125. The Synthesis of Trimethylcyclopentane-carboxylic Acids

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(1*RS*, 5*SR*)-2,2,5-Trimethylcyclopentane-1-carboxylic acid (**17**) and (1*r*, 2*RS*, 5*SR*)-1,2,5-trimethylcyclopentane-1-carboxylic acid (**19**) are the starting materials for the α-alkynone routes to (±)-capnellene and for similar efforts towards ptychanolide. Since **17** and **19** have, so far, been available only by a branching reaction from the same precursor, the cyanohydrin mixture **2/3**, a modified synthesis for **17** and a new one for **19** was developed (*Scheme 1*). The common precursor **2/3** was treated with $POCl_3$ which effected normal dehydration to **6** (47%, major path) in competition with Me migration to **8** and **9** (17%). The minor path to **8** and **9** could be reduced to 3% when $SOCl_2$ was used for the dehydration of **2/3**. This reaction was the basis for an improved synthesis of **17** from **1**, using the steps *b*, *e*, *i*, *r*, and *v* see *Scheme 1* in an overall yield of 35%. The $POCl_3$ reaction was also studied with the pure cyanohydrins **2** and **3**, the configurations of which were determined by an X-ray analysis of **2**. Me migration did not occur from **2** but only from **3** (25%), which has HO–C(1) and H–C(5) in a *cis* position. With $SOCl_2$, **3** underwent only 5% Me migration. The new synthesis of **19** started with **4** using the steps *h*, *n*, *p*, and *s* (see *Scheme 1*) in an overall yield of 68%.

1. Introduction. – In our recent syntheses of (±)-capnellene (**D**) [1] and (±)-isoptychanolide (**E**) [2], we used the acids **A** and **C**, respectively, for a cyclopentenone anellation sequence **F**→**H** which includes the high temperature α-alkynone cyclization step **G**→**H** (*cf.* [3] [4]). Both acids **A** and **C** were prepared from the same intermediate, the cyanohydrin **B**. The formation of **A** was straightforward, but the formation of **C** involved the unexpected (for our purpose [2] at that time fortunate) migration of a Me group. In view of the low yields (22% **A** and 9% **C**, both from **B**) and since more **C** was required for synthetic efforts towards ptychanolide (differing from **E** in the epoxy configuration), we restudied the transformations of **B**, thereby improving the preparation of **A**, and developed an alternative synthesis of **C**.

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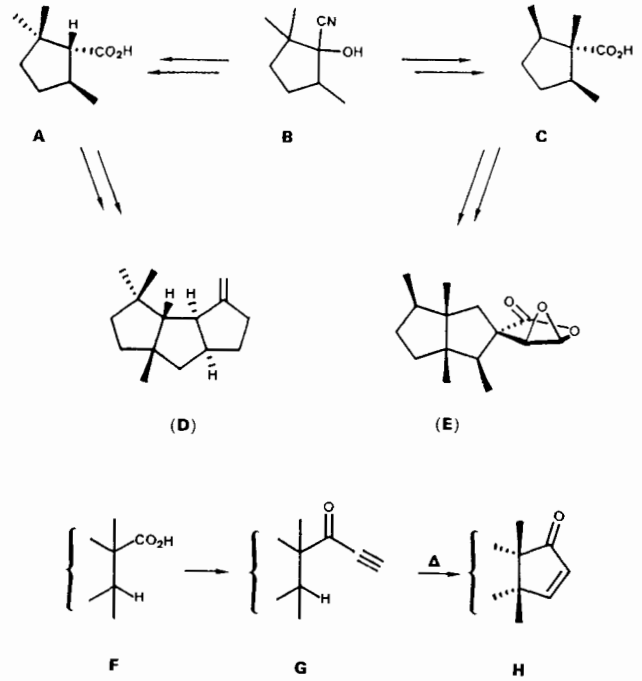
[4]) The ratio of the nitriles **6**, **8**, and **9** was determined by anal. GC (column *BP-5* at 48°) and confirmed by the ^{1}H-NMR (400 MHz) signals of the mixture (see *Exper. Part, Exper. 4*). The minor products **8** and **9** had been overlooked in [1] and in our preliminary work (*cf.* [2]), because **8** showed the same retention time as **6** on several other GC columns and because the peak now attributed to **9** appeared to be too small (6%) to be a disturbing factor. This, together with the drastic conditions required for the saponification of **6**, made it appear as if the Me migration had taken place during the latter reaction. We are grateful to Prof. *Paul Bartlett* (University of California, Berkeley) for drawing our attention to the need of reevaluating this situation.

[5]) Shaking the basic solution with Et_2O during workup removed the neutral materials, presumably unreacted **6** and partially saponified **12**.



2. Results and Discussion. – All reactions leading to the acids **17** and **19**, which are our starting materials for capnellene and ptychanolide, respectively are given in *Scheme 1*. *Cyanohydrin Formation.* The cyanohydrins **2**/**3** (98%; 18:82 mixture[6])) were obtained from **1** as in [1] by the general method of [5] and separated by *Lobar* chromatography (*Scheme 1, b*). An X-ray structure determination[7]) (see the *Figure*) of the lower-melting, minor isomer proved the *trans*-configuration of HO–C(1) and H–C(5) on the 5-membered ring in **2** and thus their *cis*-configuration in **3**. The above ratio **3**/**2** implies a *ca.* 5-times faster attack of $^{\ominus}$CN at C(1) *cis* to the Me group at C(5) than *trans*. It looks as if the transition state with pseudoaxial attack at the carbonyl C-atom and with CH_3–C(5) in pseudoequatorial position (see *Scheme 2*, **1**→**3**) is better than another one where one of these aspects is the other way round.

Dehydration of **2** *and* **3**. In a typical *anti*-elimination, the cyanohydrin (OH–C(1) and H–C(5) *trans*) underwent a normal vicinal dehydration to the α, β-unsaturated nitrile **6** (70%) under the influence of $POCl_3$ in pyridine (*Scheme 1, c*; see *Scheme 2*). There was also 5% cyanohydrin cleavage, reforming the ketone **1**.

