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INTERACTION BETWEEN NEIGHBORING AROMATIC AND POLAR GROUP—II

STUDY OF N-SUBSTITUTED 3-(3'-INDOLYL) NORBORNENE 2-CARBOXYLIC ACIDS[1]

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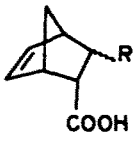
Abstract—The synthesis of a series of title compounds and of 3-isopropyl norbornene 2-carboxylic acids is described. Different pK_a values have been found for the isomeric acids *trans* 1 and *cis* 2, having the same indolic substituent. This fact can be attributed to a through space interaction between the neighboring aromatic and carboxylic groups.

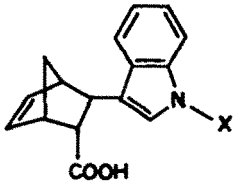
Interactions between aromatic and polar neighboring spaced groups in enzymes have been reported. For example, chemical modifications of Trp 199, which is in the vicinity of His 46 and Ser 183, of trypsine produce changes in catalytic activity of these enzymes.[2] Furthermore in bovine pancreatic trypsin inhibitor,[3] it has been found by ^1H NMR study at several different pH, that neighboring Tyr 10 and Lys 41 deviate from simple titration behaviour. In order to show the influence of an aromatic group on the properties of a carboxyl group, we have synthesized and studied a series of simple molecules of the type I.



I

It was shown previously, in the laboratory, that with acids of the type I where R = phenyl, the aromatic group influences the carboxyl properties.[1] The present work extends the study to acids I where R is the N-substituted indolyl group, in order to get informations on the influence of tryptophan upon polar groups in proteins.

pK_a's Values have been determined for both series 1 and 2 of diastereoisomeric acids where the distances between the two functional groups are different. The results are compared to the pK_a's values of the (3'-indolyl)-3-propionic acids 3 which we have determined. In this last series 3, the two interacting groups are not in a fixed orientation.



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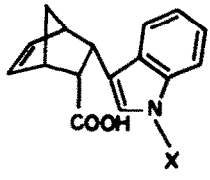

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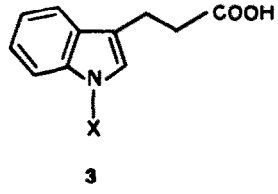

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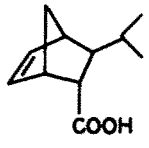
a: X = H
b: X = Me
c: X = COMe

We have also synthesized acids 4 and 5 and determined the pK_a of their carboxylic group. In these compounds, the possible interaction will be a steric one with the bulky isopropyl substituent.



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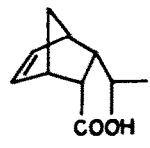

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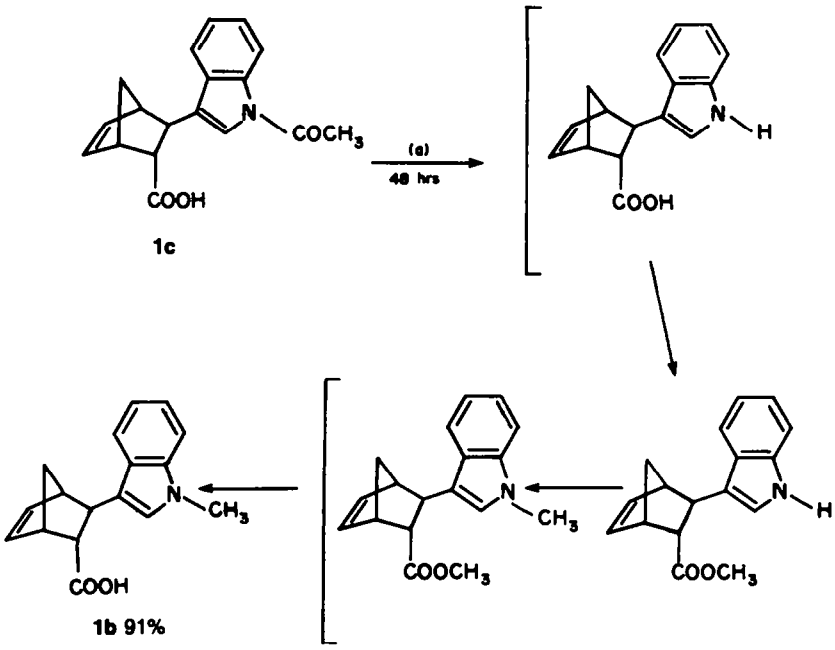
RESULTS AND DISCUSSION

