Synthesis of novel 3-heterospiro[5.5]undecanes

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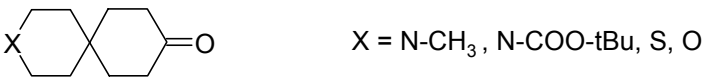
Dedicated to Professor Henk van der Plas on the occasion of his 80th anniversary

Abstract
Synthetic strategies leading to novel 3-heterospiro[5.5]undecan-9-ones are described. Starting from aliphatic 4-substituted heterocyclic aldehydes (1-methyl-4-piperidine carboxaldehyde, 4-formyl-1-piperidinecarboxylic acid 1,1-dimethylethyl ester, 2*H*-tetrahydrothiopyran-4-carboxaldehyde, and 2*H*-tetrahydropyran-4-carboxaldehyde) 3-heterospiro[5.5]undec-7-en-9-ones were made by Robinson annelation and upon further hydrogenation gave the desired 3-heterospiro[5.5]undecan-9-ones.

Keywords: 3-Heterospiro[5.5]undecan-9-one, heterocyclic carboxaldehyde, Robinson annelation, hydrogenation

Introduction

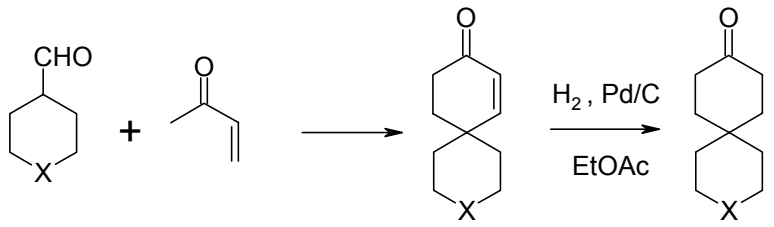
Over the last years, the preparation and reactions of new spirocyclic compounds have been among our major research interests.[1] Within this long-term project the present paper[2] deals with syntheses of novel 3-heterospiro[5.5]undecan-9-ones represented by the general formula of Scheme 1.



Scheme 1

As depicted in Scheme 2 these target systems were obtained by treatment of the appropriate 4-carboxaldehydes with methyl vinyl ketone to give 3-heterospiro[5.5]undec-7-en-9-ones via

Robinson annelation. Hydrogenation of these key intermediates then yielded the desired final products.



X = N-CH_3 , N-COO-tBu, S, O

Scheme 2

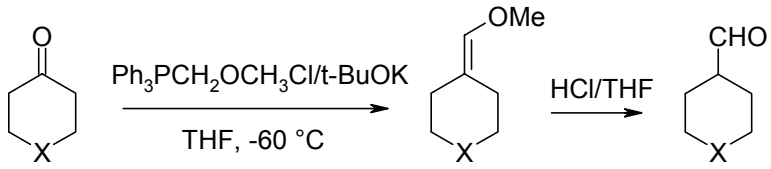
Results and Discussion

Preparation of the heterocyclic 4-carboxaldehydes

Although these products are already known, additional work had to be done to improve the yields to the extent desired for utilizing these compounds as starting materials in ensuing sequences.

1-Methyl-4-piperidinecarboxaldehyde (**3**) was prepared via a new synthetic route starting from 1-methylpiperidin-4-one (**1**). Thus, as depicted in Table 1 (X = N-CH_3) 1-methylpiperidin-4-one (**1**) was subjected to a Wittig reaction with (methoxymethyl)triphenylphosphonium chloride to form the enol ether, 4-(methoxymethylene)-1-methylpiperidine (**2**), which was hydrolyzed in acidic solution to 1-methyl-4-piperidinecarboxaldehyde (**3**) in high overall yield.

Table 1. Syntheses of heterocyclic carboxaldehydes



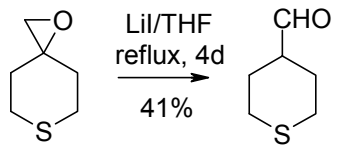
X =	Ketone	Enol ether	Yield (%)	Aldehyde	Yield (%)
N-CH_3	**1**	**2**	79	**3**	87
N-COO- *t*-Bu	**6**	**7**	88	**8**	77
S	**11**	**12**	77	**14**	76