Dehydration of cyanohydrin **3** (HO–C(1) and H–C(5) *cis*) with $POCl_3$ led to only 57% of **6** along with the two β,γ-unsaturated nitriles **8** (24%) and **9** (5%; *Scheme 1, f*)[4]). Evidently, the vicinal dehydration which, in this case, must be a *syn*-elimination is partly suppressed so that a 1,2-migration of one of the geminal Me groups can compete, leading to some **8** and **9** (*Scheme 3*).

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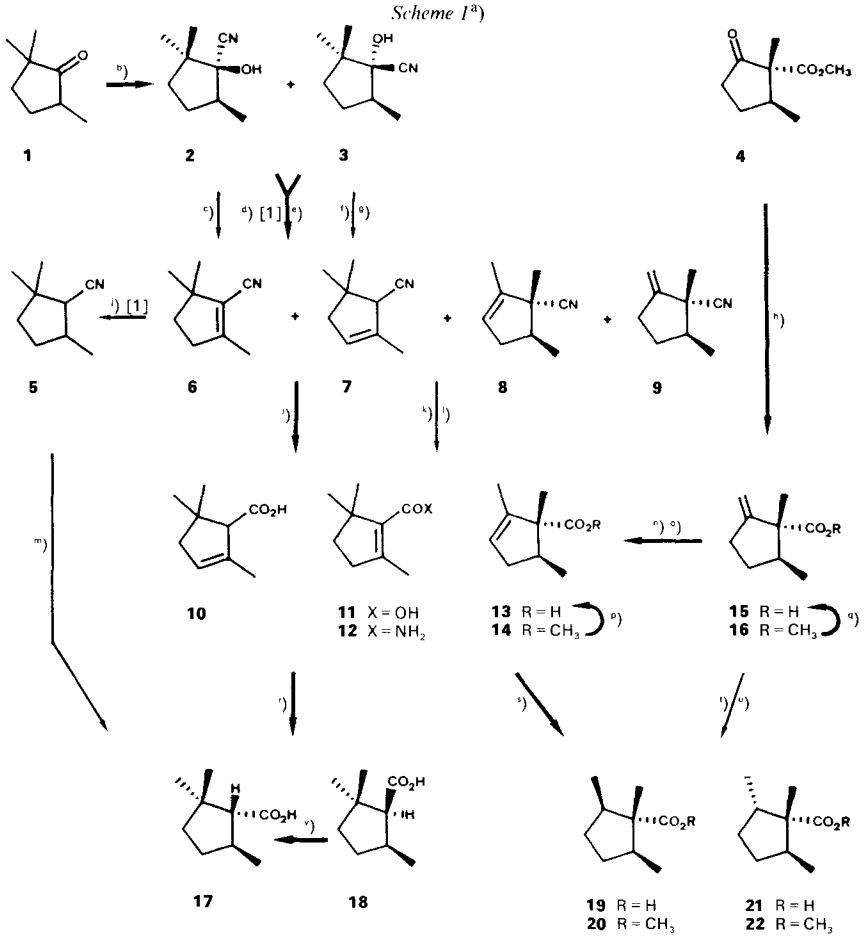
[6]) In [1], this ratio was erroneously given as 5:1.

[7]) We thank *P. Schönholzer* of *F. Hoffmann-La Roche & Co. AG*, Basel, for this analysis. The X-ray data has been submitted to *Cambridge Crystallographic Data Center*.

Scheme 1[a])



[a]) Bold-type arrows indicate the preferred synthetic paths to the acids **17** and **19**.

[b]) $(CH_3)_3SiCN$, ZnI_2, CH_2Cl_2; HCl: **1**→**2**/**3** (18:82; 98%).

[c]) $POCl_3$, Py, reflux: **2**→**1**/**6** (6:94; 75%).

[d]) $POCl_3$, Py, reflux [1]: **2**/**3** (18:82)→**6**/**8**/**9** (74:20:6; 64%)[4]).

[e]) $SOCl_2$ (neat), reflux: **2**/**3** (18:82)→**6**/**7**/**8** (86:11:3; 82%).

[f]) $POCl_3$, Py, reflux: **3**→**1**/**6**/**8**/**9** (2:68:24:6; 84%).

[g]) $SOCl_2$ (neat), reflux: **3**→**6**/**8** (94:6; 81%).

[h]) Ph_3PCH_2, THF, r.t.: **4**→**16** (85%).

[i]) KOH, diethylene glycol, 200°, 72 h: **6**/**7**/**8** (86:11:3)→**10**/**11**/**13** (21:64:15; 99% recovery); on chromatography, **10**/**11**/**13** (11:79:10; 54%).

[j]) CuH, THF, r.t. [1]: **6**/**8**/**9** (74:20:6)→**5** (69%).

[k]) KOH, diethylene glycol, 200°, 18 h: **1**/**6** (6:94)→**6**/**10**/**11**/**12** (18:6:57:19; 77% recovery).

[l]) KOH, diethylene glycol, 200°, 18 h: **1**/**6**/**8**/**9** (2:68:24:6)→**6**/**10**/**11**/**12**/**13** (2:3:30:21:44; 108% recovery); **6**/**8**/**9** (74:20:6)→**10**/**11**/**13** (9:24:67[5]); 69% recovery); on chromatography, **10** (0.4%), **11** (12%), **13** (14%).

[m]) KOH, diethylene glycol, 200°, 18 h [1]: **5**→**17** (50%).

[n]) $RhCl_3 \cdot H_2O$, EtOH, reflux: **16**→**14** (97%).

[o]) KOH, diethylene glycol, 200°, 18 h: **16**→**13**/**15** (93:7; 83% recovery); on chromatography, **13** (52%).

[p]) NaOH, MeOH/H_2O, 50°: **14**→**13** (87%).

[q]) NaOH, MeOH/H_2O, 50°: **16**→**15** (89%).

