^{13}C NMR Chemical Shift Assignment Based on ^{13}C INADEQUATE and Heteronuclear $^{13}C,^{1}H$-COSY Experiments and Absolute Configuration of a New Chiral Pentacyclic Pinocarvone Dimer

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^{13}C NMR chemical shift assignment based on two-dimensional homonuclear ^{13}C–^{13}C Incredible Natural Abundance Double Quantum Transfer Spectroscopy (INADEQUATE) and heteronuclear ^{13}C–^{1}H chemical shift correlation spectroscopy (C,H-COSY) experiments together with the absolute configuration based on X-ray crystallographic analysis of a previously unknown pentacyclic dimerization product of (1*S*)-pinocarvone, (2*S*,5*S*,1′*S*)-6,6,6′,6′-tetramethyl-3,4,5,6,7,8-hexahydro-5,7-methanospiro{2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]heptan}-3′-one, $C_{20}H_{28}O_2$ **1**, are presented. The Diels–Alder dimerization produces a new chiral centre with a definite absolute configuration from the dimerizing (1*S*)-pinocarvone molecules during the ring formation.

In conjunction with our interests in oxidation products of various terpenes such as α- and β-pinene,[1] we repeated the SeO_2 oxidation procedure described by Stallcup and Hawkins[2] for (1*S*)-(−)-β-pinene. In agreement with their report, one of the oxidation products was 6,6-dimethyl-2-methylene[3.1.1]-bicycloheptan-3-one (**2**) (pinocarvone).[1] In contrast with their arguments, however, we were unable to obtain any 3,6,6-trimethyl[3.1.1]bicyclohept-1-en-3-one (**3**) (carvopinone). Instead, a dimer of pinocarvone, 6,6,6′,6′-tetramethyl-3,4,5,6,7,8-hexahydro-5,7-methanospiro{2*H*-1-benzopyran-2,2′-bicyclo[3.1.1]heptan}-3′-one **1** was formed. A similar tendency to dimerization has also been reported for trimethyl[4.1.0]-bicycloheptane (carane) derivatives containing the corresponding exocyclic enone structure.[3] The molecular structure and absolute configuration of **1** were determined by X-ray crystallography. The complete ^{13}C NMR chemical shift assignment of **1** was obtained by means of two-dimensional INADEQUATE and C,H-COSY experiments.

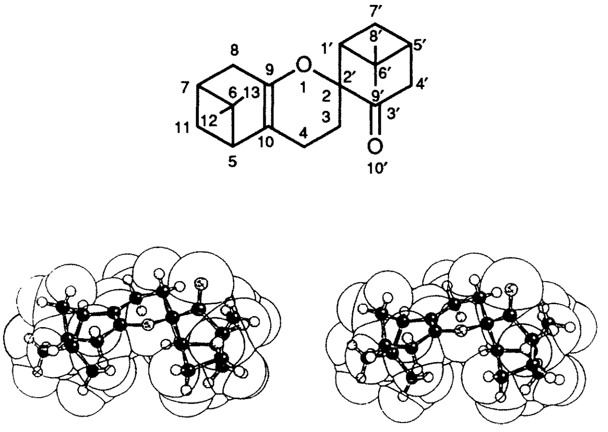

Fig. 1 A SCHAKAL plot[4] based on the X-ray structure analysis and the numbering of **1**

Experimental

Compound **1** (10%) was separated from the steam distilled reaction mixture[2] by column chromatography using chloroform–light petroleum 7:3 (v/v) as the eluent. The purity of compound **1** was verified by gas chromatography and by m.p. 102–103 °C.