This new pathway showed several advantages over the previously known routes for the preparation of 1-methyl-4-piperidinecarboxaldehyde (**3**), in which the target aldehyde was either

prepared by selective reduction of a piperidinecarboxylic ester with DIBAL-H,[3] or via a lengthy route starting from pyridinecarboxaldehyde.[4] The most important features of our reaction sequence are its shortness and the fact that the intermediate product, 4-(methoxymethylene)-1-methylpiperidine (**2**), was sufficiently stable to be stored in a freezer over a longer period of time (whereas 1-methyl-4-piperidinecarboxaldehyde (**3**) shows significant instability upon isolation). Furthermore, 4-(methoxymethylene)-1-methylpiperidine (**2**) not only can be produced on a larger scale, but also allows smooth separation from the Wittig by-product, triphenylphosphine, through sophisticated workup.[5]

4-Formyl-1-piperidinecarboxylic acid- 1,1-dimethylethyl ester (**8**) was prepared in a similar way according to the patent literature,[6] *i.e.*, starting from 4-oxo-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (**6**)[7] via the enol ether intermediate which was accessible by a Wittig reaction (Table 1, X = N-COO-*t*-Bu).

2*H*-Tetrahydrothiopyran-4-carboxaldehyde (**14**) proved to be difficult to synthesize. In our first attempts the aldehyde was prepared in analogy to the piperidines by the Wittig reaction route (Table 1, X = S). Although this sequence was already described in the patent literature,[8] and each of the two steps gave yields of approx. 76%, it turned out to be not very attractive (owing to the lengthy isolation of 4-methoxymethylene-2*H*-tetrahydrothiopyran (**12**), the handling of unpleasant- smelling compounds, and difficult separation of the enol ether from the Wittig by-product triphenylphosphine). So, a different route for the preparation of 2H-tetrahydrothiopyran-4-carboxaldehyde (**14**) was envisaged. The preparation of aldehydes through Lewis- acid- promoted rearrangement of a spiro oxirane is a known procedure, but attempts to rearrange 1-oxa-6-thiaspiro[2.5]octane (**13**)[9] by using the usual Lewis acids (*e.g.*, boron trifluoride etherate, zinc chloride, or magnesium bromide etherate) did not yield the desired product. In most cases **13** was recovered, or - under more vigorous reaction conditions - only decomposition was observed.

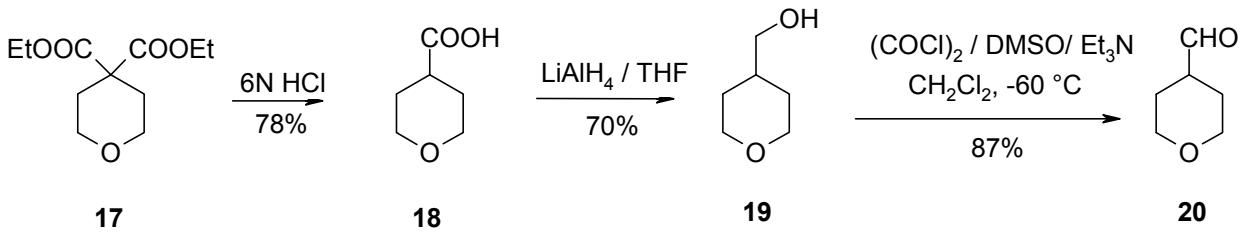


13 **14**

Scheme 3

After detailed experimental studies appropriate reaction conditions could be developed: lithium iodide (highly concentrated, and used in a large excess, in dry THF) was found to be the only Lewis- type acid for promoting the rearrangement of 1-oxa-6-thiaspiro[2.5]octane (**13**) to 2H-tetrahydrothiopyran-4-carboxaldehyde (**14**) in a reasonable yield. Additionally, the yield could be improved remarkably by use of a Soxhlet apparatus, from which lithium iodide was gradually washed into the reaction vessel.

2*H*-Tetrahydropyran-4-carboxaldehyde (**20**)[10] was accessed via a different synthetic approach, using 4H-tetrahydropyran-4,4-dicarboxylic acid diethyl ester (**17**),[11] readily available from bis-(2-chloroethyl)ether and diethyl malonate as the initial starting materials. The following saponification/decarboxylation sequence towards 2H-tetrahydropyran-4-carboxylic acid (**18**) has been described with-[12] or without-[13] isolation of the intermediate dicarboxylic acid. We have developed a modified one-pot procedure by refluxing **17** with 6M aq. HCl followed by removal of ethanol by distilling it off as ethanol/water azeotrope, in order to gain a higher reflux temperature in the reaction mixture to promote decarboxylation.



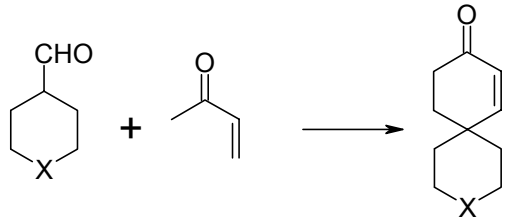
Scheme 4

The reduction of 2*H*-tetrahydropyran-4-carboxylic acid (**18**) by lithium aluminum hydride according to a known method[14] gave 2*H*-tetrahydropyran-4-methanol (**19**). Subsequent Swern oxidation[15] using a procedure with modified stoichiometry yielded the desired 2*H*-tetrahydro-pyran-4-carboxaldehyde (**20**).

