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SYNTHESIS OF *SPIRO*-ANNELATED ISOCHROMANONES BY RING EXPANSION OF BENZOCYCLOBUTENONES IN THE PRESENCE OF LITHIUM DIISOPROPYLPHOSPHIDE

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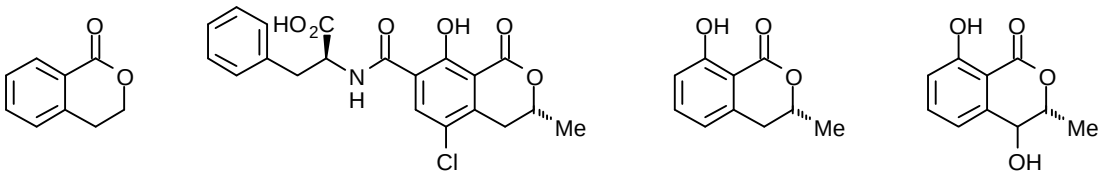
Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

Abstract – *spiro*-Annelated isochromanones are prepared by treatment of benzocyclobutenone with lithium diisopropylphosphide – borane adduct (LDP-BH_3), which is easily accessible by metalation of the air stable diisopropylphosphane-borane adduct. The reaction takes place at very mild reaction conditions and involves an oxyanion driven ring opening. As a substituted example the synthesis of the first trifluoromethyl-substituted isochromanone derivative is reported.

INTRODUCTION

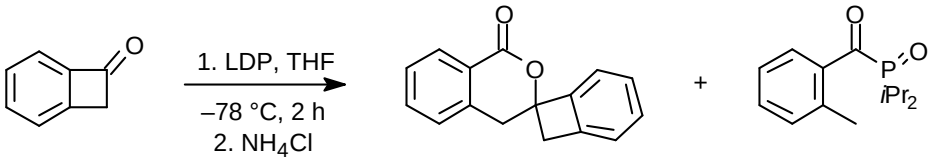
A number of derivatives of isochromanone (**1**) have been described in the literature because of their biological activities.[1, 2] For example, the nephrotoxin ochratoxin A (**2**) has been isolated from *Aspergillus ochraceus* and was shown to be carcinogenic to mice and rats.[3] Mellein (**3**) and 4-hydroxymellein (**4**) have been isolated from *Aspergillus oniki*, from *Aspergillus ochraceus* and were shown to have LD_{50} values of 250-500 and 1000-1500 mg/kg in intraperitoneally injected mice, respectively.[4-6]



1 **2** **3** **4**

Scheme 1. Selected isochromanone natural products

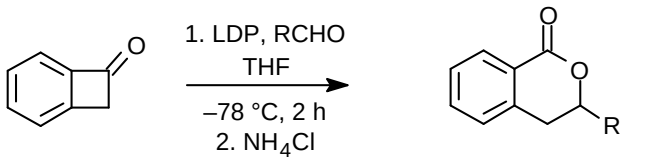
Although there are some methods for the synthesis of isochromanone derivatives known,[7-11] there are only few allowing for a control of the configuration of C-3.[9, 12, 13] We recently reported an isochromanone synthesis starting from benzocyclobutenone (**5**). Treatment of **5** with lithium diisopropylphosphide (LDP) at –78 °C afforded a 79 % yield of *spiro*-annelated isochromanone **6** in addition to acylphosphane oxide **7**, which was isolated in 14 % yield.[14] Obviously the key reaction step is the nucleophilic attack of LDP at the carbonyl group of **5** followed by an oxyanion driven ring opening.



5 **6** (79 %) **7** (14 %)

Scheme 2. *spiro*-Annelated isochromanone **6** from benzocyclobutenone (**5**)

While the formation of **6** is a reaction of two molecules of **5**, high dilution reaction conditions allowed the reaction of **5** with aldehydes resulting in 3-substituted isochromanones **8** and **9**.[14]

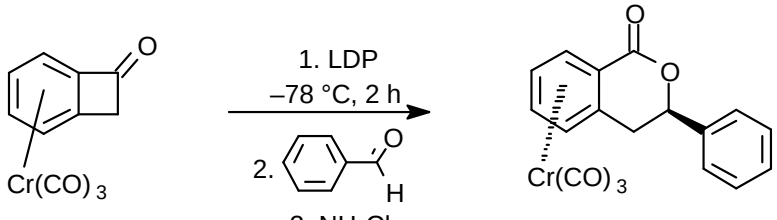


5

8 (R = *p*-O_2NPh, 78 %)
9 (R = Pr, 57 %)

Scheme 3. 3-Substituted isochromanones **8** and **9** from benzocyclobutenone (**5**)