1. *Syntheses*

We have previously reported the preparation of the acids **1a**, **1c**, **2a** and **2c**.[4,5] The acids **1b**, **2b** and **3b** have been obtained from the acids **1c**, **2c** and **3c** respectively, using a new method of N-alkylation of indole described by Barco *et al.*[6] This alkylation has been achieved by the reaction of dimethylsulfate in benzene and 35% sodium hydroxide in the presence of a phase transfer catalyst. Under these conditions **1b** and **3b** were obtained with excellent yields from **1c** and **3c** and it was possible during the reaction to notice the presence of intermediary products as described in the following scheme for the synthesis of **1b**.

The same reaction applied to the acid **2c** led to the epimeric acid **7b** as the only product.

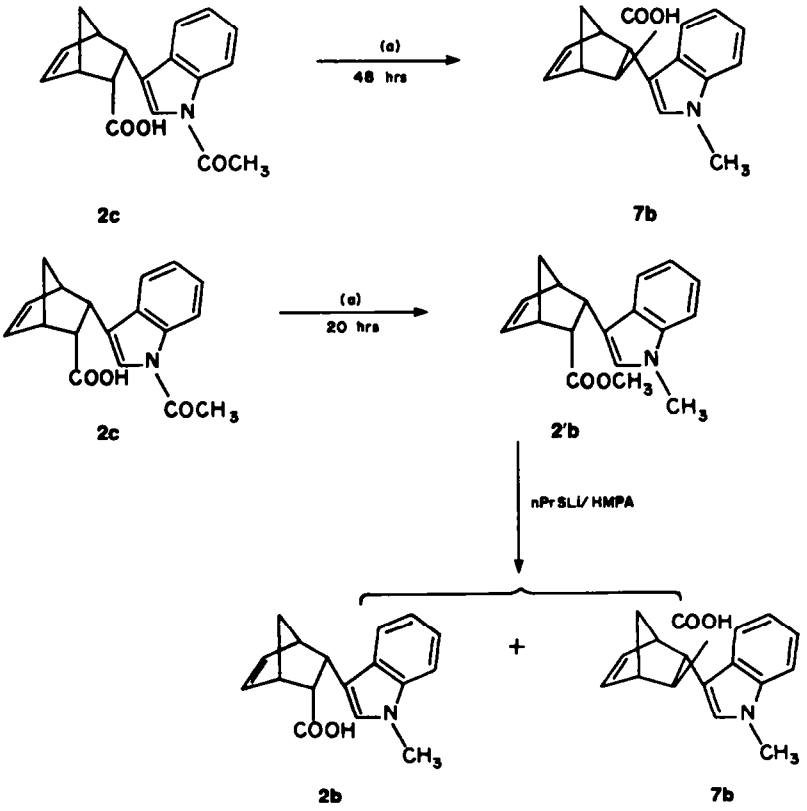
It was therefore necessary to isolate the intermediary ester **2'b** and to cleave the O–Me bond by means of lithium n-propyl mercaptide in HMPA.[7] Nevertheless even under these conditions, the two epimeric compounds *cis* **2b** and *trans* **7b** were obtained in ap-



(a) $SO_4(CH_3)_2$, $Bu_4N^+ HSO_4^-$, C_6H_6, 35% NaOH

proximatively 1/1 ratio. It was then possible to isolate **2b** by means of crystallisation.

The acid *endo trans* **4** and *endo cis* **5** were prepared by Diels–Alder reaction between cyclopentadiene and *trans* or *cis* 4-methyl 2-pentenoic acid. The *endo* acid **4** was separated from isomeric *exo* material after transformation into the corresponding iodolactone which was submitted to a reductive cleavage by Zn/CH_3COOH to



give 4. From the *cis* 4-methyl 2-pentenoic acid, acid 5 was found to be the only product of the Diels-Alder reaction.

The stereochemistries of all these compounds were determined from their ^{1}H NMR spectra.[5]

2. *pK_a Determinations*

The pK_a's values of the acids 1, 2 and 3, measured by potentiometry, are given in Table 1. In Table 2, with the pK_a's of 4 and 5, we have included for comparison, the pK_a of bicyclo[2.2.1.] 2-endo carboxylic acid 6.