Robinson annelation to 3-heterospiro[5.5]undec-7-en-9-ones

This reaction step, consisting of a condensation and an ensuing Michael-type addition, was carried out under basic conditions using Triton B solution[16] in all cases, except for preparing 3-oxaspiro[5.5]undec-7-en-9-one (**21**). The latter was obtained in higher yield using phosphoric acid as catalyst. It turned out that under these conditions the formation of difficultly separable by-products was diminished, although the conversion of the starting aldehyde was not complete.

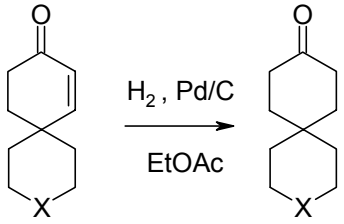
Table 2. Robinson annelation



Enone	X =	Catalyst	Solvent	Yield (%)
4	N-CH_3	Triton B	*t*-BuOH	50
9	N-COO-*t*-Bu	Triton B	*t*-BuOH	60
15	S	Triton B	*t*-BuOH	47
21	O	H_3PO_4	Benzene	72

Hydrogenation reaction. This step was straightforward for all spiro ketones, which could be obtained in high yields. The hydrogenation had to be performed in ethyl acetate as solvent in order to avoid possible ketalization, which might occur on performing the reaction in the commonly used solvent methanol.[17] The hydrogenation was mostly done at ambient temperature, except for the synthesis of 3-thiaspiro[5.5]undecan-9-one (**16**), where an elevated temperature together with a larger amount of hydrogenation catalyst and longer reaction time was required for complete conversion in order to overcome the catalyst- poisoning exhibited by the sulfur atom.

Table 3. Hydrogenation of enones



Ketone	X =	Reaction conditions	Yield (%)
5	N-CH_3	4.5 bar, 18h, ambient temperature	91
10	N-COO-*t*-Bu	4.5 bar, 18h, ambient temperature	84
16	S	4.5 bar, 8d, 50 °C	91
22	O	4.5 bar, 18h, ambient temperature	81

The title compounds obtained are of interest as synthetic building blocks in heterocyclic chemistry and are currently being investigated as intermediates for the synthesis of pharmaceutically relevant substituents.

Experimental Section

General Procedures. THF was purified by distillation from sodium/benzophenone: methylene chloride was distilled from P_2O_5. Silica gel (0.040-0.063 mm) was purchased from Merck. (Methoxymethyl)triphenylphosphonium chloride and 1-methylpiperidin-4-one (**1**) were purchased from Aldrich, methyl vinyl ketone and potassium tert-butoxide were purchased from Fluka. 4-Oxo-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (**6**),[7] 4*H*-tetrahydrothiopyran-4-one (**11**),[18] 1-oxa-6-thiaspiro[2.5]octane (**13**),9 and 4H-tetrahydropyran-4,4-dicarboxylic acid diethyl ester (**17**)1[1] were prepared according to known methods. The synthesis of 3-methyl-3-azaspiro[5.5]undecan-9-one (**5**) by the present method has already been described by a former member of our group in a Chinese journal.[19] 9-Oxo-3-azaspiro[5.5]undecane-3-carboxylic acid 1,1-dimethylethyl ester (**10**) has been mentioned in recent patent literature, without physical data.[20]

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC-200 FT-NMR spectrometer. Melting points were determined on a Kofler hot stage and are uncorrected. Elemental analyses were performed at the Microanalytical Laboratory of the Institute of Physical Chemistry at the University of Vienna.