[r]) H_2, 10% Pt/C, EtOAc: **10**/**11**/**13** (11:79:10)→**17**/**18**/**19** (23:69:8; 97%).

[s]) H_2, 10% Pt/C, EtOAc: **13**→**19** (95%).

[t]) H_2, 10% Pt/C, EtOAc: **16**→**20**/**22** (39:61; 98%).

[u]) H_2, 10% Pt/C, EtOAc: **15**→**19**/**21** (37:63; 85%).

[v]) NaH, BuLi, Et_2O, r.t.: **17**/**18**/**19** (23:69:8)→**17** (83%).

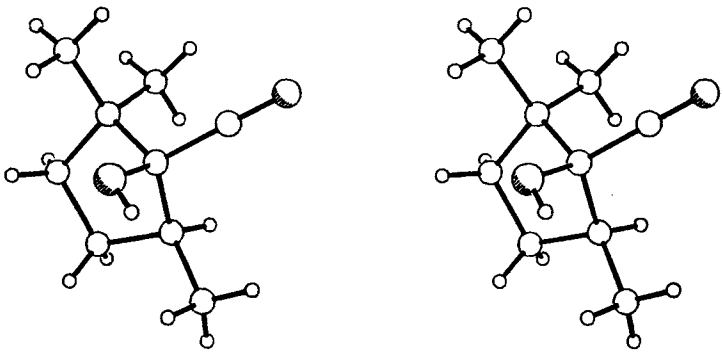
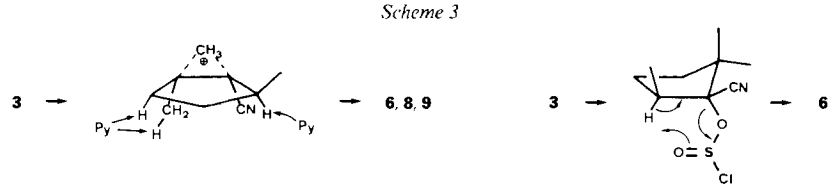


Figure. *Stereoscopic view of the X-ray-determined structure of the cyanohydrin* **2**

Scheme 2

The isomers **8** and **9** could not be separated from **6**, but their structures were derived from separately visible signals in the difference ^{1}H-NMR spectrum (**6** subtracted) of the mixture, namely from two signals due to CH_3–CHR_2 and two due to CH_3–CR_3 for **8** and **9**, and from two due to CH_3–CR=CHR for **8** and two due to CH_2=CR_2 for **9** (see *Exper. Part, Exper. 4*).

Scheme 3



When neat $SOCl_2$ was used as dehydrating agent for **3** instead of $POCl_3$/Py, the product was mostly **6** (only 5% of **8**; *Scheme 1, g*). $SOCl_2$ dehydration of the 18:82 mixture **2**/**3** afforded 71% of **6**, 9% of **7** and only 2% of rearranged product **8** (*Scheme 1, e*). The structure of **7** was derived from the separately visible signals in the difference ^{1}H-NMR spectrum (**6**/**8** substracted) of the product mixture. The $SOCl_2$ reaction seems to involve a concerted *syn*-elimination of the intermediate chlorosulfite [6] of **3** (see *Scheme 3*), so that the Me migration is suppressed. The higher ratio of rearranged (**8** and **9**) to unrearranged (**6**) products with $POCl_3$/Py (30:68) is attributed to a participation of the Me group *(Scheme 3)*. In accord with this mechanism is that the rearranged nitriles **8** and **9** possess the (1*RS*,5*SR*)-configuration, meaning that only the Me group *trans* to the nucleofuge had migrated.

Saponification of the Nitriles. The α,β-unsaturated nitrile **6** was highly resistant to saponification. Even after heating it for 18 h at 200° with KOH in diethylene glycol about 14% of **6** remained unchanged and as much as 15% were saponified only to the amide

stage, *i.e.* to **12** (*Scheme 1, k*). To the extent of *ca.* 5%, the double bond migrated into the β,γ-position to yield **10**, while the rest (44%) was transformed to the expected α,β-unsaturated acid **11**. Evidently, no Me migration had taken place under the alkaline conditions[4]). The saponification of **6**/**8**/**9** (68:24:6; containing 2% of **1**) yielded a 2:3:30:21:44 mixture **6**/**10**/**11**/**12**/**13** (*Scheme 1, l*). From a larger-scale experiment, it was possible to isolate the unsaturated acids **10** (0.4%), **11** (12%)[8]), and **13** (14%), after removal of **6** and **12** during workup.

Synthesis of **19**. The β,γ-unsaturated acid **13**, so far available only as a minor by-product (9% in 3 steps from **1**) [1], was synthesized specifically starting with the known keto ester **4** [7] (72% in 3 steps): A *Wittig* reaction transformed **4** into the unsaturated ester **16** (*Scheme 1, h*). Attempts to hydrogenate the exocyclic double bond in **16** or in the corresponding acid **15** led to *ca.* 2:3 mixtures of the stereoisomeric esters **20** and **22** (98%; *Scheme 1, t*) or acids **19** and **21** (85%; *Scheme 1, u*), respectively. To avoid the formation of the undesired stereoisomers **21** and **22**, the double bond of the ester **16** was first shifted into the ring with a Rh(III) catalyst [4] to give the endocyclic isomer **14** (97%; *Scheme 1, n*) and hence the acid **13**. Hydrogenation of **13** afforded the saturated acid **19** (95%) of C_s symmetry, which is the starting material needed for our planned further synthetic work in the ptychanolide field.

Complete saponification of a 86:11:3 mixture **6**/**7**/**8** gave a 11:79:10 mixture of the acids **10**, **11**, and **13** (54%; *Scheme 1, i*). Hydrogenation of this mixture over Pt/C led to the saturated acids **17**/**18**/**19** (ratio 23:69:8; 97%; *Scheme 1, r*). The structure of **18** was derived from the separately visible signals in the difference ^{1}H-NMR spectrum (**17** [1]/**19** subtracted). The desired acid **17** was obtained (83%) from the Na salt of **18** by enolization (60 min) with BuLi at r.t. (*Scheme 1, v*); it is identical with the substance used in [1] as the starting material of our capnellene synthesis.