NMR Measurements.—The proton broadband decoupled (BBD) ^{13}C NMR spectrum and the two-dimensional C,H-COSY and INADEQUATE chemical shift correlation maps were recorded with a JEOL GSX-270 FT NMR spectrometer working at 67.9 MHz (^{13}C) and 270.1 MHz (^{1}H) for 1 mol dm^{-3} or saturated (INADEQUATE) $CDCl_3$ solutions at 30 °C. In BBD ^{13}C NMR measurements, the spectral width was 15 kHz and number of data points 32K, which gave a digital resolution of 0.92 Hz. ^{13}C NMR chemical shifts were referenced to the signal of internal Me_4Si ($\delta_C = 0$). In C,H-COSY and INADEQUATE experiments the olefinic and carbonyl signals were left outside the observed region to reduce the size of the two-dimensional matrix and to improve the digital resolution. Both two-dimensional experiments were performed by using the standard pulse sequences available in the software of the spectrometer. For the INADEQUATE experiment, a saturated solution of **1** in $CDCl_3$ (458.3 mg in 800 μl, 1.9 mol) at 30 °C was used in order to improve S/N ratio and shorten the measuring time. The total duration of the INADEQUATE experiment was 12 h, during which the digital resolution was kept to < 7 Hz.

X-Ray Data Collection and Reduction.—Data were collected from a colourless crystal 0.10 × 0.40 × 0.45 mm. Of 1784 collected reflections 935 were unique ($R_{int} = 0.015$), recorded with an Enraf-Nonius CAD4 diffractometer using graphite monochromatized Mo-Kα radiation [λ(Mo-Kα) = 0.7107 Å] and $\omega/2\theta$ scan mode (scan width in degrees: $0.48 + 0.35 \tan \theta$) to $2\theta = 40°$ (h: $0 \longrightarrow 11$, k: $0 \longrightarrow 14$ and l: $-12 \longrightarrow 12$), 873 reflections with $I > 1.5\sigma I$ were used for refinement. An empirical absorption [μ(Mo-Kα) = 0.069 mm^{-1}] correction[5] was applied to the data with the minimum and maximum correction coefficients 0.867 and 1.113, respectively.

X-Ray Structure Solution and Refinement.—The structure was solved by direct methods[6] and subjected to full-matrix refinement. All except the methyl carbons (in order to reduce the number of parameters) of the non-H atoms were refined anisotropically.[7] The hydrogen atoms were calculated to their idealised positions (C–H distance 1.00 Å) and refined as riding atoms with fixed isotropic temperature factors (U = 0.08 Å^2). The F_o/parameter ratio = 4.88 and the final R value was 0.042 and $R_w = 0.051$ for 179 parameters: w =