4-(Methoxymethylene)-1-methylpiperidine (2). A solution of potassium tert-butoxide (31.76 g, 283 mmol) in dry THF (250 ml) was added to a well stirred suspension of (methoxymethyl)triphenylphosphonium chloride (97%, 100 g, 283 mmol) in anhydrous THF (250 ml) at -20 °C under nitrogen, and the resulting dark red mixture was stirred for 90 min at -20 °C. Then it was cooled to -60 °C and a solution of 1-methylpiperidin-4-one (**1**) (26.71 g, 236 mmol) in dry THF (250 ml) was added, at which the reaction mixture turned yellow-orange. Stirring was continued for 2 h at -60 °C, then the temperature was allowed to rise and stirring was continued for another 16 h at ambient temperature. After hydrolysis, the organic layer was separated and the aqueous phase extracted with diethyl ether. The combined organic phases were extracted exhaustively with 8% acetic acid, and the organic layer containing only triphenylphosphine oxide was discarded. The combined aqueous layers were made alkaline with 20% sodium hydroxide solution and extracted exhaustively with diethyl ether. The combined organic phases were dried over anhydrous magnesium sulfate and filtered, and the solvent evaporated. The residue was distilled under reduced pressure to give a colorless liquid (26.25 g, 79%, storage in a freezer is recommended). bp 72-73 °C/16 mbar; η_D^{20} = 1.4749; ^{1}H-NMR ($CDCl_3$): 5.77 (s, 1H, =CH-O-), 3.52 (s, 3H, -O-CH_3), 2.33 (t, 2H, H3, *J* = 5.3 Hz), 2.31 (s, 4H, H2, H6), 2.24 (s, 3H, -N-CH_3), 2.06 (t, 2H, H5, *J* = 5.3 Hz); ^{13}C-NMR ($CDCl_3$): 139.7 (d, =CH-O-), 114.0 (s, C4), 59.3 (q, -O-CH_3), 57.3, 56.1 (2t, C2, C6), 46.4 (q, -N-CH_3), 29.7 (t, C5), 25.1 (t, C3). Anal. Calcd for $C_8H_{15}NO$ (141.21): C, 68.04; H, 10.71; N, 9.92; Found: C, 68.10; H, 10.92; N, 10.07.

1-Methyl-4-piperidinecarboxaldehyde (3). Concentrated hydrochloric acid (6.5 ml) was added to a solution of 4-(methoxymethylene)-1-methylpiperidine (**2**) (10.0 g, 70.8 mmol) in THF (130 ml) and stirred for one hour. The lower layer was made alkaline with 20% sodium hydroxide

solution and extracted with diethyl ether; the upper layer was concentrated, made alkaline with 20% sodium hydroxide solution, and extracted with diethyl ether. The combined ethereal layers were dried over anhydrous magnesium sulfate, filtered, and the solvent was distilled off at atmospheric pressure. The resulting yellow liquid was distilled under reduced pressure to give a moderately stable colorless liquid (7.82 g, 87%), bp 60-62 °C/8 mbar (lit.[21] bp 62 °C/5 Torr). ^{1}H-NMR ($CDCl_3$): 9.64 (s, 1H, -CHO), 2.75 (ddd, 2H, H-2_{eq}, H-6_{eq}, J_{AB} = 11.7 Hz, $^3J(eq, ax)$ = $^3J(eq, eq)$ = 4.0 Hz), 2.26 (s, 3H, -N-CH_3), 2.20 (m, 1H, H4, $^3J(H\text{-}4, ax)$ = 10.5 Hz), 2.06 (ddd, 2H, H-2_{ax}, H-6_{ax}, J_{AB} = 11.7 Hz, $^3J(ax, ax)$ = 10.4 Hz, $^3J(ax, eq)$ = 2.7 Hz), 1.88 (dddd, 2H, H-3_{eq}, H-5_{eq}, $^3J(eq, eq)$ = 4.0 Hz, $^3J(eq, ax)$ = 2.7 Hz), 1.71 (dddd, 2H, H-3_{ax}, H-5_{ax}, $^3J(H4, ax)$ = 10.5 Hz, $^3J(ax, ax)$ = 10.4 Hz, $^3J(ax, eq)$ = 3.6 Hz); ^{13}C-NMR ($CDCl_3$): 203.7 (d, -CHO), 54.4 (t, C2, C6), 47.2 (d, C4), 46.3 (q, -N-CH_3), 25.3 (t, C3, C5).