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Experimental Part

General. See [3]. Compounds which were separated analytically by GC (to obtain product ratios) or preparatively by *Lobar* chromatography are always listed in the order of their elution sequence. NMR: *Varian XL-200* and *Bruker AM-400;* ^{1}H-NMR decoupling: irradiated signal in square brackets [δ], followed by the multiplicity and J of the ensuing signal.

1. (*1*RS,*5*RS)- *and* (*1*RS,*5*SR)-*1-Hydroxy-2,2,5-trimethylcyclopentane-1-carbonitriles* (**2** and **3**). A stirred soln. of 2,2,5-trimethylcyclopentanone (**1**); 15.28 g, 121 mmol [1] and ZnI_2 0.86 g, 3mmol in CH_2Cl_2 (120 ml) was allowed to react with $(CH_3)_3SiCN$ [5] (18 ml, 145 mmol) for 4 h. The solvent was evaporated to leave a mixture of trimethylsilyloxy-nitriles which was dissolved in THF (20 ml) and treated with 10% HCl (50 ml) for 24 h at 40°. The cooled mixture was extracted with Et_2O (5 × 80 ml), and the combined extracts were washed with 10% $Na_2S_2O_3$ soln. (20 ml), H_2O, and brine, dried over $MgSO_4$, evaporated, and dried at 22°/14 Torr leaving a colourless solid consisting of **2** and **3** (18.16 g, 98%) in a ratio 18:82[6]) (by anal. GC (*SE-52*, 91°)). Chromatography (*Lobar C*, hexane/EtOAc 97:3) of 4.35 g of this solid afforded (in two runs) 0.70 g (16%) of **2** and 3.40 g (76%) of **3**. **2**:

[8]) A quantum-mechanical study on the geometry [8] and a crystal-structure analysis [9] of 2,5,5-trimethylcyclopent-1-ene-1-carboxylic acid (**11**) have been reported. The sample used in the latter work had been prepared by Prof. *H.O. Huisman* and collaborators, University of Amsterdam, in connection with the synthesis of the 5-membered ring analog of vitamin A (private communication on unpublished work).

Colourless needles, m.p. 49.5–50.5° from hexane. IR ($CHCl_3$): 3600*m*, 3600–3130*m* (br.), 2970*s*, 2880*m*, 2235*w* (C≡N), 1465*m*, 1390*m*, 1380*m*, 1370*m*, 1130*m*, 1040*m*, 1000*m*, 990*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.68–2.46 (*m*, H–C(5)); 2.28–1.30 (*m*, 2 H–C(3), 2 H–C(4), HO; 1 H exchangeable with D_2O); 1.17 (*s*, 2 CH_3–C(2)); 1.15 (*d*, *J* = 6.2, CH_3–C(5)). MS (70 eV): 153 (2, M^+), 138 (22, $M^+ - 15$), 126 (25), 111 (10), 97 (17), 84 (100), 70 (29), 55 (62).

3: Colourless needles, m.p. 57.5–58.6° from hexane. IR ($CHCl_3$): 3590*m*, 3600–3100*m* (br.), 2970*s*, 2880*m*, 2235*w* (C≡N), 1470*m*, 1390*m*, 1375*m*, 1160*m*, 1080*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.49 (*s*, HO, exchangeable with D_2O); 2.42–2.18 (*m*, H–C(5)); 2.08–1.85 (*m*, 1 H); 1.78–1.52 (*m*, 2 H); 1.48–1.28 (*m*, 1 H); 1.24 (*d*, *J* = 6.9, CH_3–C(5)); 1.23 (*s*, CH_3–C(2)); 1.03 (*s*, CH_3–C(2)). MS (70 eV): 153 (1, M^+), 138 (64, $M^+ - 15$), 126 (22), 111 (47), 97 (68), 83 (29), 70 (96), 55 (100).

2. *Dehydration of* **2** *with* $POCl_3$ *in Pyridine.* A stirred soln. of pure **2** (450 mg, 2.9 mmol) in pyridine (3.8 ml) was treated at r.t. with $POCl_3$ (1.0 ml, *ca.* 11.2 mmol) and then heated to reflux for 5 h. The cooled mixture was poured onto ice (15 g) and conc. HCl (3.5 ml). After separation of the org. layer, the aq. phase was extracted with Et_2O (6 × 5 ml). The combined org. phases were washed with H_2O and brine, dried over $MgSO_4$, and evaporated to leave 289 mg (*ca.* 75%) of yellow oil consisting of the ketone **1** and *2,5,5-trimethylcyclopent-1-ene-1-carbonitrile* (**6**) in a ratio 6:94 (anal. GC (*SE-52*, 94°)). An anal. sample of **6** was obtained by column chromatography (*Lobar A*, C_6H_6), followed by bulb-to-bulb distillation at 119°/35 Torr. IR (film): 2960*s*, 2870*s*, 2845*m*, 2220*s* (C≡N), 1645*s*, 1380*m*, 1370*s*, 1330*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.42 (*tq*, *J* = 7.2, 1.2, 2 H–C(3)); 1.93 (*t*, *J* = 1.2, CH_3–C(2)); 1.78 (*t*, *J* = 7.2, 2 H–C(4)); 1.16 (*s*, 2 CH_3–C(5)); ([1]: ^{1}H-NMR (90 MHz)). MS (70 eV): 136 (1, $M^+ + 1$), 135 (9, M^+), 120 (100, $M^+ - 15$), 93 (32), 77 (13).