In addition, the pK_a's of acids 1a, 2a and 3a have been determined at several temperatures between 10 and 35°, showing no appreciable variation in the pK_a's values of these representative acids of the three series.

DISCUSSION

Table 1 indicates that the *cis* acids 2, where the aromatic group is near the carboxylic function, are characterized by higher pK_a's values than those of acids 3 where indolyl and carboxyl groups are in the *trans* position. The lower acidity of the *cis* compounds 2 may be explained by a steric hindrance of the aromatic ring which affects the accessibility of the carboxylate anion by solvent molecules.[6] This first interpretation is confirmed by the greater pK_a value of 5 compared with acid 4 (Table 2). In acid 5, the bulky isopropyl group is in the vicinity of the polar group and renders the solvation of the carboxylate anion more difficult. Nevertheless, steric hindrance is not the only effect which can explain the anomalous high pK_a's values of *cis* acids 2. Accordingly from the values of Table 2, it can be seen that the isopropyl group affects the pK_a values even when it is *trans* to the COOH: $\Delta pK_a(4\text{–}6) = 0.21$. This is not the case for the indolyl group. $\Delta pK_a(1a\text{–}6) \simeq 0$, $\Delta pK_a(1c\text{–}6) = -0.3$, and then if the pK_a difference between the *cis* and *trans* acids: $\Delta pK_a(4\text{–}5) = 0.34$ is about the same as $\Delta pK_a(2c\text{–}1c) = 0.38$, the difference $\Delta pK_a(2a\text{–}1a) = 0.50$ is rather greater and cannot be explained only by the steric hindrance.

Let us now consider the effect of the substituent of the indolyl nitrogen on the pK_a's values of the acids 1, 2 and 3 (Table 1), we can see that the electronic properties of the substituent are better transmitted for *cis* compounds 2: $\Delta pK_a(2a\text{–}2c) = 0.47$ than for *trans* 1: $\Delta pK_a(1a\text{–}1c) = 0.35$ and than 3: $\Delta pK_a(3a\text{–}3c) = 0.27$. We can say that the electronic effect of the substituent is transmitted through two sp^3 carbons by an inductive effect in compounds 3. In acids 1 and 2 the electronic effect of the substituent is not only transmitted by the C–C bound but also through space, particularly in the case of the *cis* acids 2 for which we note a marked influence of X.

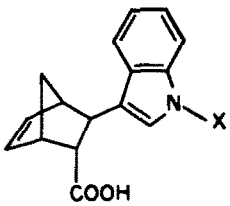
CONCLUSION

From the above discussion, we can state that the indolyl group modifies the chemical properties of the carboxyl group by at least two mechanisms.

(a) Steric hindrance, which affects the carboxylate anion accessibility to the solvent.

(b) Specific aromatic interaction which most likely involves the electronic distribution on the aromatic ring.

Table 1. pK_a's values of acids 1, 2 and 3[a]



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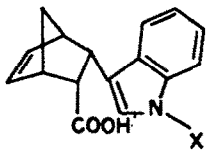

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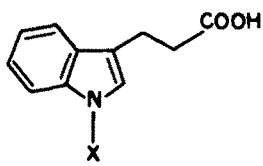


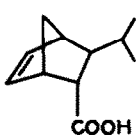
3

X	1	2	3
a: H	6.36	6.86	5.92
b: Me	6.29	6.65[b]	5.91
c: COMe	6.01	6.39	5.65

[a]Determined by potentiometry in CH_3OH/H_2O 60/40 v/v at 25.0 ± 0.1°, $\mu = 0.1$ (KCl).

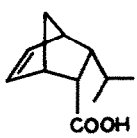
[b]This value was obtained on a sample containing about 5 to 8% of the isomeric trans acid 7b as judged from the ^{1}H NMR spectra (see experimental part). Assuming a pK_a value of 6.3 for 7b[1] a calculated value for the pK_a of pure 2b would be 6.8.

Table 2. pK_a's values of acids 4, 5 and 6[a]



4

6.52



5

6.86

6

6.31

[a]Same conditions as above.

The first mechanism seems to be the most important in the models we have chosen, the second is now under study by means of fluorescence.