In addition, we reported a diastereoselective ring expansion starting from (benzocyclobutenone)-tricarbonylchromium (**10**), which led to *exo*-3-phenylisochromanone complex **11** as the only isolated product in 55 % yield (Scheme 4). As **10** is planar chiral and available in enantiomerically pure form, and because oxidative decomplexation of tricarbonylchromium complexes is a routine operation usually affording the organic ligand in quantitative yield, the sequence gives access to enantiomerically pure 3-phenylisochromanone, which has some antifungal activity.[14]



10 **11**

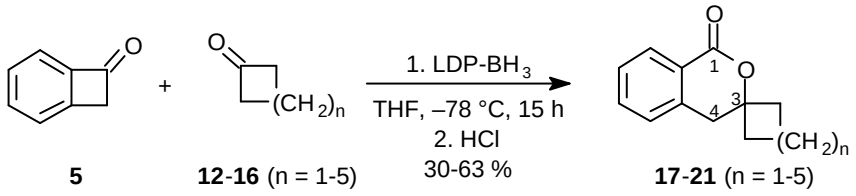
Scheme 4. Diastereoselective synthesis of 3-phenylisochromanone complex **11** from **10**

RESULTS AND DISCUSSION

While numerous isochromanone derivatives with a variety of substitution patterns have been prepared, the synthesis of representatives having a *spiro*-annelation at C-3 has not yet been systematically investigated. Kanda reported a comparatively lengthy synthesis of the *spiro* cyclohexyl substituted derivative,[15] and Dominguez achieved a similar synthesis of the cyclopentane analogue.[16] We felt that a synthesis starting from benzocyclobutenone (**5**) and cycloalkanones might be a feasible way to these derivatives. Here we report the synthesis of some derivatives by this route. In addition, we present LDP-BH_3 as a more user friendly alternative to the usual LDP.[17]

In analogy to earlier work by Imamoto[18] a solution of chlorodiisopropylphosphane was treated with a borane-THF complex solution in THF at 0 °C. Subsequent reduction with lithium aluminum hydride afforded the lithium diisopropylphosphide-borane adduct as an air stable clear liquid in 93 % yield.[17] Treatment of the adduct with butyllithium at 0 °C gave LDP-BH_3, which was used *in situ* for the syntheses of *spiro*-annelated isochromanones from benzocyclobutenone (**5**).

When a highly diluted, –78 °C cold solution of benzocyclobutenone (**5**) was slowly added over 2 h to a –78 °C cold solution of LDP-BH_3 in THF the ring opening reaction to the borane stabilized benzylic phosphacyl anion is achieved without formation of the *spiro*-annelated dimer **6**. Addition of 1.2 equiv. of a diluted THF solution of the respective cycloalkanone **12-16** over 30 min and subsequent warming of the reaction mixture to 25 °C over 14 h afforded after chromatographic purification the respective *spiro*-annelated isochromanones **17**-**21** in 30-63 % yield (Scheme 5, Table 1).



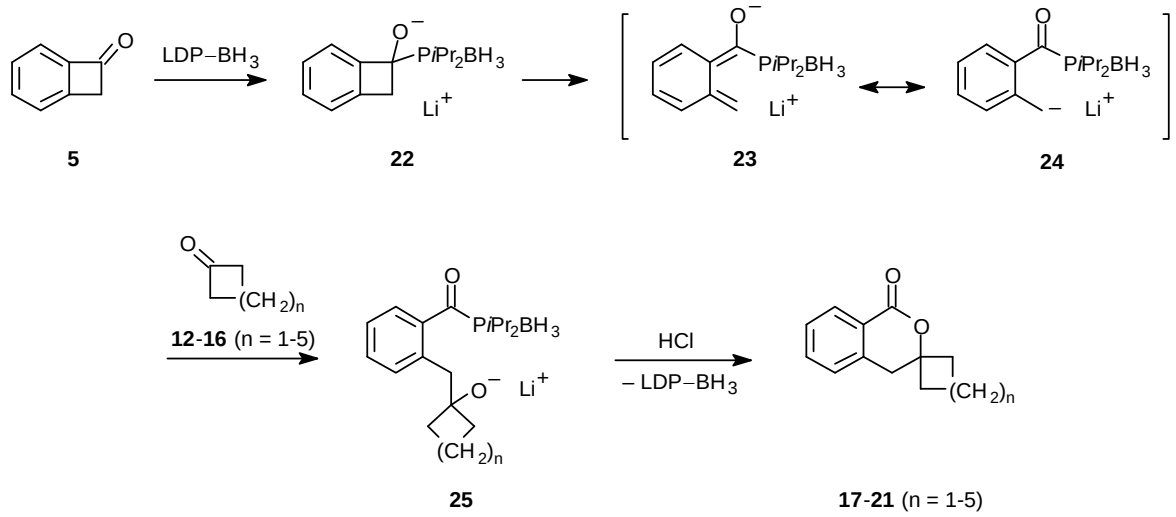
5 **12**-**16** (n = 1-5) **17**-**21** (n = 1-5)