3. *Dehydration of* **2**/**3** *with* $SOCl_2$. A soln. of **2**/**3** (8.48 g, 55 mmol; ratio 18:82, anal. GC (*SE-52*, 91°)) in $SOCl_2$ (80 ml) was heated to reflux for 48 h, poured onto ice (400 g), stirred for 1 h, extracted with pentane (3 × 100 ml), washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. Bulb-to-bulb distillation at 119°/35 Torr yielded 6.12 g (82%) of a colourless oil consisting of *2,5,5-trimethylcyclopent-2-ene-1-carbonitrile* (**7**), **8**, and **6** in a ratio of 11:3:86 (anal. GC (*BP-5*, 48°)). Subtraction of the ^{1}H-NMR of **8**/**6** obtained in *Exper. 5* from the ^{1}H-NMR of **7**/**8**/**6** afforded the ^{1}H-NMR of **7**. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.48–5.44 (*m*, H–C(3)); 3.17–3.14 (*m*, H–C(1)); 2.26, 2.21 (*AB* of *ABX*$_3$, J_{AB} = 16.3, J_{AX} = 2.2, J_{BX} = 2.3, 2 H–C(4)); 1.84–1.82 (*m*, X_3 of *ABX*$_3$, CH_3–C(2)); 1.20 (*s*, CH_3–C(5)); 1.12 (*s*, CH_3–C(5)). GC-MS (70 eV): 136 (4, $M^+ + 1$), 135 (40, M^+), 120 (100, $M^+ - 15$), 93 (77), 77 (24).

4. *Dehydration of* **3** *with* $POCl_3$ *in Pyridine.* Using the procedure described in *Exper. 2*, 1.00 g (6.53 mmol) of **3** was transformed (reaction time 45 min) into 744 mg (*ca.* 84%) of a yellow oil consisting of **1**, *(1*RS,*5*SR*)-1,2,5-trimethylcyclopent-2-ene-1-carbonitrile* (**8**), **6** and *(1*RS,*2*SR*)-1,2-dimethyl-5-methylidenecyclopentane-1-carbonitrile* (**9**) in a ratio of 2:24:68:6 (anal. GC (*BP-5*, 48°)). We were not able to separate this mixture with several separation techniques (*Lobar*, HPLC or semi-prep. GC) under various conditions. The assignment of ^{1}H-NMR signals to certain protons of **8** and **9** was possible from the difference spectrum after computer subtraction of the ^{1}H-NMR of **6** from the ^{1}H-NMR of **6**/**8**/**9**. ^{1}H-NMR (400 MHz, $CDCl_3$): Signals due to **8**: 5.44–5.41 (*m*, H–C(3)); 2.71–2.61 (*m*, H–C(5)); 1.81–1.78 (*m*, CH_3–C(2)); 1.17 (*s*, CH_3–C(1)); 1.09 (*d*, *J* = 6.6, [2.65] *s*, CH_3–C(5)); signals due to **9**: 5.24, 5.04 (both *t*, *J* = 2.4, CH_2=C(5)); 1.23 (*s*, CH_3–C(1)); 1.04 (*d*, *J* = 6.8, [2.41] *s*, CH_3–C(2)); ^{1}H-NMR ratio of **6**/**8**/**9**, 70:20:7 (*cf.* GC ratio; ratio of **8**/**9** from olefinic signals (5.42 for **8**, 5.24/5.04 for **9**); ratio of **6** + **8**/**8** from the CH_3 signals (*ca.* 1.17 for **6** and for **8**) of the mixture spectrum and the difference spectrum (**6** subtracted).

5. *Dehydration of* **3** *with* $SOCl_2$. Using the procedure described in *Exper. 3*, 885 mg (5.8 mmol) of **3** were dehydrated (reaction time 15 h) to yield, after bulb-to-bulb distillation at 119°/35 Torr, 634 mg (81%) of a colourless oil consisting of **8**/**6** in a ratio of 6:94 (anal. GC (*BP-5*, 48°)).

6. *Methyl (1*RS,*2*SR*)-1,2-dimethyl-5-methylidenecyclopentane-1-carboxylate* (**16**). To a stirred soln. of methyl 1,*t*-2-dimethyl-5-oxocyclopentane-*r*-1-carboxylate (**4**; 4.99 g, 29.3 mmol) [7] in THF (10 ml) under N_2, a *ca.* 0.45 M solution of methylidene(triphenyl)phosphorane (73 ml, *ca.* 33 mmol; prepared according to [10]) was added dropwise within 2 h at r.t. After 2 h of stirring at r.t., 1 ml of acetone was added, the soln. was stirred for 1 h and evaporated. The brown semi-solid residue was extracted with pentane (4 × 100 ml) and the combined extract evaporated. After bulb-to-bulb distillation at 85°/14 Torr, 4.21 g (85%) of **16** was obtained as a colourless oil of 92% purity (anal. GC (*SE-52*, 71°)). An anal. sample of **16** was obtained by chromatography (*Lobar A*, hexane/EtOAc 99:1) followed by bulb-to-bulb distillation. IR (film): 3080*w* (C=CH_2), 2955*s*, 2880*s*, 2840*w*, 1735*s* (C=O), 1655*m* (C=C), 1260*s*, 1170*s*, 1100*m*, 895*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.92, 4.89 (both *t*, *J* = 2.5, CH_2=C(5)); 3.69 (*s*, CH_3OOC–C(1)); 2.73–2.52 (*m*, [0.93] *dd*, *J* = 11.0, 6.5, H–C(2)); 2.52–2.38 (*m*, 2 H); 1.94–1.78 (*m*, 1 H);

1.48–1.19 (*m*, 1 H); 1.14 (*s*, CH_3–C(1)); 0.93 (*d*, *J* = 7.0, CH_3–C(2)). MS (70 eV): 153 (2, $M^+ - 15$), 139 (3), 109 (100), 93 (9), 67 (25). Anal. calc. for $C_{10}H_{16}O_2$ (168.24): C 71.39, H 9.59; found: C 71.64, H 9.33.