The through space interaction we have observed on small molecules is of some interest when considering enzymatic catalysis. It would act directly, affecting the properties of the polar group; for example it could explain the high pK_a value (6.5) of the relatively exposed Glu 35 in lysozyme, which is known to lie in a predominantly non-polar region including the indolyl moiety of Trp 108.[9]

We are going to extend our study to the interaction between aromatic and amino groups. Such interactions having already been reported in proteins for instance that one involving Lys 41 in a trypsin inhibitor[3] mentioned at the beginning of this paper. Besides, pK_a perturbations of ionizable basic residues have been mentioned, in the alcohol deshydrogenase-NADH complex, attributed to a screening effect of the nicotinamide moiety of NADH.[10]

EXPERIMENTAL

The pK_a values were determined by potentiometric titration of acidic soln (2×10^{-3} M) in MeOH/H_2O (60/40, v/v), ionic strength $\mu = 0.1$ (KCl) by 0.04 M NaOH at 25.0 ± 0.1°. The titrations were made using a Radiometer automatic system including a Autoburette ABU 12 monitored by a TTT 60 Titrator in conjunction with a PHM 64 pH-meter and REA 160 recorder. IR spectra were obtained using a Perkin–Elmer 257 spectrophotometer. A Perkin–Elmer R-32 90 MHz spectrometer was used to obtain NMR spectra excepted special indication. The chemical shifts of the NMR spectra were δ values in ppm and coupling constants, J, were in hertz.

3 - exo - [3' - (N - Methyl)*indolyl*] *bicyclo* [2.2.1] *hept* - 5 - *ene* 2 - endo - *carboxylic acid* **1b**. N-acetyl acid **1c** (0.6 mmol; 177 mg), 25 mg tetrabutylammonium hydrogen sulfate, 0.4 ml dimethyl sulfate 2 ml 35% NaOHaq and 2 ml benzene were shaken for 48 hr at 40° under N_2.

Then 150 ml water was added to the mixture. The aqueous soln was washed with ether and carefully acidified and then ether extracted. The ethereal layer was washed with water and dried with $MgSO_4$ to give 146 mg (91%) of **1b** after removal of ether, Colorless crystals m.p. 176° (ether); IR (KBr) ν_{CO} 1693 cm^{-1} RMN ($CDCl_3$) δ: 1.59 and 1.76 (AB_q, J = 8.5, 2H, H_{7a} and H_{7a}) 3.05 (m, 2H, H_1 and H_3) 3.3 (m, 2H, H_2 and H_4) 3.7 (s, 3H, NCH_3) 6.15 (dd, $J_{5-6} = 5.5$ $J_{5-4} = 3$, 1H, H_5) 6.45 (dd, $J_{6-5} = 5.5$, $J_{6-1} = 3$, 1H, H_6) 6.85 (s, 1H, indolyl H_2) 7.2 (m, 3H, indolyl H_4, H_5 and H_6) 7.7 (m, 1H, indolyl H_7). (Found: C, 76.42; J, 6.47; N, 5.22; 0, 11,97. CHNO requires: C, 76.38: H, 6.41; N, 5.24; 0, 11.97%).

Methyl 3 - endo - [(N - *methyl*) *indolyl* - 3'] *bicyclo* [2.2.1] *hept* - 5 *ene* - 2 endo *carboxylate* **2'b**. N-acetyl acid **2c** (0.678 mmol; 200 mg), 25 mg tetrabutylammonium hydrogensulfate, 1.4 ml dimethyl sulfate, 2 ml 35% NaOHaq, 2 ml benzene were stirred together at 45° for 20 hr. After dilution with 150 ml water the mixture was extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and gave after removal of the solvent 183 mg (96%) of the ester **2'b** as colorless crystals, m.p. 83–85°. IR (KBr) ν_{CO} 1720 cm^{-1}; RMN ($CDCl_3$) δ: 1.54 (m, $\Delta\omega_{1/2} = 4$, 2H, H_{7a} and H_{7a}) 3.05–3.25 (m (with s at 3.11), 5H, H_1, H_4 and NCH_3) 3.48 (dd, $J_{2-3} = 11$, $J_{2-1} = 3$, 1H, H_2) 3.6 (s, 3H, OCH_3) 4.12 (dd, $J_{3-2} = 11$, $J_{3-4} = 3$, 1H, H_3) 6.17 (dd, $J_{5-6} = 5$, $J_{5-4} = 3$, 1H, H_5) 6.60 (dd (and s at 6.62), $J_{6-5} = 5$, $J_{6-1} = 3$, 2H, H_6 and indolyl H_2) 7.1 (m, 3H, indolyl H_4, H_5 and H_6) 7.7 (m, 1H, indolyl H_7). (Found: C, 76.25; H, 6.85; N, 4.87; 0, 12.0 CHNO requires: C, 76.84, H, 6.81; N, 4.98; 0, 11.37%).