3-Methyl-3-azaspiro[5.5]undec-7-en-9-one (4). Methyl vinyl ketone (8.62 g, 123 mmol) was added to a solution of 1-methyl-4-piperidinecarboxaldehyde (**3**) (7.82 g, 61.5 mmol) in dry *t*-butanol (150 ml) at 15 °C, under nitrogen. Then Triton-B (40% in methanol, 16.71 g, 40 mmol) was added, causing a spontaneous rise of temperature to 40 °C. Stirring at ambient temperature was continued for 1 h, then the red reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with saturated sodium bicarbonate solution twice, and concentrated. Then 8% acetic acid was added and the solution washed with ethyl acetate. The aqueous phase was made alkaline with 20% sodium hydroxide solution, and extracted with ethyl acetate. After addition of charcoal, drying over anhydrous sodium sulfate, and filtration, the solvent was distilled off. The resulting brown oil was chromatographed over silica gel (impregnated with triethylamine, eluent methanol: ethyl acetate = 1:10), and the crude product was subjected to Kugelrohr distillation under reduced pressure to give a colorless oil (5.53 g, 50%). bp 80-90 °C/0.04 Torr; ^{1}H-NMR ($CDCl_3$): 6.82 (d, 1H, H7, J = 10.2 Hz), 5.91 (d, 1H, H8, J = 10.2 Hz), 2.45 (m, 4H, H2, H4), 2.43 (t, 2H, H10, J = 6.7 Hz), 2.31 (s, 3H, -N-CH_3), 1.92 (t, 2H, H11, J = 6.7 Hz), 1.70 (m, 4H, H1, H5); ^{13}C-NMR ($CDCl_3$): 199.3 (s, C9), 157.3 (d, C7), 127.7 (d, C8), 51.1 (t, C2, C4), 46.2 (q, -N-CH_3), 35.2 (t, C1, C5), 33.4 (t, C10), 33.0 (s, C6), 32.5 (t, C11).

3-Methyl-3-azaspiro[5.5]undecan-9-one (5). A solution of 3-methyl-3-azaspiro[5.5]undec-7-en-9-one (**4**) (0.91 g, 5.1 mmol) in ethyl acetate (200 ml) was shaken with palladium on charcoal (0.1 g) under hydrogen (4.5 bar, 18 h, ambient temperature). The catalyst was filtered off over Hyflo, washed with ethyl acetate and the solvent was evaporated. The resulting oil was subjected to Kugelrohr distillation at reduced pressure to give colorless crystals (0.84 g, 91%). bp 80 °C/0.02 Torr, mp 55-60 °C; ^{1}H-NMR ($CDCl_3$): 2.45 (t, 4H, H2, H4, J = 5.6 Hz), 2.33 (t, 4H, H8, H10, J = 6.9 Hz), 2.33 (s, -N-CH_3), 1.74 (t, 4H, H7, H11, J = 6.9 Hz), 1.66 (t, 4H, H1, H5, J = 5.6 Hz); ^{13}C-NMR ($CDCl_3$): 211.9 (s, C9), 51.4 (t, C2, C4), 46.1 (q, -N-CH_3), 36.8 (t, C8, C10), 35.5 (t, C7, C11), 34.9 (t, C1, C5), 29.1 (s, C6); Anal. Calcd for $C_{11}H_{19}NO$ (181.28): C, 72.88; H, 10.56; N, 7.73; Found: C, 72.75; H, 10.61; N, 7.67.

9-Oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylic acid 1,1-dimethylethyl ester (9). Methyl vinyl ketone (1.68 g, 24 mmol) was added to a solution of 4-formyl-1-piperidinecarboxylic acid 1,1-dimethyl ethyl ester (**8**) (2.57 g, 12 mmol) in dry *t*-butanol (30 ml) at 15 °C under nitrogen atmosphere. Then Triton-B (40% in methanol, 3.26 g, 7.8 mmol) was added, causing a spontaneous rise of the temperature to 35 °C. Stirring at ambient temperature was continued for 1 h, then the red reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic phases were washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, filtered, and evaporated. The resulting brown oil was chromatographed over silica gel (impregnated with triethylamine, eluent: petroleum/ethyl acetate = 2:1) and the crude product was triturated with petroleum/ether to give a colorless powder (1.91 g, 60%). mp 90-94 °C; bp 110-120 °C/0.02 Torr; ^{1}H-NMR ($CDCl_3$): 6.77 (d, 1H, H7, J = 10.2 Hz), 5.92 (d, 1H, H8, J = 10.3 Hz), 3.48 (ddd, 2H, H-2a, H-4a, J_{AB} = 13.7 Hz, ^3J = 6.6 Hz, ^3J = 4.4 Hz), 3.41 (ddd, 2H, H-2b, H-4b, J_{AB} = 13.7 Hz, ^3J = 7.6 Hz, ^3J = 4.2 Hz), 2.43 (t, 2H, H10, J = 6.7 Hz), 1.93 (t, 2H, H11, J = 6.7 Hz), 1.56 (m, 4H, H1, H5), 1.43 (s, 9H, -C(CH_3)$_3$); ^{13}C-NMR ($CDCl_3$): 198.9 (s, C9), 156.0 (d, C7), 154.6 (s, -CO-O-), 128.2 (d, C8), 79.5 (s, -O-tert C), 39.3 (t, C2, C4), 34.8 (t, C1, C5), 33.9 (s, C6), 33.3 (t, C10), 31.9 (t, C11), 28.2 (q, -CH_3); Anal. Calcd for $C_{15}H_{23}NO_3$ (265.35): C, 67.90; H, 8.74; N, 5.28; Found: C, 67.69; H, 9.04; N, 5.43.