7. *Complete Saponification of* **6**/**7**/**8**. A soln. of a 86:11:3 mixture **6**/**7**/**8** (1.71 g, 12.6 mmol) and KOH (7.10 g, 126.5 mmol) in diethylene glycol (15 ml) was heated at 200° for 72 h. After cooling, H_2O (40 ml) was added and the mixture extracted with Et_2O (5 × 60 ml). The combined Et_2O extracts yielded, after shaking with H_2O and brine, drying over $MgSO_4$, and evaporation, according to GC, not a trace of **6** or of **12**. The aq. alkaline phase was acidified at 0° with conc. HCl and extracted with Et_2O (5 × 60 ml). The combined Et_2O extracts were washed with H_2O and brine, dried over $MgSO_4$, and evaporated to yield 1.70 g (99% recovery) of a brown solid which, by anal. GC (*SE-52*, 90°) of an aliquot esterified with an Et_2O soln. of CH_2N_2, contained **10**/**13**/**11** in a ratio of 21:15:**64**. *Lobar* purification (hexane/EtOAc/AcOH 975:25:10) of a 1.21 g sample afforded 0.75 g (54%) of a 11:10:79 mixture **10**/**13**/**11** as pale yellow solid.

8. *Incomplete Saponification of* **6**. Using the procedure described in *Exper. 7*, **6** (239 mg, 1.8 mmol; containing 6% of **1**) was saponified for 18 h and subjected to the same workup. The Et_2O extracts of the alkaline mixture contained 37 mg (15% recovery) of a brown oil which consisted of recovered **6** and **12** in a ratio of 94:5 (anal. GC (*SE-52*, 100°)). Acidification and subsequent extraction of the aq. alkaline soln. yielded 148 mg (62% recovery) of a brown oil which, by anal. GC (*SE-52*, 90°) of an aliquot esterified with an Et_2O soln. of CH_2N_2, contained **10**/**11**/**12** in a ratio of 7:71:22. ^{1}H-NMR (200 MHz): signals of all the compounds synthesized in later experiments separately visible.

9. *Saponification of* **6**/**8**/**9**. Using the procedure described in *Exper. 8*, 271 mg (2.0 mmol) of **1**/**8**/**6**/**9** (ratio 2:24:68:6, anal. GC (*BP-5*, 48°)) was saponified and subjected to the same workup. The Et_2O extracts of the alkaline mixture contained 41 mg (15% recovery) of brown oil which contained **6**/**12** in a ratio of 14:51 (anal. GC (*SE-52*, 100°)). This oil was dissolved in boiling hexane, treated with charcoal, filtered, and the filtrate evaporated to yield 19 mg (6%) of *2,5,5-trimethylcyclopent-1-ene-1-carboxamide* (**12**) as colourless solid with a purity of 93% (anal. GC (*BP-5*, 150°)). After crystallisation from hexane, 10 mg of **12** were obtained as colourless needles, m.p. 152.8–154.7°. IR (KBr): 3370*s*, 3175*s*, 2955*m*, 2935*m*, 2860*m*, 1640*s* (amide I), 1615*s* (amide II), 1410*s*, 1360*m*, 1115*m*, 850–620*m* (br.). ^{1}H-NMR (400 MHz, $CDCl_3$): 5.63, 5.40 (2 br. *s*, NH_2); 2.33 (*tq*, *J* = 7.4, 1.1, 2 H–C(3)); 1.88 (*t*, *J* = 1.1, CH_3–C(2)); 1.69 (*t*, *J* = 7.4, 2 H–C(4)); 1.21 (*s*, 2 CH_3–C(5)). MS (70 eV): 153 (43, M^+), 138 (100, $M^+ - 15$), 121 (89), 109 (17), 95 (70), 84 (26), 77 (21), 67 (39), 55 (21), 44 (20). Anal. calc. for $C_9H_{15}NO$ (153.22): C 70.55, H 9.87, N 9.14; found: C 70.66, H 9.91, N 9.42.

Acidification and subsequent extraction of the aq. soln. yielded 253 mg (93% recovery) of a brown oil which, by anal. GC (*SE-52*, 90°) of an aliquot esterified with an Et_2O soln. of CH_2N_2, contained **10**/**13**/**11**/**12** in a ratio of 4:46:33:14.

The same saponification was performed with **8**/**6**/**9** (10.44 g, 77 mmol; ratio 20:74:6; anal. GC (*BP-5*, 48°)) and KOH (43.30 g, 773 mmol) in diethylene glycol (100 ml) at 200° for 20 h. After cooling, H_2O (800 ml) was added, the mixture was acidified with conc. HCl and extracted with Et_2O (5 × 100 ml). The combined extracts were washed with H_2O and extracted with 1N NaOH (3×). The combined aq. alkaline solns. were acidified to pH 1–2 with conc. HCl and extracted with Et_2O (3 × 100 ml). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated to yield 7.14 g (69% recovery) of a brown oil which, by anal. GC (*SE-52*, 90°) of an aliquot esterified with an Et_2O solution of CH_2N_2, contained **10**/**13**/**11** in a ratio of 9:67:24. By repeated column chromatography (300 g of silica gel, hexane/EtOAc/AcOH 975:25:10), 1.45 g (12%) of *2,5,5-trimethylcyclopent-1-ene-1-carboxylic acid* (**11**), 1.65 g (14%) of *(1RS,5SR)-1,2,5-trimethylcyclopent-2-ene-1-carboxylic acid* (**13**), and 50 mg (0.4%) of *2,5,5-trimethylcyclopent-2-ene-1-carboxylic acid* (**10**) were obtained. **11**[8]): Colourless solid, m.p. 75–78°. IR ($CHCl_3$): 3600–2300*m* (br.), 1675*s* (C=O), 1625*m*, 1410*w*, 1370*w*, 1360*w*, 1340*w*, 1310*w*, 1280*m*, 1040*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.42 (*tq*, *J* = 7.4, 1.1, 2 H–C(3)); 2.09 (*t*, *J* = 1.1, CH_3–C(2)); 1.70 (*t*, *J* = 7.4, 2 H–C(4)); 1.24 (*s*, 2 CH_3–C(5)). MS (70 eV): 154 (10, M^+), 139 (100, $M^+ - 15$), 121 (22), 111 (21), 93 (43), 77 (18), 67 (18), 55 (13). Anal. calc. for $C_9H_{14}O_2$ (154.21): C 70.10, H 9.15; found: C 70.28, H 9.25.

