = −13.4, J_{4a} = 13.1 Hz, H3a), 1.50 (1 H, dddd, J_{4a} = 12.9, J_{5e} = −12.9, J_{6a} = 13.2, J_{6e} = 3.8 Hz, H5a).

***t*-5-Phenyl-*t*-2-benzoylcyclohexane-*r*-1-carboxylic acid 5.** NaOH (0.4 g) was added to a solution of **2** (1 g) in EtOH (10 ml) and water (3 ml) and refluxed for 1 h. After cooling, water (5 ml) and HCl (10%) were added dropwise until the pH reached 3 followed by evaporation to half-volume. Upon cooling, the solid that separated out was suction-filtered off, washed with water (10 ml), and then dried to yield crude **5** (0.75 g). Crystallisation from a mixture of EtOH (10 ml) and water (5 ml) yielded pure **5** (0.39 g), mp 189–190 °C; IR: νCO 1698.9, 1681.5 cm^{-1}. (Found: C, 77.73; H, 6.47. $C_{20}H_{20}O_3$ (308.178) requires C, 77.88; H, 6.54%). ^{13}C NMR ($CDCl_3$, 27 °C) δ 202.42 (C8), 180.37 (C7), 144.68 (C13), 135.99 (C9), 132.79 (C12), 128.71 (C11), 128.48 (C15), 128.38 (C10), 127.02 (C14), 126.11 (C16), 43.75 (C2), 40.40 (C1), 38.43 (C5), 31.73 (C6), 29.36 (C4), 25.63 (C3). ^{1}H NMR ($CDCl_3$, 27 °C) δ 7.95 (2 H, m, H10), 7.57 (1 H, m, H12), 7.48 (2 H, m, H11), 7.31 (2 H, m, H15), 7.30 (2 H, m, H14), 7.20 (1 H, m, H16), 3.98 (1 H, ddd, J_{1a} = 5.2, J_{3a} = 5.3, J_{3e} = 4.8 Hz, H2a), 3.30 (1 H, ddd, J_{2a} = 5.2, J_{6a} = 6.5, J_{6e} = 4.9 Hz, H1a), 2.95 (1 H, dddd, J_{4a} = 4.3, J_{4e} = 8.3, J_{6a} = 4.1, J_{6e} = 8.6 Hz, H5e), 2.41 (1 H, ddd, J_{1a} = 4.9, J_{5e} = 8.6, J_{6a} = −13.8 Hz, H6e), 2.21 (1 H, ddd, J_{1a} = 6.5, J_{5e} = 4.1, J_{6e} = −13.8 Hz, H6a), 2.02 (1 H, dddd, J_{2a} = 4.8, J_{3a} = −9.4, J_{4a} = 8.8, J_{4e} = 9.4 Hz, H3e), 1.9 (1 H, m, J_{2a} = 5.3, J_{3e} = −9.4, H3a), 1.9 (1 H, m, J_{3e} = 9.4, J_{4a} = −12.9, J_{5e} = 8.3 Hz, H4e), 1.82 (1 H, m, J_{3e} = 8.8, J_{4e} = −12.9, J_{5e} = 4.3 Hz, H4a). ^{13}C NMR (($CD_3)_2CO$, −100 °C) δ (major) 202.93 (C8), 177.28 (C7), 142.81 (C13), 135.76 (C9), 134.35 (C12), 129.77 (C11), 129.51 (C15), 129.35 (C10), 128.15 (C14), 126.68 (C16), 46.58 (C2), 39.80 (C1), 35.73 (C5), 32.92 (C6), 28.46 (C4), 25.92 (C3). ^{13}C NMR (($CD_3)_2CO$, −100 °C) δ (minor) 203.36 (C8), 176.10 (C7), 147.47 (C13), 136.35 (C9), 133.94 (C12), 127.16 (C14), 127.13 (C16), 42.16 (C2), 41.14 (C1), 40.85 (C5), 32.01 (C6), 26.78 (C3). ^{1}H NMR (($CD_3)_2CO$, −100 °C) δ (major) 8.20 (2 H, m, H10), 7.76 (1 H, m, H12), 7.64 (2 H, m, H11), 7.49 (2 H, m, H15), 7.56 (2 H, m, H14), 7.32 (1 H, m, H16), 3.98 (1 H, ddd, J_{1a} = 11.8, J_{3a} = 12.3, J_{3e} = 3.1 Hz, H2a), 3.35 (1 H, m, H5e), 2.98 (1 H, ddd, J_{2a} = 11.8, J_{6a} = 12.0, J_{6e} = 2.1 Hz, H1a), 2.85 (1 H, m, J_{1a} = 2.1, J_{6a} = −12.6 Hz, H6e), 2.51 (1 H, m, J_{4a} = −12.8 Hz, H4e), 2.2 (1 H, m, J_{3a} = 13, J_{4e} = −12.8 Hz, H4a), 2.1 (1 H, m, J_{1a} = 12.0, J_{6e} = −12.6 Hz, H6a), 2.0 (1 H, m, J_{2a} = 3.1, J_{3a} = −13 Hz, H3e), 1.31 (1 H, m, J_{2a} = 12.3, J_{3e} = −13 Hz, J_{4a} = 13 Hz, H3a). ^{1}H NMR (($CD_3)_2CO$, −100 °C) δ (minor) 8.12 (2 H, m, H10), 7.76 (1 H, m, H12), 7.66 (2 H, m, H11), 7.38 (2 H, m, H15), 7.27 (2 H, m, H14), 7.27 (1 H, m, H16), 4.27 (1 H, m, H2e), 3.35 (1 H, m, J_{6a} = 12.4 Hz, H5a), 2.64 (1 H, m, J_{5a} = 12.4, J_{6e} = −12.4 Hz, H6a), 1.62 (1 H, m, J_{3a} = −11.5 Hz, H3e), 1.38 (1 H, m, J_{3e} = −11.5, J_{4a} = 12.1 Hz, H3a).