Scheme 5. *spiro*-Annelated isochromanones from benzocyclobutenone (**5**) and cycloalkanones

Table 1. *spiro*-Annelated isochromanones from benzocyclobutenone (**5**)

n	Cycloalkanone	*spiro*-Annelated isochromanone	Yield [%]
1	cyclobutanone	**17**	63
2	cyclopentanone	**18**	53
3	cyclohexanone	**19**	54
4	cycloheptanone	**20**	52
5	cyclooctanone	**21**	30

The reaction mechanism (Scheme 6) most likely includes a nucleophilic attack of the LDP-BH_3 at benzocyclobutenone (**5**) with formation of **22**. A subsequent oxyanion driven ring opening accounts for the intermediacy of benzylic anion, for which two resonance formulas **23** and **24** are given. Nucleophilic attack of intermediate **23** at the cycloalkanone carbonyl carbon atom results in the formation of alkoxide **25**, which causes ring closure by attack at the acylphosphane carbon atom with release of LDP-BH_3 yielding **17**-**21**.



Scheme 6. Presumed mechanism for the formation of *spiro*-annelated isochromanones from benzocyclobutenone (**5**)

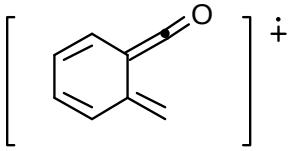
Table 2. Selected NMR chemical shifts δ [ppm] of *spiro*-annelated isochromanones **17**-**21**

n	***spiro*-Annelated isochromanone**	**^{1}H NMR: δ(4-H)**	**^{13}C NMR: δ(C-1)**	**^{13}C NMR: δ(C-3)**	**^{13}C NMR: δ(C-4)**
1	**17**	3.09	164.7	81.4	36.3
2	**18**	3.02	165.8	91.6	37.8
3	**19**	3.02	165.0	81.8	38.2
4	**20**	3.02	165.3	86.4	38.9
5	**21**	3.01	165.2	86.1	39.2

The *spiro*-annelated isochromanones were characterized spectroscopically with the lactone carbonyl groups absorbing in the IR spectra in the range of 1709-1714 cm^{-1} with the precise wavenumber correlating to the lactone ring size. The ^{1}H NMR signals are observed in the expected range without any clear correlation to the lactone ring size. In the ^{13}C NMR spectra the signals of the carbonyl carbon atoms C-1

appear in the expected range. The signals for the quarternary *spiro* carbon atom C-3 are observed in the range of δ = 81.4 – 91.6 ppm, again without a clear correlation to the lactone ring size. In contrast, however, the chemical shift of the signals assigned to the benzylic methylene carbon atoms C-4 show a clear trend, being increasingly deshielded with growing lactone ring size (Table 2).

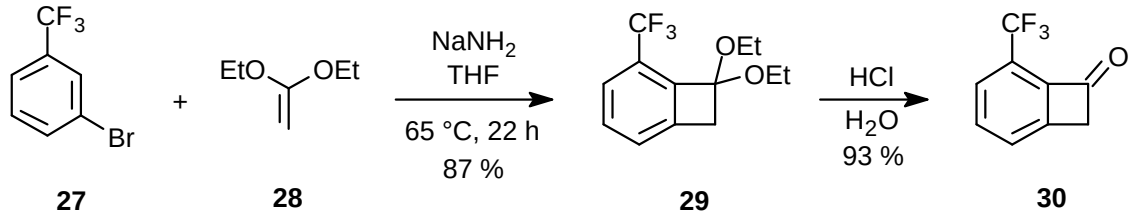
In all mass spectra the base peak is observed at *m/z* = 118, corresponding to a Diels Alder cycloreversion pathway liberating the cycloalkanone and benzocyclobutenone (**5**) or, more likely, its ring opened isomer **26** (Scheme 7).



26
(*m/z* = 118)

Scheme 7. Radical cation assigned to the base peak in the mass spectra of **17**-**21**

As an example for a substituted benzocyclobutenone as starting material we chose 6-trifluoromethylbenzocyclobutenone (**30**), which displays an enhanced carbonyl reactivity as can easily be seen from respective resonance formulas. Compound **30** is accessible in 93 % yield from diethyl acetal **29**, which is obtained following a route developed by Stevens.[19] Dehydrobromination of 3-bromo(trifluoromethyl)benzene (**27**) with sodium amide regioselectively affords 3-trifluoromethylbenzyne, which underwent a [2+2] cycloaddition with 1,1-diethoxyethene (**28**) to give **29** in 87 % yield (Scheme 8).