9-Oxo-3-azaspiro[5.5]undecane-3-carboxylic acid 1,1-dimethylethyl ester (10). A solution of 9-oxo-3-azaspiro[5.5]undec-7-ene-3-carboxylic acid 1,1-dimethylethyl ester (**9**) (2.0 g, 7.5 mmol) in ethyl acetate (200 ml) was shaken with palladium on charcoal (0.45 g) under hydrogen (4.5 bar, 18 h, ambient temperature). The catalyst was filtered off over Hyflo, washed with ethyl acetate, and the solvent was evaporated. The resulting oil was subjected to Kugelrohr distillation at reduced pressure to give colorless crystals (1.70 g, 84%). mp 70-73 °C; bp 120 °C/0.02 Torr; ^{1}H-NMR ($CDCl_3$): 3.44 (t, 4H, H2, H4, J = 5.8 Hz), 2.35 (t, 4H, H8, H10, J = 6.9 Hz), 1.76 (t, 4H, H7, H11, J = 6.9 Hz), 1.55 (t, 4H, H1, H5, J = 5.8 Hz), 1.46 (s, 9H, -C(CH_3)$_3$); ^{13}C-NMR ($CDCl_3$): 211.5 (s, C9), 154.7 (s, -CO-O-), 79.4 (s, -O-tert C), 39.6 (t, C2, C4), 36.8 (t, C8, C10), 35.1, 34.7 (2t, C1, C5, C7, C11), 30.7 (s, C6), 28.3 (q, -CH_3); Anal. Calcd for $C_{15}H_{25}NO_3$ (267.37): C, 67.38; H, 9.42; N, 5.24; Found: C, 67.17; H, 9.51; N, 5.09.

2*H*-Tetrahydrothiopyran-4-carboxaldehyde (14). The synthesis of this compound via the enol ether route has been described previously.[8] Alternatively, **14** was prepared by refluxing 1-oxa-6-thiaspiro[2.5]octane (**13**) (5 g, 38.4 mmol) in a solution of lithium iodide (25 g, 185 mmol) in anhydrous THF (300 ml). For this purpose, the lithium iodide was placed in a Soxhlet extractor and gradually washed into the reaction by refluxing solvent. After four days of reflux the dark brown reaction mixture was cooled, water was added, and the reaction mixture was concentrated. The dark brown residue consisting of two phases was extracted exhaustively with methylene chloride. The organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated. The resulting red-brown oil was subjected to Kugelrohr distillation to yield a colorless liquid (2.04 g, 41%). bp 100-101 °C/18 mbar; ^{1}H-NMR ($CDCl_3$): 9.60 (s, 1H, -CHO), 2.68 (m, 4H, H-2, H-6), 2.27 (m, 3H, H-3a, H-4, H-5a), 1.78 (m, 2H, H-3b, H5-b); ^{13}C-NMR ($CDCl_3$): 203.1 (d, -CHO), 49.1 (d, C-4), 27.4, 27.0 (2 t, C-2, C-3, C-5, C-6).

3-Thiaspiro[5.5]undec-7-en-9-one (15). Methyl vinyl ketone (1.59 g, 22.7 mmol) was added to a solution of 2H-tetrahydrothiopyran-4-carboxaldehyde (**14**) (1.48 g, 11.4 mmol) in dry *t*-butanol (30 ml) at 15 °C under nitrogen atmosphere. Then Triton-B (40% in methanol, 3.09 g, 7.4 mmol) was added, causing a spontaneous rise of the temperature to 33 °C. Stirring at ambient temperature was continued for 1 h, then the red reaction mixture was diluted with water and extracted with diethyl ether (4x). The combined organic phases were washed with 8% acetic acid (2x), water (2x), and brine (2x), dried over anhydrous sodium sulfate, filtered, and evaporated. The resulting yellow-brown oil was subjected to Kugelrohr distillation under reduced pressure and the resulting colorless oil (0.98 g, 47%) crystallized upon storage in the freezer. bp 70-80 °C/0.04 Torr; mp 36-41 °C; ^{1}H-NMR ($CDCl_3$): 6.77 (d, 1H, H7, J = 10.3 Hz), 5.93 (d, 1H, H8, J = 10.3 Hz), 2.67 (m, 4H, H2, H4), 2.44 (t, 2H, H10, J = 6.7 Hz), 1.94 (t, 2H, H11, J = 6.7 Hz), 1.88 (m, 4H, H1, H5); ^{13}C-NMR ($CDCl_3$): 198.9 (s, C9), 156.6 (d, C7), 128.0 (d, C8), 36.3 (t, C1, C5), 34.3 (s, C6), 33.0 (t, C10), 31.9 (t, C11), 23.2 (t, C2, C4). Anal. Calcd for $C_{10}H_{14}OS$ (182.28): C, 65.89; H, 7.74; Found: C, 66.11; H, 7.79.