13: Colourless solid, m.p. 48.5–51.0°. IR (KBr): 3600–2700*s* (br.), 1690*s* (C=O), 1650*m*, 1460*m*, 1450*m*, 1410*m*, 1380*m*, 1285*s*, 1185*m*, 1110*m*, 1020*m*, 955*m*, 810*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.44 (br. *s*, H–C(3)); 2.74 (*sext.*, *J ca.* 7.5, [1.03] *t*, *J ca.* 7.5, H–(5)); 2.58–2.37 (*m*, H–C(4)); 2.03–1.82 (*m*, H–C(4)); 1.76–1.66 (*m*, CH_3–C(2)); 1.10 (*s*, CH_3–C(1)); 1.03 (*d*, *J* = 6.9, CH_3–C(5)). MS (70 eV): 154 (9, M^+), 125 (5), 109 (100), 93 (8), 81 (9), 67 (28), 55 (12). Anal. calc. for $C_9H_{14}O_2$ (154.21): C 70.10, H 9.15; found: C 69.87, H 8.95.

10: Colourless oil. IR (film): 3650–2200*s* (br.), 1705 (C=O), 1460*w*, 1410*m*, 1370*w*, 1310*w*, 1270*m*, 1220*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.49 (br. *s*, H–C(3)); 2.98 (br. *s*, H–C(1)); 2.32 (*dq*, *J* = 16, 2, H–(4)); 2.11 (*dm*, *J* = 16, H–(4)); 1.74 (br. *s*, CH_3–C(2)); 1.20, 1.11 (both *s*, 2 CH_3–C(5)). MS (70 eV): 154 (31, M^+), 139 (7), 131

(7), 111 (100), 93 (16), 81 (10), 67 (40), 55 (19). Anal. calc. for $C_9H_{14}O_2$ (154.21): C 70.10, H 9.15; found: C 69.80, H 9.25.

10. *Methyl (1RS,5SR)-1,2,5-Trimethylcyclopent-2-ene-1-carboxylate* (**14**). A soln. of **16** (2.74 g, 16.3 mmol) and $RhCl_3 \cdot H_2O$ (157 mg; *ca.* 40% Rh) in 95% EtOH (26 ml) was stirred for 17 h at reflux, cooled, diluted with H_2O (10 ml), and extracted with CH_2Cl_2 (5 × 10 ml). The combined org. extracts were washed with brine, dried over $MgSO_4$, and evaporated to leave a red oil which was filtered through a short SiO_2 column with hexane/Et_2O 9:1. The filtrate was evaporated and bulb-to-bulb distilled at 70°/14 Torr to yield 2.67 g (97%) of **14** of 88% purity (anal. GC (*SE-52*, 71°)) as a yellow oil. An anal. sample resulted from chromatography (*Lobar A*, hexane/EtOAc 99:1), followed by bulb-to-bulb distillation. IR (film): 3040*w*, 2960*s*, 2870*m*, 1730*s* (C=O), 1653*w* (C=C), 1250*s*, 1125*m*, 1100*s*, 800*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.42 (br. *s*, H–C(3)); 3.70 (*s*, CH_3OOC–C(1)); 2.78–2.58 (*m*, H–C(5)); 2.52–2.34 (*m*, H–C(4)); 2.00–1.80 (*m*, H–C(4)); 1.70–1.62 (*m*, CH_3–C(2)); 1.08 (*s*, CH_3–C(1)); 1.00 (*d*, *J* = 7.1, CH_3–C(5)). MS (70 eV): 168 (5, M^+), 139 (2), 109 (100), 93 (7), 81 (9), 67 (29). Anal. calc. for $C_{10}H_{16}O_2$ (168.24): C 71.39, H 9.59; found: C 71.65, H 9.85.

11. *Saponification of* **16**. Using the procedure described in *Exper. 8*, 168 mg (1 mmol) of **16** was saponified to yield 139 mg (83% recovery) of a brown oil consisting of **15** and the isomeric acid **13** in a ratio of 7:93 (anal. GC (*BP-5*, 120°)). The oily product was filtered through a short SiO_2 column using hexane/CH_2Cl_2 1:1 and the filtrate evaporated to leave a colourless solid which, after recrystallisation from pentane at −30°, yielded 80 mg (52%) of **13** as colourless prisms, m.p. 48.2–51.0°.

12. *Saponification of* **14**. A soln. of **14** (2.55 g, 15.2 mmol) and NaOH (3.60 g, 90 mmol) in MeOH (20 ml) and H_2O (26 ml) was stirred for 13 h at 45–50°, cooled, acidified with conc. HCl, and extracted with CH_2Cl_2 (5 × 40 ml). The combined extracts were dried over $MgSO_4$ and evaporated to leave a yellow semi-solid, which was filtered through a short SiO_2 column with C_6H_6/Et_2O 9:1. The filtrate was evaporated to yield 2.03 g (87%) of **13** of 100% purity (anal. GC (*SE-52* 101°)) as a colourless solid, after crystallisation from pentane at −30°, as colourless prisms, m.p. 52.9–53.6°. Spectral data: identical to the ones described for **13** in *Exper. 9*.