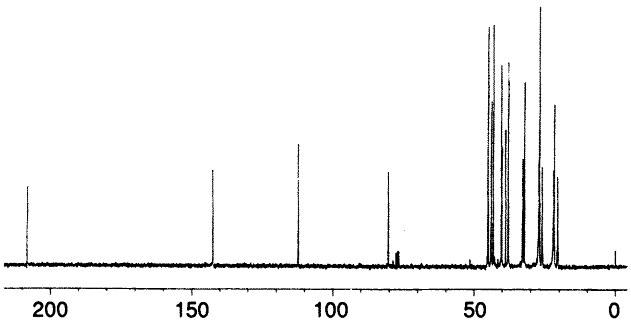

Fig. 2 ^{13}C NMR spectrum for **1**

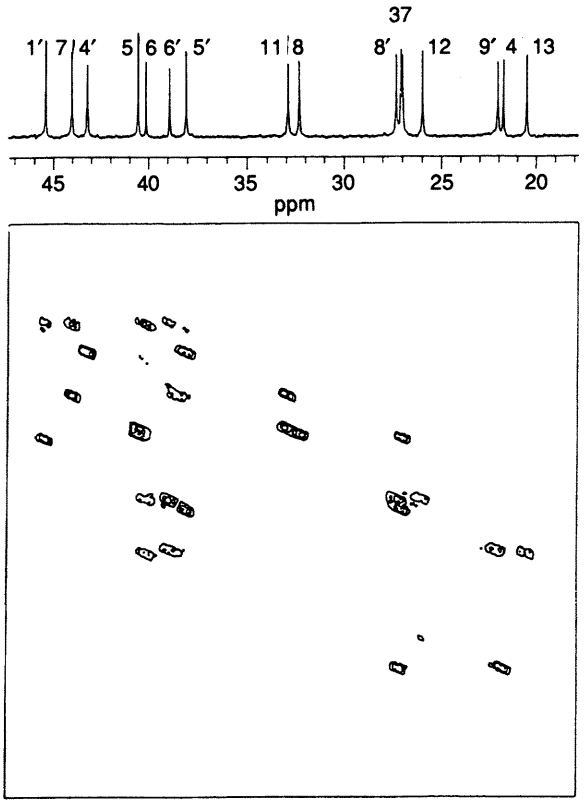

Fig. 3 A partial INADEQUATE contour plot of the aliphatic region of **1**

$w'[1.0 - (\Delta F/6\cdot\sigma F)^2]^2$, where w' = Chebychev polynomial for F_c with three coefficients (4.11, 2.23, 2.63). Convergence, max. shift/error was < 0.01. A final difference map displayed no electron density higher than 0.31 e $Å^{-3}$.

Results and Discussion

Crystal data of **1**. $C_{20}H_{28}O_2$, M_r = 300.44, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 10.538(2), b = 13.573(3), c = 11.883(2) Å, V = 1700(1) $Å^3$, Z = 4, D_c = 1.174 g cm^{-3}, $F(000)$ = 656, T = 296 ± 1 K. The fractional coordinates with esds in parentheses and equivalent isotropic temperature factors for **1** have been deposited at the Cambridge Crystallographic Data Centre* together with the bond distances (Å) and angles (°).

NMR Data of **1**. The ^{13}C NMR spectrum of compound **1** shows 19 resolved lines with two partially overlapping signals at δ = 27.0–27.1 revealing the presence of 20 carbon atoms in the molecular framework. The proton coupled ^{13}C NMR and C,H-COSY spectrum differentiates all methyl, methylene, methine and quaternary carbons unambiguously. The assignment of signals at δ = 208.2, 142.5, 112.2 and 80.3 to carbons 3', 9, 10 and 2(2') is straightforward (Fig. 2).

Table 1 ^{13}C NMR chemical shifts (ppm, TMS) of **1**

Carbon number	δ_C
2	80.3
3	27.1
4	21.7
5	40.5
6	40.1
7	43.9
8	32.3
9	142.5
10	112.2
11	32.9
12	25.9
13	20.5
1'	45.1
2'	80.3
3'	208.2
4'	43.2
5'	38.0
6'	38.9
7'	27.0
8'	27.3
9'	22.1

In order to assign all sixteen ^{13}C NMR resonance lines located in the area of δ_C = 20.5–45.1, a ^{13}C INADEQUATE[8] experiment, using a value of the one-bond ^{13}C–^{13}C spin–spin coupling constant of 35 Hz[9] typical for β-pinene, was utilized. In this experiment, the spiro carbon 2 located at 80.3 ppm was included in the observed region, in order to ascertain the assignment of carbons 3 and 4.

The INADEQUATE experiment at natural abundance based on ^{13}C–^{13}C spin–spin coupling constants[8] is very insensitive and demands a large sample concentration and therefore good solubility. In the present case a saturated solution of **1** in $CDCl_3$ provided carbon–carbon connectivities sufficient to allow the complete assignment of the ^{13}C NMR spectrum (Table 1). In addition, the ^{13}C NMR chemical shift data of some simple monoterpenoids such as pinocarvone **2**, α-pinene[1] **4** and 6,6-dimethyl[3.1.1]bicycloheptan-3-one[10] **5** as well as proton-coupled ^{13}C NMR spectrum and two-dimensional ^{13}C–^{1}H chemical shift correlated spectroscopy (COSY)[11] were utilized. For example, a heteronuclear ^{13}C–^{1}H COSY experiment revealed the ^{13}C NMR signal at δ = 27.0–21.1 to have four cross peaks with the proton signals at δ = 1.70, 1.88, 2.30 and 2.46. This means that, in reality, the ^{13}C NMR signal at δ = 27.0–27.1 represents overlapping signals of two methylene carbons. The ^{13}C NMR chemical shift assignment in Table 1 is based on the following concluding steps.

(1) The ^{13}C–^{1}H COSY experiment revealed that the lines at δ = 38.9 and 40.1 ppm represent two quaternary carbons, 6' and 6, but their unambiguous assignment is not possible based on this knowledge alone.