3 - endo [(N - *Methyl*) *indolyl* - 3'] *bicyclo* [2.2.1] *hept* - 5 - *ene* 2 - endo - *carboxylic acid* **2b**. A soln of PrSLi in HMPA was prepared (according to Bartlett and Johnson[7]) from 0.6 g finely ground lithium hydride and 2 ml of n-propyl mercaptan in dry HMPA (made oxygen-free by nitrogen bubbling). This soln was immediately utilized. 172 mg (0.61 mmol) of the ester **2'b** were dissolved in 10 ml mercaptide soln, and stirred at room temp. under N_2 for 4 hr. Then 150 ml 10% HClaq was added and the white ppt extracted with ether. The organic layer was washed with water and extracted with 10% Na_2CO_3aq. The alcaline soln was washed with ether and carefully acidified at low temp. and then extracted with ether. Removal of the solvent after drying ($MgSO_4$) left 157 mg (96%) of an oily material which contains both N-methyl acids *endo cis* **2b** and *exo trans* **7b** in the same ratio (from the NMR spectra). The acidic mixture was dissolved in 0.5 ml $CHCl_3$ and upon standing overnight at room temp. gave 35 mg (21%) of **2b** *endo cis* whose stereochemistry is established by NMR, colorless crystals m.p. 171–173°. IR (KBr) ν_{CO} 1700 cm^{-1}; ($CDCl_3$–60 MHz (Brucker W.P. 60)) δ: 1.6 (dd, J = J' = 1.8, H_{7a} and H_{7a}) 3.25 (m, 2H, H_1 and H_4) 3.53 (dd, $J_{2-3} = 10.5$, $J_{2-1} \simeq 3.5$, 1H, H_2) 3.65 (s, 3H, N–CH_3) 3.73 (s, 0.2 H, impurity: N–CH_3 of exo **7b**) 4.21 (dd, $J_{3-2} = 10.5$, $J_{3-4} = 3.5$, 1H, H_3) 6.28 (dd, $J_{5-6} = 5.5$, $J_{5-4} = 3.3$, 1H, H_5) 6.6 (dd, $J_{6-5} = 5.5$, $J_{6-1} = 3.3$, 1H, H_6) 6.72 (s, 1H, indolyl H_2) 7.4 (m, 3H, indolyl H_4, H_5 and H_6) 7.75 (M, 1 H, indolyl H_7) Mass spectra: M^+267 m/e 201 (retro Diels–Alder [11]).

3 - (- 3' - *Indolyl*) *propionic acid* **3a**. This acid is the commercial product (Fluka).

3 - [(N - *Acetyl*) - 3' - *indolyl*] *propionic acid* **3c**. 3 - [(n-acetyl) - 3' - indolyl] acrylic acid (2 mmol; 458 mg) prepared from (N-acetyl) indolaldehyde[5] dissolved in 10 ml dimethylformamide, was hydrogenated in the presence of 100 mg 5% Pd/C, by 49 ml of H_2 within 1 hr. 369 mg (80%) of the acid **3c** were obtained as white crystals. m.p. 136° (benzene) IR (KBr) ν_{CO} 1685 and 1715 cm^{-1}; RMN (DMSO-d_6) δ: 2.4–2.8 (m(with s at 2.45), 7H, $(CH_2)_2$ and $COCH_3$) 6.9–7.4 (m, 4H, indolyl protons) 8.15 (m, 1H, indolyl H_7); (Found: C, 67.46; H, 5.65; N, 5.66; O, 20.66. CHNO requires: C, 67.52; H, 5.66; N, 6.06; 0, 20.75%.