13. *(1RS,2SR)-1,2-Dimethyl-5-methylidenecyclopentane-1-carboxylic acid* (**15**). Using the procedure described in *Exper. 12*, 100 mg (0.59 mmol) of **16** was saponified to yield **15** (81 mg, 89%) of 99% purity (anal. GC (*BP-5*, 150°)) as a colourless solid. Crystallisation from pentane at −30° afforded **15** as colourless needles, m.p. 54.4–55.1°. IR ($CHCl_3$): 3560–2200*m* (br.), 1695*s* (C=O), 1650*m*, 1295*m*, 1280*m*, 1185*m*, 895*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.02, 4.99 (2 *t*, *J* = 2.4, CH_2 = C(5)); 2.72–2.52 (*m*, [0.96] *dd*, *J* = 11.0, 6.5, H–C(2)); 2.52–2.38 (*m*, 2 H); 1.98–1.78 (*m*, 1 H); 1.50–1.22 (*m*, 1 H); 1.16 (*s*, CH_3–C(1)); 0.96 (*d*, *J* = 6.9, CH_3–C(2)). MS (70 eV): 154 (2, M^+), 125 (8), 109 (100), 93 (8), 81 (10), 67 (35), 55 (17).

14. *Hydrogenation of* **10**/**11**/**13**. A stirred soln. of 730 mg (4.7 mmol) of a 11:79:10 mixture of **10**/**11**/**13** (as obtained in *Exper. 7*) in EtOAc (50 ml) was hydrogenated at atmospheric pressure and r.t. for 60 h in the presence of 10% Pt/C (260 mg). The suspension was filtered through *Celite* and the filtrate evaporated to leave 720 mg (97%) of a colourless oil which, by anal. GC (*SE-52*, 71°) of an aliquot esterified with an Et_2O soln. of CH_2N_2, contained *(1RS,5RS)-2,2,5-trimethylcyclopentane-1-carboxylic acid* (**18**), **17**, and **19** in a ratio of 69:23:8. Subtraction of the ^{1}H-NMR of **17** [1]/**19** from the ^{1}H-NMR of **18**/**17**/**19** enabled the assignement of signals to certain protons of **18**. ^{1}H-NMR (400 MHz, $CDCl_3$): Signals due to **18**: 2.57–2.47 (*m*, H–C(5)); 2.41 (*d*, *J* = 7.1, H–C(1)); 1.95–1.81 (*m*, 2 H); 1.11 (*s*, CH_3–C(2)); 1.08 (*s*, CH_3–C(2)); 1.07 (*d*, *J* = 7.2, [2.52] *s*, CH_3–C(5)).

15. *(1r,2RS,5SR)-1,2,5-Trimethylcyclopentane-1-carboxylic Acid* (**19**). A stirred soln. of **13** (6.14 g, 39.9 mmol) in EtOAc (500 ml) was hydrogenated at atmospheric pressure and r.t. in the presence of 10% Pt/C (2 g) until the expected amount of H_2 (*ca.* 900 ml) was consumed. The suspension was filtered through *Celite* and the filtrate evaporated to leave **19** (5.89 g, 95%) as colourless solid (purity 99%, anal. GC (*SE-52*, 90°) of an aliquot esterified with an Et_2O soln. of CH_2N_2). An anal. sample of **19** was obtained after recrystallisation from pentane at −30° as colourless prisms, m.p. 71–73°. IR ($CHCl_3$): 3600–2200*s* (br.), 1695*s* (C=O), 1455*w*, 1410*w*, 1380*w*, 1295*m*, 1190*w*, 1090*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.56–2.28 (*m*, H–C(2), H–C(5)); 2.00–1.76 (*m*, 2 H); 1.40–1.10 (*m*, 2 H); 0.93 (*d*, *J* = 7.0, CH_3–C(2), CH_3–C(5)); 0.89 (*s*, CH_3–C(1)). ^{13}C-NMR (25.2 MHz, $CDCl_3$): 184.8 (*s*, CO_2H); 54.5 (*s*, C(1)); 43.1 (*d*, C(2), C(5)); 30.7 (*t*, C(3), C(4)); 14.8 (*q*, CH_3–C(2), CH_3–C(5)); 9.1 (*q*, CH_3–C(1)). MS (70 eV): 156 (7, M^+), 141 (41, $M^+ - 15$), 114 (35), 101 (100), 95 (39), 83 (24), 69 (52), 55 (82). Anal. calc. for $C_9H_{16}O_2$ (156.23): C 69.19, H 10.32; found: C 69.16, H 10.31.

16. *Hydrogenation of* **16**. Using the same conditions as in *Exper. 15*, 200 mg (1.19 mmol) of **16** was hydrogenated affording 196 mg (98%) of a colourless oil consisting of *methyl (2RS,5RS)-1,2,5-trimethylcyclopentane-1-carboxylate* (**22**) and its diastereoisomer **20** in a ratio of 61:39 (anal. GC (*SE-52*, 71°)).

17. *Hydrogenation of* **15**. Under the same conditions as in *Exper. 15*, 27 mg (0.18 mmol) of **15** was hydrogenated affording 23 mg (85%) of a colourless solid consisting of *(2*RS,*5*RS*)-1,2,5-trimethylcyclopentane-1-carboxylic acid* (**21**) and its diastereoisomer **19** in a ratio of 63:37 (anal. GC (*SE-52*, 101°)).

18. *(1*RS,*5*SR*)-2,2,5-Trimethylcyclopentane-1-carboxylic Acid* (**17**). To the stirred suspension of NaH (*ca.* 4.8 mmol; obtained by washing 212 mg of a 55–60% dispersion of NaH in oil) in Et_2O (10 ml), was added, at r.t., soln. of a 23:69:8 mixture **17**/**18**/**19** (712 mg, 4.6 mmol; as obtained in *Exper. 14*) in Et_2O (25 ml) and HMPT (5 ml). After 30 min, BuLi (3 ml; *ca.* 4.8 mmol; 1.6 M in hexane) was added at r.t., and the pale red mixture was stirred for 60 min, poured onto ice (70 g), acidified with conc. HCl, and extracted with Et_2O (3 × 30 ml). The Et_2O layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated to give 876 mg of pale yellow oil. Repeated bulb-to-bulb distillation at 130°/14 Torr yielded 593 mg (83%) of a colourless oil which, by GC (*SE-52*, 100°), was shown to be 87% pure. Spectral data of an anal. sample obtained after *Lobar* purification and bulb-to-bulb distillation: identical to the ones described for **17** in [1].

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