3-Thiaspiro[5.5]undecan-9-one (16). A solution of 3-thia-spiro[5.5]undec-7-en-9-one (**15**) (1.39 g, 7.6 mmol) in ethyl acetate (200 ml) was shaken with palladium on charcoal (0.8 g) under hydrogen pressure (4.5 bar, 50 °C, 8 d). The catalyst was filtered off using Hyflo, washed with ethyl acetate, and the solvent was evaporated. The resulting yellow oil was subjected to Kugelrohr distillation at reduced pressure to give a colorless oil (1.28 g, 91%). bp 140-150 °C/15 mbar; ^{1}H-NMR ($CDCl_3$): 2.65 (m, 4H, H2, H4), 2.33 (t, 4H, H8, H10, J = 7.0 Hz), 1.83 (m, 4H, H1, H5), 1.74 (t, 4H, H7, H11, J = 7.0 Hz); ^{13}C-NMR ($CDCl_3$): 211.5 (s, C9), 36.5, 36.3, 35.3 (3t, C1, C5, C7, C8, C10, C11), 30.9 (s, C6), 23.5 (t, C2, C4); Anal. Calcd for $C_{10}H_{16}OS$ (184.30): C, 65.17; H, 8.75; Found: C, 65.46; H, 8.83.

2*H*-Tetrahydropyran-4-carboxylic acid (18). 4*H*-Tetrahydropyran-4,4-dicarboxylic acid di-ethyl ester (**17**) (23.0 g, 100 mmol) was heated under refluxed in 6*N* hydrochloric acid (150 ml) for 16 h. As soon as the reaction mixture had turned into a clear solution, indicating complete saponification of the diester, heating was increased and ethanol/water azeotrope was distilled off over a Dean-Stark trap until complete removal of ethanol. After cooling of the reaction mixture and exhaustive extraction with diethyl ether, the organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was recrystallized from methylene chloride/petroleum to yield colorless crystals (10.17 g, 78%). mp 87-89 °C (lit.[20] 88 °C); bp 145-150 °C/18 mbar (lit.[22] 152-154 °C/20 Torr); ^{1}H-NMR ($CDCl_3$): 10.45 (bs, 1H, -OH), 3.97 (ddd, 2H, H-2$_{eq}$, H-6$_{eq}$, J_{AB} = 11.6 Hz, $^3J(eq, ax) = {}^3J(eq, eq)$ = 3.7 Hz), 3.46 (ddd, 2H, H-2$_{ax}$, H-6$_{ax}$, J_{AB} = 11.6 Hz, $^3J(ax, ax)$ = 10.1 Hz, $^3J(ax, eq)$ = 3.5 Hz), 2.57 (dddd, 1H, H-4, $^3J(ax, ax)$ = 10.0 Hz, $^3J(ax, eq)$ = 5.0 Hz), 1.80 (m, 4H, H-3, H-5); ^{13}C-NMR ($CDCl_3$): 180.1 (s, -COOH), 66.8 (t, C2, C6), 39.6 (d, C4), 28.2 (t, C3, C5).

2*H*-Tetrahydropyran 4-carboxaldehyde (20). A solution of oxalyl choride (6.98 g, 55 mmol) in anhydrous methylene chloride (125 ml) was cooled to -60 °C with stirring, under a nitrogen atmosphere. A solution of anhydrous DMSO (4.30 g, 55 mmol) in dry methylene chloride (25 ml) was added dropwise within 5 min and stirred at -60 °C for 10 min. A solution of 2H-tetra-