3 - [(N - *Methyl*) - 3' - *indolyl*] *propionic acid* **3b**. Acid **3a** (2 mmol; 378 mg), 75 mg tetrabutylammonium hydrogen sulfate 2 ml dimethyl sulfate, 5 ml 35% NaOHaq and 5 ml benzene was stirred at 45° under N_2 for 48 hr. 200 ml water was added to the mixture and the acidic fraction extracted with ether. The organic layer was washed with water and dried ($MgSO_4$) to give 403 mg (99%) of **3b** as colorless crystals. m.p. 125° (ether) (lit. 124–125°, R' 75%[12]). RMN ($CDCl_3$ + DMSO-d_6) δ: 2.94 (m, 4H, $(CH_2)_2$) 3.68 (s, 3H, N–CH_3) 6.87 (s, 1H, indolyl H_2) 7.2 (m, 3H, indolyl H_4, H_5 and H_6) 7.6 (s, 1H, indolyl H_7).

trans - 4 - *Methyl* 2 - *pentenoic acid*. This acid was prepared from 2-methyl propanal according to Goldberg and Linstead.[13] E = 123–125°/25 mm (lit: 113°/20 mm[13]) RMN ($CDCl_3$) δ: 1.07 (d, J = 6.5, 6H, $(CH_3)_2$) 2.48 (m, J = J' ≃ 6.5, J'' = 1.5, 1H, $CH(CH_3)_2$) .5.75 (dd, J = 15.5, J' = 1.5, 1H, = CH COOH) 7.05 (dd, J = 15.5, J' = 6.5, 1H, iPrCH=).

Diels–Alder condensation of cyclopentadiene and trans - 4 - *methyl* 2 - *pentenoic acid. trans* - 4 - Methyl 2-pentenoic acid (50 mmol; 5.7 g) and 8 ml freshly distilled cyclopentadiene was dissolved in 50 ml cyclohexane and refluxed under N_2 for 10 days, 2 ml cyclopentadiene being added to the mixture each day. After that time about 35% of the bicyclic acids were formed (NMR). The acid fraction was extracted with a 10% Na_2CO_3aq and gave 6 g of a mixture of acids *endo* **4** and *exo* in the same ratio (NMR) accompanied by starting material. The *endo*-acid **4** was separated by iodolactonization according to Rondestvedt and Ver Nooy.[14] 1.77 g of the iodolactone of **4** were obtained. m.p. 82° (cyclohexane). IR ($CHCl_3$) ν_{CO} 1780 cm^{-1}; RMN ($CDCl_3$) δ: 0.95 (dd, J = J' = 5.5, 6H, $(CH_3)_2$, 1.2–1.6 (m, 2H, H_3 and $CH(CH_3)_2$) 1.85 (m, $J_{7a-7s} = 11.5$, $J_{7a-5} = 2.5$, $J_{7a-1} = 1.5$, 1H, H_{7a}) 2.2 (d, $J_{7a-7s} = 11.5$, 1H, H_{7s}) 2.25 (d, $J_{2-1} = 4.5$, 1H, H_2) 2.67 (s(broad $\Delta\omega_{1/2} = 5$), 1H, H_4) 3.1 (m, $J_{1-6} \simeq J_{1-2} \simeq 4.5$, $J_{1-7s} \simeq 1.5$, 1H, H_1) 3.81 (D, $J_{5-7A} = 2.5$, 1H, H_5) 5.08 (d, $J_{6-1} = 4.5$, 1H, H_6). (Found: C, 43.19; H, 5.02; 0, 10.12, CHO requires: C, 43.16; H, 4.94; 0, 10.45%).

3 - *exo* - *Isopropyl bicyclo* [2.2.1] *hept* - 5 - *ene* 2 - *endo* - *carboxylic acid* **4**. Iodolactone of **4** (5.65 mmol; 1.73 g) in 6 ml AcOH and 2.26 g Zn dust was stirred at 45–50° for 4 hr. The Zn salts formed and excess Zn was filtered off and carefully washed with ether. The acid was extracted with 10% Na_2CO_3aq, the aqueous soln was made acidic, extracted with ether and after vacuum evaporation afforded 0.93 g (91%) of **4** as white crystals m.p. 97° (cyclohexane). IR ($CHCl_3$) ν_{CO} 1700 cm^{-1}; RMN ($CDCl_3$) δ: 1 (dd, J ≃ J' ≃ 3, 6H, $(CH_3)_2$) 1.2–1.7 (m, 4H, H_{7s}, H_{7s}, H_3 and $CH(CH_3)_2$) 2.55 (dd, $J_{2-1} \simeq J_{2-3} \simeq 4$, 1H, H_2) 2.76 (m, $\Delta\omega_{1/2} = 6$, 1H, H_4) 3.15 (m, $\Delta\omega_{1/2} = 7$, 1H, H_1) 6.0 (dd, $J_{6-5} = 5.5$, $J_{6-1} = 2.7$, 1H,