***t*-4-Phenyl-*t*-2-benzoylcyclohexane-*r*-1-carboxylic acid 6.** Oxoacid **4** (1.0 g; mp 214–216 °C) was treated as above to yield crude **6** (0.54 g). Crystallisation from aqueous EtOH (90%, 25 ml) resulted in pure **6** (0.23 g), mp 262–265 °C, IR: νC=O 1694.0, 1666.9 cm^{-1}. (Found: C, 77.72; H, 6.45. $C_{20}H_{20}O_3$ (308.178) requires C, 77.88; H, 6.54%). ^{13}C NMR ($CDCl_3$, 27 °C) δ 202.26 (C8), 178.97 (C7), 145.27 (C13), 135.91 (C9), 133.07 (C12), 128.65 (C11), 128.54 (C15), 128.40 (C10), 126.68 (C14), 126.54 (C16), 47.06 (C2), 43.68 (C4), 43.57 (C1), 36.72 (C3), 33.36 (C5), 29.33 (C6). ^{1}H NMR ($CDCl_3$, 27 °C) δ 7.96 (2 H, m, H10), 7.54 (1 H, m, H12), 7.44 (2 H, m, H11), 7.27 (2 H, m, H15), 7.18 (1 H, m, H16), 7.17 (2 H, m, H14), 3.78 (1 H, ddd, J_{1a} = 10.8, J_{3a} = 12.7, J_{3e} = 3.4 Hz, H2a), 3.07 (1 H, ddd, J_{2a} = 10.8, J_{6a} = 12.5, J_{6e} = 3.6 Hz, H1a), 2.74 (1 H, dddd, J_{3a} = 12.5, J_{3e} = 3.3, J_{5a} = 12.3, J_{5e} = 3.2 Hz, H4a), 2.40 (1 H, dddd, J_{1a} = 3.6, J_{5a} = 3.4, J_{5e} = 3.3, J_{6a} = −12.7 Hz, H6e), 2.19 (1 H, dddd, J_{2a} = 3.4, J_{3a} = −13.0, J_{4a} = 3.3, J_{5e} = 1.8 Hz, H3e), 2.07 (1 H, ddddd, J_{3e} = 1.8, J_{4a} = 3.2, J_{5a} = −12.8, J_{6a} = 3.2, J_{6e} = 3.3 Hz, H5e), 1.71 (1 H, dddd, J_{1a} = 12.5, J_{5a} = 12.5, J_{5e} = 3.2, J_{6e} = −12.7 Hz, H6a), 1.60 (1 H, dddd, J_{4a} = 12.3, J_{5e} = −12.8, J_{6a} = 12.5, J_{6e} = 3.4 Hz, H5a), 1.49 (1 H, ddd, J_{2a} = 12.7, J_{3e} = −13.0, J_{4a} = 12.5 Hz, H3a).

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