hydropyran-4-methanol (**19**) (5.81 g, 50 mmol) in dry methylene chloride (50 ml) was added dropwise within 5 min and the reaction mixture was stirred at -60 °C for 15 min. Then triethylamine (25.3 g, 250 mmol) was added within 5 min at -60 °C and stirring was continued at the same temperature for 10 min before the reaction mixture was allowed to warm up to ambient temperature. The reaction mixture was diluted with water and stirred for 10 min. The phases were separated and the aqueous phase extracted with methylene chloride. The combined organic phases were dried over magnesium sulfate, filtered, and the solvent evaporated. The crude product was distilled under reduced pressure to yield a colorless liquid (5.06 g, 87%). bp 67 °C/11 mbar (lit.[23] bp 74-77 °C/11 Torr); ^{1}H-NMR ($CDCl_3$): 9.62 (s, 1H, -CHO), 3.94 (ddd, 2H, H-2_{eq}, H-6_{eq}, J_{AB} = 11.6 Hz, $^3J(eq, ax) = {}^3J(eq, eq)$ = 3.9 Hz), 3.48 (ddd, 2H, H-2_{ax}, H-6_{ax}, J_{AB} = 11.6 Hz, $^3J(ax, ax)$ = 10.3 Hz, $^3J(ax, eq)$ = 2.9 Hz), 2.49 (dddd, 1H, H4, $^3J(ax, ax)$ = 10.4 Hz, $^3J(ax, eq)$ = 4.4 Hz), 1.84 (m, 2H, H-3_{eq}, H-5_{eq}, J_{AB} = 13.6 Hz), 1.70 (dddd, 2H, H-3_{ax}, H-5_{ax}, J_{AB} = 13.6 Hz, $^3J(ax, ax) = {}^3J(ax, H4)$ = 10.4 Hz, $^3J(ax, eq)$ = 4.2 Hz); ^{13}C-NMR ($CDCl_3$): 202.8 (d, -CHO), 66.6 (t, C2, C6), 46.8 (d, C4), 25.6 (t, C3, C5).

3-Oxaspiro[5.5]undec-7-en-9-one (21). 2*H*-Tetrahydropyran-4-carboxaldehyde (**20**) (4.56 g, 40 mmol), methyl vinyl ketone (5.61 g, 80 mmol) and phosphoric acid (2 ml) were heated at reflux in anhydrous benzene (150 ml) for 5 h. After cooling of the dark brown reaction mixture saturated sodium bicarbonate solution was added and shaken. The aqueous phase was extracted exhaustively with ethyl acetate. The combined organic phases were dried over magnesium sulfate, filtered, and evaporated. Starting material was distilled off at 11 mbar and the residue was subjected to Kugelrohr distillation under reduced pressure to give a colorless liquid (3.40 g, 72%) which solidified on storage in a freezer. bp 70 °C/0.02 Torr; mp 40-45 °C; ^{1}H-NMR ($CDCl_3$): 6.89 (d, 1H, H7, J = 10.3 Hz), 5.95 (d, 1H, H8, J = 10.3 Hz), 3.75 (t, 4H, H2, H4, J = 5.4 Hz), 2.46 (t, 2H, H10, J = 6.7 Hz), 2.00 (t, 2H, H11, J = 6.7 Hz), 1.69 (ddd, 2H, H-1a, H-5a, J_{AB} = 13.6 Hz, ^3J = 5.4 Hz), 1.63 (ddd, 2H, H-1b, H-5b, J_{AB} = 13.6 Hz, ^3J = 5.4 Hz); ^{13}C-NMR ($CDCl_3$): 199.1 (s, C9), 156.3 (d, C7), 128.1 (d, C8), 63.5 (t, C2, C4), 35.6 (t, C1, C5), 33.3 (t, C10), 33.2 (s, C6), 32.9 (t, C11). Anal. Calcd for $C_{10}H_{14}O_2$ (166.22): C, 72.26; H, 8.49. Found: C, 71.95; H, 8.77.

3-Oxaspiro[5.5]undecan-9-one (22). A solution of 3-oxaspiro[5.5]undec-7-en-9-one (**21**) (2.20 g, 13.2 mmol) in ethyl acetate (200 ml) was shaken with palladium on charcoal (0.45 g) under hydrogen pressure (4.5 bar, 18 h, ambient temperature). The catalyst was filtered off over Hyflo, the solution washed with ethyl acetate, and the solvent was evaporated. The resulting oil was subjected to Kugelrohr distillation at reduced pressure to give a colorless oil (1.80 g, 81%). bp 100-110 °C/16 mbar; ^{1}H-NMR ($CDCl_3$): 3.70 (t, 4H, H2, H4, J = 5.4 Hz), 2.33 (t, 4H, H8, H10, J = 6.9 Hz), 1.80 (t, 4H, H7, H11, J = 6.9 Hz), 1.60 (t, 4H, H1, H5, J = 5.4 Hz); ^{13}C-NMR ($CDCl_3$): 211.5 (s, C9), 63.6 (t, C2, C4), 36.7 (t, C8, C10), 35.5 (t, C1, C5, C7, C11), 30.0 (s, C6). Anal. Calcd for $C_{10}H_{16}O_2$ (168.24): C, 71.39; H, 9.59. Found: C, 71.25; H, 9.60.

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