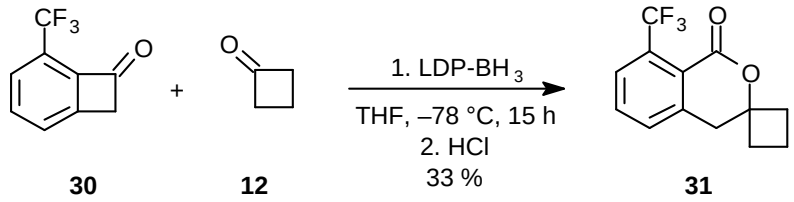


27 **28** **29** **30**

Scheme 8. Synthesis of 6-trifluoromethylbenzocyclobutenone (**30**)

3-Bromo(trifluoromethyl)benzene (**27**) was used instead of the 2-bromo isomer, which is commercially not available. Treatment of **30** with LDP-BH_3 in THF at –78 °C followed by cyclobutanone afforded the trifluoromethyl-substituted isochromanone **31** in 33 % yield as a bright yellow oil (Scheme 9). **31**, which was characterized spectroscopically, is the first isochromanone derivative bearing a trifluoromethyl substituent. The reduced yield as compared to that of **17** presumably is a result of the reduced nucleophilicity

of the intermediate corresponding to **24** as a result of the electron withdrawal of the trifluoromethyl substituent.



30 **12** **31**

Scheme 9. Trifluoromethyl-substituted *spiro*-annelated isochromanone **31** from **30** and **12**

In conclusion we have presented a method for the synthesis of *spiro*-annelated isochromanones from benzocyclobutenones based on an oxyanion-driven ring opening, by treatment with LDP-BH_3. The reaction conditions are very mild, and LDP-BH_3 has proven to be easily accessible from the air stable diisopropylphosphane-borane adduct.

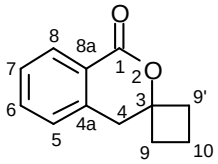
EXPERIMENTAL

General. All operations involving air sensitive compounds were performed by using the Schlenk technique with argon as the protective gas. All glassware was heated under vacuum prior to use in order to remove residual humidity and then set under normal pressure with argon. Toluene and tetrahydrofuran (THF) were dried by heating at reflux in the presence of sodium/potassium alloy or sodium and benzophenone and distilled under argon. Dichloromethane, petroleum ether (PE), and *tert*-butylmethyl ether (TBME) were dried over sodium hydride and distilled under argon. Column chromatography was performed with silica gel (Acros, 0.035-0.070 mm) as the stationary phase. 1,1-Diethoxyethene (**28**) was obtained as a donation from Wacker Chemie AG. Starting materials were either purchased and used as received or prepared according to published procedures. Melting points (uncorr.) were determined with an instrument Büchi Electrothermal IA 9200. ^{1}H NMR spectra were recorded with instruments Bruker AVS 200 (200.1 MHz) or AVS 400 (400.1 MHz). Chemical shifts δ refer to signals of incompletely deuterated solvents as internal standards. ^{13}C NMR spectra were recorded with the instrument Bruker AVS 400 (100.6 MHz). Chemical shifts δ refer to the solvent signals as internal standards. Signal multiplicities were determined by APT or DEPT measurements.[20] Positive (+) signal phases indicate quarternary (C) or secondary (CH_2), negative (–) signal phases tertiary (CH) or primary (CH_3) carbon atoms. Mass spectra (MS) and highly resolved mass spectra (HRMS) were recorded with spectrometers Finnigan MAT 112 or MAT 312 under fractional evaporation conditions. IR spectra were recorded with Perkin-Elmer FT IR spectrometers 580 or 1170 using the Golden Gate ATR technique. Signal intensities are indicated as s (strong), m (medium), and w (weak). Atom numbers are arbitrary and refer to the formulas depicted.

Diisopropylphosphane-Borane Adduct:[17] At 0 °C a 1 M borane-THF complex solution in THF (40.0 mL, 40.0 mmol) was added to chlorodiisopropylphosphane (5.0 g, 30.3 mmol) in THF (20 mL). $LiAlH_4$ (1.6 g, 40.5 mmol) was added in 4 portions, and the mixture was stirred for 2 h at 25 °C. The mixture was poured into a stirred mixture of conc. hydrochloric acid (20 mL) and ice water (100 g), from which the product was isolated by extraction with toluene (3 x 50 mL). The organic layers were dried over $MgSO_4$, filtered, and the solvent was removed at reduced pressure. Diisopropylphosphane-borane adduct (3.8 g, 28.0 mmol, 93 %) was obtained as a clear liquid and identified by comparison of the ^{1}H NMR data with those published.[17]