(2) These quaternary carbons belong to different ring systems and thus their INADEQUATE connectivities can primarily be used in differentiating the carbons belonging to these structural fragments. The connectivities of the carbon at δ = 40.1 are to δ = 43.9 (CH), 25.9 (CH_3) and 20.5 (CH_3). Thus three of four possible connectivities were identified. All four connectivities of the other quaternary carbon at δ = 38.9 to the carbons at δ = 45.1 (CH), 38.0 (CH), 27.3 (CH_3) and 22.1 ppm (CH_3) were observed. Consequently, the only remaining methine carbon at

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* For details of the CCDC deposition scheme, see 'Instructions for Authors (1993),' *J. Chem. Soc., Perkin Trans. 2,* 1993, issue 1.

$\delta = 40.5$ must belong to the same ring as the quaternary carbon at $\delta = 40.1$.

(3) A CH_2 at $\delta = 32.9$ is attached to a CH-carbon at $\delta = 43.9$, which is further bound to a CH_2 at $\delta = 32.3$. There exist only two alternatives for this kind of connectivity namely through carbons 5′ and 7.

(4) Comparison of above CH_2 chemical shifts with those of simple model compounds, pinocarvone **2**[1] and the compound **5**,[10] in which the two methylene groups resonate at $\delta = 42.6$ and 44.8 (C-4), 31.6 and 32.6 (C-7) and α-pinene **4**, in which the corresponding values are $\delta = 31.5$ and 31.6, reveals that the methylene shifts at $\delta = 32.9$ and 32.3 belong to the chroman system and thus represent carbons 11 and 8.

(5) The assignment of carbons 11 and 8 is based on the fact that, in the aliphatic area, carbon 8 at $\delta = 32.3$ is not connected to any other carbon but the carbon 11 also with the CH-carbon at $\delta = 40.5$. Consequently, the signal at $\delta = 43.9$ must represent the methine carbon 7. The methine carbon 5 of this ring system is thus located at $\delta = 40.5$.

(6) Two CH_2-carbon resonances at $\delta = 43.2$ and 27.0 represent the corresponding carbons 4′ and 7′ of the other ring system.

(7) The two remaining methylene lines at $\delta = 27.1$ and 21.7 originate from carbons 3 and 4 of the chroman ring system. Their assignment was determined by the connectivities of the spirocarbon 2 at $\delta = 80.3$ to the carbon resonances at $\delta = 45.1$ and 27.1. The third connection to carbon 9′ was outside the observed region. The assignment of the bridgehead carbon 1′ at $\delta = 45.1$ is clear and consequently carbon 3 must possess the chemical shift value of 27.1 ppm.

(8) The two remaining methine signals at $\delta = 45.1$ and 38.0 were assigned based on their INADEQUATE connectivities to carbons 1′ and 5′, respectively.

(9) The assignment of the quaternary carbon signals at $\delta = 40.1$ and 38.9 to carbons 6 and 6′ was made possible after differentiation of the two ring systems.

(10) The assignment of the geminal methyl pairs was made by comparison of their shifts with those of the model compounds **2**, **4** and **5**.

Conclusions

A Diels–Alder dimerization reaction of a pure enantiomer, (*S*)-pinocarvone, (structurally an exocyclic enone) formed by SeO_2 oxidation of (1*S*)-(−)-β-pinene, leads to formation of a pure enantiomer (2*S*,5*S*,1′*S*)-6,6,6′,6′-tetramethyl-3,4,5,6,7,8-hexahydro-5,7-methanospiro{2*H*-1-benzopyran-2,2′-bicyclo-[3.1.1]heptan}-3′-one **1**. The oxidation reaction used leaves the chiral centre of (1*S*)-β-pinene unchanged.[1] Thus, the X-ray coordinate set corresponding to (*S*)-pinocarvone leads to the unambiguous determination of the chiral spiro-carbon, which also proved to be (*S*)-form (Fig. 1).

For the complete assignment of the ^{13}C NMR chemical shifts of the dimer **1**, characterized by two structurally related fragments, ^{13}C INADEQUATE experiments combined with heteronuclear ^{13}C–^{1}H COSY measurements provided a convenient means.

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