H_6) 6.25 (dd, $J_{5-6} = 5.5$, $J_{5-4} = 3$, 1H, H_5). (Found: C, 73.32; H, 8.72; 0, 17.44 CHO requires; C, 73.30: H, 8.95; 0, 17.75%).

cis - 4 - *Methyl* 2 - *pentenoic acid.* This acid was prepared by a Favorsky rearrangement of 1 - 3 - dibromo 4 - methyl 2 - pentanone,[15] m.p. 16–17° (lit. 15.5–17.5[15]). RMN ($CDCl_3$) δ: 1(d, $J = 6.8$, 6H, $(CH_3)_2$ 3.6 (m, $J = 6.8$, $J' = 10$, $J'' = 0.6$, 1H, $CH(CH_3)_2$ 5.67 (dd = A part of an ABX pattern, $J_{AB} = 11.6$, $J_{AX} = 10$, 1H, iPrCH=) 6.12 (dd = B part of an ABX pattern, $J_{AB} = 11.6$, $J_{BX} = 0.6$, 1H, CH–COOH).

Diels–Alder condensation of cyclopentadiene and cis - 4 - *methyl* 2 - *pentenoic acid. cis* - 4 - methyl 2 - pentenoic acid (12.5 mmol; 1.425 g) and 2 ml freshly distilled cyclopentadiene was dissolved in 8 ml cyclohexane and refluxed under N_2. 1 ml cyclopentadiene was added to the mixture each day. After 10 days 1.765 g of acidic components were separated from the mixture. The iodolactonization reaction[14] from 1.63 g of the acidic mixture gave 2.04 g of the iodolactone. From the filtrate 411 mg of oily products were isolated which contained more than 85% of starting material (NMR spectra). Iodolactone: m.p. 79–80° (cyclohexane). IR ($CHCl_3$) ν_{CO}: 1780 cm^{-1}; RMN ($CDCl_3$) δ: (dd, $J = J' = 6$, 6H, $(CH_3)_2$) 1.3–1.9 (m, 3H, $CH(CH_3)_2$, H_3 and H_{7a}) 2.35 (dd, $J_{7s-7a} = 11.5$, $J' = 1.5$, 1H, H_{7s}) 2.65 (m, 2H, H_2 and H_4) 3.21 (m, $J_{1-6} \simeq J_{1-2} \simeq 5$, $J_{1-7s} \simeq J_{1-7a} \simeq J' \simeq 1.5$, 1H, H_1) 4.05 (d, $J_{5-7a} = 2.3$, 1H, H_5) 5.1 (d, $J_{6-1} = 5$, 1H, H_6). (Found: C, 43.22; H, 5.09; 0, 10.26 CHO requires: C, 43.16; H, 4.94; 0, 10.45%).

3 - endo - *Isopropyl bicyclo* [2.2.1] *hept* - 5 - *ene* 2 - endo - *carboxylic acid* 5. Iodolactone (5.26 mmol; 1.6 g) dissolved in 6 ml AcOH and 2.1 g Zn dust was stirred at 45–50° for 4 hr. 736 mg (78%) of 5 were obtained as colorless crystals m.p. 115° (hexane). IR ($CHCl_3$) ν_{CO} 1700 cm^{-1}; RMN ($CDCl_3$) δ: 0.85 (dd, $J = J' = 7$, 6H, $(CH_3)_2$) 1.1–1.7 (m, 3H, H_{7a}, H_{7s} and $CH(CH_3)_2$) 2.08 (m, $J_{3-CH(CH_3)^2} = 11$, $J_{3-2} = 9.5$, $J_{3-4} = 4.5$, 1H, H_3) 3.0 (m, 3H, H_1, H_2 and H_4) 6.17 (m, $\Delta\omega_{1/2} = 5$, 2H, H_5 and H_6) (Found: C, 73.28; H, 8.86; 0, 17.48. CHO requires: C, 73.30; H, 8.95; 0, 17.75%).

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