General Procedure for the Synthesis of spiro-Annelated Isochromanone Derivatives (GP1): A solution of butyllithium in hexane (10 mL, 1.6 M) is added dropwise over 2 h with stirring to a solution of diisopropylphosphane-borane adduct (900 mg, 6.9 mmol) in THF (100 mL). The solution of LDP-BH_3 thus formed is cooled to –78 °C, and a pre-cooled (–78 °C) solution of the benzocyclobutenone derivative (5.1 mmol**)** in THF (40 mL) is slowly added causing the color of the reaction mixture to change from yellow to deep red. After completed addition a solution of the cycloalkanone (1.2 equiv.) in THF (40 mL) is added dropwise over 30 min at –78 °C. Then the solution is allowed to warm to 25 °C and stirred over 14 h. The mixture is hydrolyzed by addition of 1 M HCl (20 mL), and the mixture is extracted with TBME (3 x 20 mL), dried over $MgSO_4$ and filtered. After solvent removal at reduced pressure the crude product is purified by column chromatography (SiO_2, 300 x 30 mm).

*3:4-Benzo-1-oxaspiro[3.5]nonan-2-one (**17**):*



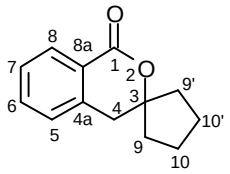
17

GP1, benzocyclobutenone (**5**, 600 mg, 5.1 mmol), cyclobutanone (**12**, 450 mg, 6.3 mmol), column chromatography (TBME / PE 1:10). **17** (597 mg, 3.2 mmol, 63 %), orange-yellow oil.

IR: $\tilde{\nu}$ = 2938 cm^{-1} (w), 2372 (w), 1714 (s, C=O), 1606 (w), 1459 (m), 1290 (s, C–O), 1120 (s), 1069 (m), 1030 (m), 963 (w), 740 (w), 718 (w). – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.58-1.70 (m, 1H, 10-H), 1.87 (ttd, $^2J_{H,H}$ = –21.3 Hz, $^3J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 3,7 Hz, 1H, 10-H), 2.00-2.06 [m, 2H, 9(9')-H], 2.32 [ddd, $^2J_{H,H}$ = – 19.7 Hz, $^3J_{H,H}$ = 10.0 Hz, $^3J_{H,H}$ = 2.5 Hz, 2H, 9(9')-H], 3.09 (s, 2H, 4-H), 7.23 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, 5-H), 7.31 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, 7-H), 7.48 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, 6-H), 7.98 (d, $^3J_{H,H}$ = 7.9 Hz, 1H, 8-H) ppm. – ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 12.6 (CH_2, C-10), 33.6 [CH_2, C-9(9')], 36.3 (CH_2, C-4), 81.4 (C_q, C-3), 125.2 (C_q, C-8a), 127.5 (CH, C-7), 128.2 (CH, C-5), 129.8 (CH, C-8), 133.7 (CH, C-6),

137.9 (C_q, C-4a), 164.7 (C_q, C-1) ppm. – MS: *m/z* (%) = 188 (78) [M^+], 160 (58) [$M^+ - C_2H_4$], 134 (25) [$M^+ - C_2H_4 - C_2H_2$], 118 (100) [$M^+ - C_2H_4 - C_2H_2 - O$], 90 (78) [$M^+ - C_2H_4 - C_2H_2 - O - CO$], 77 (15) [$M^+ - C_2H_4 - C_2H_2 - O - CO - CH_2 + 1$]. – HRMS ($C_{12}H_{12}O_2$): calcd. 188.0837, found 188.0836. – Anal. calcd. for $C_{12}H_{12}O_2$: C 76.57, H 6.43. Found C 76.66, H 6.49.

*3:4-Benzo-1-oxaspiro[4.5]decan-2-one (**18**)*:[16]



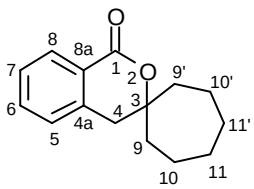
18

GP1, benzocyclobutenone (**5**, 600 mg, 5.1 mmol), cyclopentanone (**13**, 454 mg, 5.9 mmol), column chromatography (TBME / PE 1:10). **18** (543 mg, 2.7 mmol, 53 %), yellow oil.

IR: $\tilde{\nu}$ = 2961 cm^{-1} (w), 2873 (w), 2367 (w), 1713 (s, C=O), 1605 (w), 1460 (m), 1283 (s, C–O), 1114 (m), 1083 (m), 1030 (m), 929 (w), 741 (m), 717 (w). – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.67-1.70 [m, 4H, 9(9')-H, 10(10')-H], 1.90-1.96 [m, 2H, 10(10')-H], 2.01-2.05 [m, 2H, 9(9')-H], 3.02 (s, 2H, 4-H), 7.23 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, 5-H), 7.37 (t, $^3J_{H,H}$ = 7.5 Hz, 1H, 7-H), 7.51 (dt, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 1.4 Hz, 1H, 6-H), 8.07 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, 8-H) ppm. – ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 23.9 [CH_2, C-10(10')], 37.8 (CH_2, C-4), 38.7 [CH_2, C-9(9')], 91.6 (C_q, C-3), 125.4 (C_q, C-8a), 127.6 (CH, C-7), 127.7 (CH, C-5), 130.2 (CH, C-8), 133.7 (CH, C-6), 139.0 (C_q, C-4a), 165.8 (C_q, C-1) ppm. – MS: *m/z* (%) = 202 (79) [M^+], 160 (59) [$M^+ - C_3H_6$], 134 (23) [$M^+ - C_3H_6 - C_2H_2$], 118 (100) [$M^+ - C_3H_6 - C_2H_2 - O$], 90 (75) [$M^+ - C_3H_6 - C_2H_2 - O - CO$], 77 (11) [$M^+ - C_3H_6 - C_2H_2 - O - CO - CH_2 + 1$]. – HRMS ($C_{13}H_{14}O_2$): calcd. 202.0994, found 202.0991.

*3:4-Benzo-1-oxaspiro[5.5]undecan-2-one (**19**):*[15] GP1, benzocyclobutenone (**5**, 511 mg, 4.3 mmol), cyclohexanone (**14**, 500 mg, 5.1 mmol), column chromatography (TBME / PE 1:10). **19** (497 mg, 2.3 mmol, 54 %), bright yellow oil, identified by comparison of the spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, MS, HRMS) with those published.[15]

*3:4-Benzo-1-oxaspiro[5.6]dodecan-2-one (**20**):*

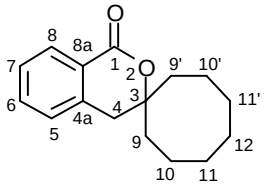


20

GP1, benzocyclobutenone (**5**, 576 mg, 4.9 mmol), cycloheptanone (**15**, 560 mg, 5.0 mmol), column chromatography (TBME / PE 1:10). **20** (575 mg, 2.5 mmol, 52 %), yellow solid (m. p. 65 °C).

IR: $\tilde{\nu}$ = 2933 cm^{-1} (w), 1712 (s, C=O), 1605 (w), 1460 (m), 1272 (s, C–O), 1117 (m), 1083 (m), 741 (m), 717 (w).– ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.52-1.83 [m, 10H, 9(9')-H, 10(10')-H, 11(11')-H], 2.00-2.06 [m, 2H, 9(9')-H], 3.02 (s, 2H, H-4), 7.20 (d, $^{3}J_{H,H}$ = 7.2 Hz, 1H, 5-H), 7.36 (t, $^{3}J_{H,H}$ = 7.5 Hz, 1H, 7-H), 7.51 (dt, $^{3}J_{H,H}$ = 7.5 Hz, $^{3}J_{H,H}$ = 1.0 Hz, 1H, 6-H), 8.07 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1H, 8-H) ppm. – ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 22.4 [CH_2, C-10(10')], 29.8 [CH_2, C-11(11')], 38.9 (CH_2, C-4), 39.4 [CH_2, C-9(9')], 86.4 (C_q, C-3), 125.4 (C_q, C-8a), 127.6 (CH, C-7), 128.2 (CH, C-5), 130.1 (CH, C-8), 133.8 (CH, C-6), 138.1 (C_q, C-4a), 165.3 (C_q, C-1) ppm. – MS: *m/z* (%) = 230 (48) [M^+], 160 (43) [$M^+ - C_5H_{10}$], 134 (21) [$M^+ - C_5H_{10} - C_2H_2$], 118 (100) [$M^+ - C_5H_{10} - C_2H_2 - O$], 90 (56) [$M^+ - C_5H_{10} - C_2H_2 - O - CO$], 77 (12) [$M^+ - C_5H_{10} - C_2H_2 - O - CO - CH_2 + 1$]. – HRMS ($C_{15}H_{18}O_2$): calcd. 230.1307, found 230.1310.

*3:4-Benzo-1-oxaspiro[5.7]tridecan-2-one (**21**):*

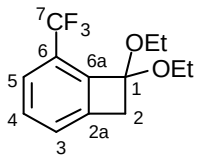


21

GP1, benzocyclobutenone (**5**, 550 mg, 4.6 mmol), cyclooctanone (**16**, 630 mg, 5.0 mmol), column chromatography (PE). **21** (337 mg, 1.4 mmol, 30 %), yellow solid (m. p. 93 °C).

IR: $\tilde{\nu}$ = 2923 cm^{-1} (w), 2372 (w), 1709 (s, C=O), 1460 (m), 1265 (s, C–O), 1114 (m), 745 (m), 717 (w). – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.21-1.94 [m, 14H, 9(9')-H, 10(10')-H, 11(11')-H, 12-H], 3.01 (s, 2H, 4-H), 7.20 (d, $^{3}J_{H,H}$ = 7.2 Hz, 1H, 5-H), 7.34 (t, $^{3}J_{H,H}$ = 7.5 Hz, 1H, 7-H), 7.52 (dt, $^{3}J_{H,H}$ = 7.5 Hz, $^{3}J_{H,H}$ = 1.1 Hz, 1H, 6-H), 8.07 (d, $^{3}J_{H,H}$ = 7.5 Hz, 1H, 8-H) ppm. – ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 24.5 [CH_2, C-10(10')], 30.1 (CH_2, C-12), 30.8 [CH_2, C-11(11')], 39.2 (CH_2, C-4), 44.8 [CH_2, C-9(9')], 86.1 (C_q, C-3), 125.5 (C_q, C-8a), 127.6 (CH, C-7), 128.1 (CH, C-5), 130.1 (CH, C-8), 133.9 (CH, C-6), 138.0 (C_q, C-4a), 165.2 (C_q, C-1) ppm. – MS: *m/z* (%) = 244 (48) [M^+], 160 (43) [$M^+ - C_6H_{12}$], 134 (21) [$M^+ - C_6H_{12} - C_2H_2$], 118 (100) [$M^+ - C_6H_{12} - C_2H_2 - O$], 90 (54) [$M^+ - C_6H_{12} - C_2H_2 - O - CO$], 77 (11) [$M^+ - C_6H_{12} - C_2H_2 - O - CO - CH_2 + 1$]. – HRMS ($C_{16}H_{20}O_2$): calcd. 244.1463, found 244.1461.

*1,1-Diethoxy-6-trifluoromethylbenzocyclobutene (**29**):*

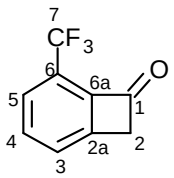


29

1,1-Diethoxyethene (**28**, 40.0 g, 340 mmol) and 3-bromotrifluoromethylbenzene (**27**, 12.5 g, 55.1 mmol) were added dropwise to a suspension of sodium amide (4.6 g, 120.2 mmol) in THF (40 mL). The mixture was stirred at reflux for 22 h, then no starting material could be detected by TLC (silica gel 60 F_{254}, PE / TBME 5:1). The deep brown suspension was allowed to cool to 25 °C and then poured into ice water (100 mL). After addition of water (100 mL) the mixture was extracted with dichloromethane (4 x 50 mL). The collected organic layers were washed with sat. aqu. NaCl solution (100 mL), dried over $MgSO_4$, and filtered. After solvent removal at reduced pressure the product was purified by column chromatography (SiO_2, deact. with NEt_3, 200 x 330 mm, TBME / PE 1:7) affording 1,1-diethoxy-6-trifluoromethylbenzocyclobutene (**29**, 12.6 g, 48.0 mmol, 87 %) as a yellow oil.

IR (ATR): $\tilde{\nu}$ = 2978 (w) cm^{-1}, 2935 (w), 2884 (w), 1614 (w), 1483 (w), 1433 (w),1366 (w), 1319 (s, C-F), 1241 (s), 1170 (s), 1127 (s), 1087 (m), 1060 (s), 992 (w), 929 (w), 786 (w). – ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 1.24 (t, 6H, ^3J = 7.0 Hz, 2 CH_3), 3.42 (s, 2H, 2-H), 3.72 (dd, 4H, ^3J = 7.2 Hz, 2 CH_2), 7.38 - 7.44 (m, 3H, 4-H, 3-H, 5-H). – ^{13}C NMR (100.6 MHz, acetone-d_6, APT): δ = 15.2 (2 CH_3), 44.0 (CH_2, C-2), 59.5 (2 CH_2), 104.9 (C_q, C-1), 123.7 (q, C_q, $^1J_{C\text{-}F}$ = 271 Hz, C-7), 124.8 (CH, C-3), 126.7 (CH, C-4), 130.1 (q, CH, $^3J_{C\text{-}F}$ = 4.0 Hz, C-5), 137.0 (C_q,$^2J_{C\text{-}F}$ = 37.0 Hz, C-6), 143.2 (+, C-2a), 155.1 (+, C-6a). - MS (70eV): *m/z* (%) = 260 (2) [M^+], 245 (4), 215 (31), 187 (100) [M – C_4H_9O] , 167 (59), 136 (51), 119 (12), 104 (28), 89 (8), 77 (8), 63 (7). - HRMS ($C_{13}H_{15}O_2F_3$): calcd. 260.1024, found 260.1021.

*6-Trifluoromethylbenzocyclobutenone (**30**):*



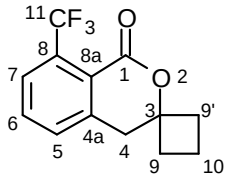
30

At 0 °C 1,1-diethoxy-6-trifluoromethylbenzocyclobutene (**29**, 12.0 g, 46.0 mmol) was added to hydrochloric acid (100 mL, 1 M) and the mixture was stirred for 24 h at 25 °C. The mixture was extracted with dichloromethane (4 x 50 mL), and the organic layers were dried over $MgSO_4$ and filtered. After solvent removal at reduced pressure the crude product was purified by column chromatography (SiO_2, 300 x 30

mm, TBME / PE 1:5) to give 6-trifluoromethylbenzocyclobutenone (**30**, 7.9 g, 43.3 mmol, 93 %), yellow solid (mp 45 °C).

IR: (ATR) $\tilde{\nu}$ = 3530 (w) cm^{-1}, 3049 (w), 2359 (w), 1771 (s, C=O), 1653 (w), 1613 (w), 1585 (m), 1489 (m), 1412 (m), 1325 (s, C-F), 1248 (s), 1163 (s), 1100 (s), 996 (m), 968 (s), 916 (w), 803 (s), 754 (w), 739 (m), 728 (m), 686 (w). – ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 4.15 (s, 2H, 2-H), 7.80 (d, 1H, ^3J = 7.8 Hz, 5-H), 7.83 (dd, 1H, ^3J = 7.9 Hz, ^3J = 7.2 Hz, 4-H), 7.85 (d, 1H, ^3J = 7.3 Hz, 3-H). – ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 52.7 (CH_2, C-2), 121.0 (C_q, $^1J_{C,F}$ = 273.1 Hz, C-7), 122.2 (d, C_q, $^2J_{C,F}$ = 36 Hz, C-6), 123.7 (C_q, C-2a), 125.1 (q, CH, $^3J_{C,F}$ = 4.5 Hz, C-5), 127.6 (CH, C-4), 135.4 (CH, C-3), 152.2 (C_q, C-6a), 183.3 (C_q, C-1). – MS (70 eV): *m/z* (%) = 186 (100) [M^+], 167 (8), 158 (79), 138 (42), 119 (3), 108 (7), 99 (2), 89 (3), 81 (1), 63 (2). – Anal. Calcd for $C_9H_5F_3O$: C 58.08, H 2.71. Found C 57.91, H 2.81.

*8-Trifluoromethyl-(3:4-benzo)-1-oxaspiro[3.5]nonan-2-one (**31**):*



31

GP1, 6-trifluoromethylbenzocyclobutenone (**30**, 550 mg, 4.6 mmol), cyclobutanone (**12**, 450 mg, 6.3 mmol), upon addition the color changes from yellow to dark green. Column chromatography (TBME / PE 1:9). **31** (422 mg, 1.7 mmol, 33 %), orange-yellow oil.

IR: $\tilde{\nu}$ = 2935 cm^{-1} (w), 2367 (w), 1732 (s, C=O), 1612 (w), 1455 (m), 1314 (s, C–F), 1283 (s, C–O), 1129 (s), 1104 (m), 1060 (m), 966 (w), 763 (w), 722 (w). – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.62-1.74 [m, 2H, 10(10')-H], 2.02-2.08 [m, 2H, 9(9')-H], 2.41 [ddd, $^2J_{H,H}$ = –19.5 Hz, $^3J_{H,H}$ = 10.0 Hz, $^3J_{H,H}$ = 2.6 Hz, 2H, 9(9')-H], 3.17 (s, 2H, 4-H), 7.50 (d, $^3J_{H,H}$ = 7.5 Hz, 1H, 5-H), 7.62 (t, $^3J_{H,H}$ = 8.4 Hz, 1H, 6-H), 7.76 (d, $^3J_{H,H}$ = 7.9 Hz, 1H, 7-H) ppm. – ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 12.8 (CH_2, C-10), 33.2 [CH_2, C-9(9')], 37.5 (CH_2, C-4), 80.8 (C_q, C-3), 121.6 (C_q, C-11), 124.8 (CH, C-7), 126.8 (C_q, C-8a), 128.6 (C_q, C-8), 132.0 (CH, C-5), 132.6 (CH, C-6), 140.2 (C_q, C-4a), 160.8 (C_q, C-1) ppm. – MS: *m/z* (%) = 256 (32) [M^+], 228 (16) [$M^+ - C_2H_4$], 186 (100) [$M^+ - C_2H_4 - C_2H_2 - O$], 158 (44) [$M^+ - C_2H_4 - C_2H_2 - O - CO$]. – HRMS ($C_{13}H_{11}O_2F_3$): Calcd. 256.0711, found 256.0712.

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