1. Synthesis of the ABC Ring System of Azaspiracid: Effect of D Ring Truncation on Bisspirocyclization.

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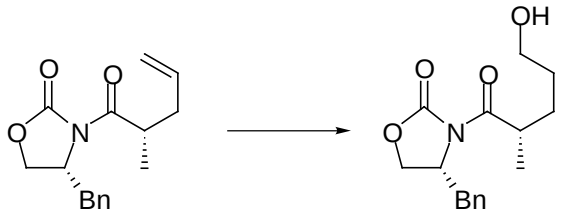
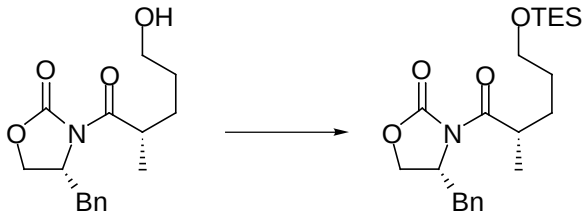
Electronic Supplementary Information



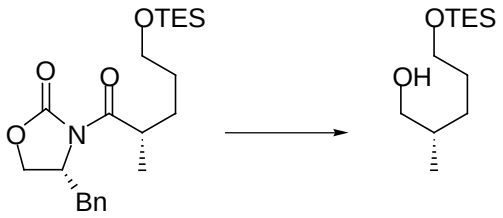
18 **14**

Alcohol 14:[1] To a stirred solution of **18** (800 mg, 2.93 mmol) in THF at 0°C was added dithexylborane (3.67 mL, 4.4 mmol, 1.2 M in THF) dropwise *via* syringe. After 1 h, the reaction was quenched with aq. phosphate buffer (6 mL, pH 7) and H_2O_2 (6 mL, 30% aqueous). After 1.5 h, the solution was diluted with H_2O (50 mL) and extracted with Et_2O (4 X 75 mL). The dried ($MgSO_4$) extract was filtered through a small plug of Florisil,® rinsed with Et_2O and concentrated *in vacuo* to give **14** as a crude oil.



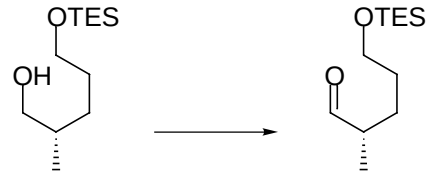
14 **19**

TES Alcohol 19: To a stirred solution of crude **14** (2.93 mmol) in CH_2Cl_2 (14.7 mL) at -78°C was added sequentially 2,6-lutidine (628 mg, 680 µL, 5.86 mmol) and TESOTf (1.164 g, 1.0 mL, 4.4 mmol). An additional portion of 2,6-lutidine (943 mg, 1.02 mL, 8.8 mmol) and TESOTf (2.325 g, 2.0 mL, 8.8 mmol) was added during the course of the reaction. After 3 h, the reaction was quenched with sat. aq. NH_4Cl (50 mL) and extracted with Et_2O (4 X 75 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 2-20% EtOAc / hexanes, to give **19** (878 mg, 2.17 mmol, 74% over 2 steps) as a colorless oil: ($[\alpha]_D^{23}$ -20.0° (c 1.17, $CHCl_3$); IR (neat) 2954, 1770, 1683, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21-7.36 (m, 5H), 4,65-4.72 (m, 1H), 4.14-4.22 (m, 2H), 3.73-3.80 (m, 1H), 3.59-3.67 (m, 2H), 3.32 (dd, J = 3.1, 13.2 Hz, 1H), 2.70 (dd, J = 10.0, 13.2 Hz, 1H), 1.52-1.82 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.60 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 153.3, 135.6, 129.6, 129.2, 127.5, 66.2, 62.9, 55.6, 38.3, 37.5, 30.6, 30.3, 17.1, 7.0, 4.6; HRMS (FAB+) calcd. for $C_{22}H_{36}O_4NSi$ (M+H) 406.2414, found 406.2410.



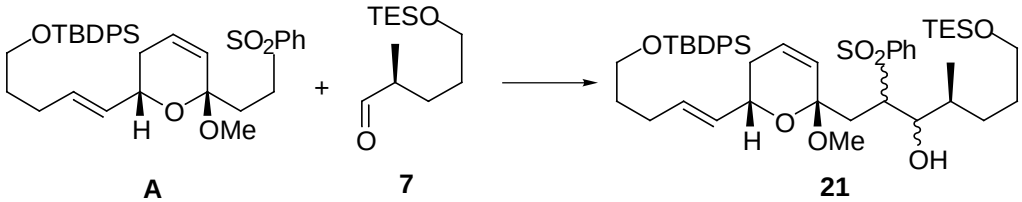
19 **20**

Alcohol 20: To a stirred solution of **19** (197 mg, 0.486 mmol) in THF (4.2 mL) at 0°C was added sequentially MeOH (16.6 mg, 21 µL, 0.518 mmol) and $LiBH_4$ (0.29 mL, 0.58 mmol, 2.0 M in THF). After 45 min, the reaction was warmed to r.t. After 3.5 h, the reaction was quenched with aq. sodium tartrate (25 mL, 10%) and extracted with Et_2O (4 X 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-40% EtOAc / hexanes, to give **20** (93 mg, 0.423 mmol, 87%) as a colorless oil: $[\alpha]_D^{23}$ -6.2° (c 2.05, $CHCl_3$); IR (neat) 3366, 2952, 2875, 1458, 1238, 1095, 1007, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (t, J = 6.5 Hz, 2H), 3.50 (dd, J = 6.0, 10.6 Hz, 1H), 3.43 (dd, J = 6.2, 10.6 Hz, 1H),1.75 (bs, OH), 1.42-1.67 (m, 4H), 1.09-1.22 (m, 1H), 0.86 - 1.03 (m, 12H), 0.60 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.4, 63.4, 35.7, 30.3, 29.4, 16.8, 7.0, 4.6; HRMS (FAB+) calcd. for $C_{12}H_{29}O_2Si$ (M+H) 233.1937, found 233.1939.



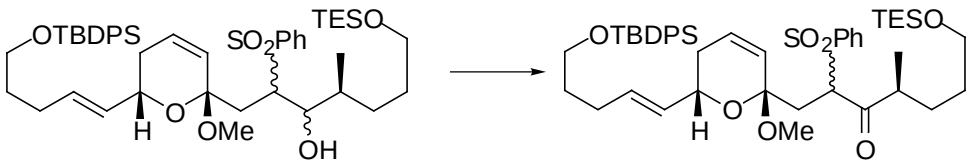
20 **7**

Aldehyde 7: To a stirred solution of **20** (90 mg, 0.410 mmol) in CH_2Cl_2 (1.8 mL) with powdered 4 Å mol. sieves (100 mg) was added sequentially NMO (76 mg, 0.65 mmol) and TPAP (7.6 mg, 0.022 mmol). After 35 min, the reaction was diluted with 10% EtOAc / hexanes (10 mL), filtered through a small plug of silica gel (10% EtOAc / hexanes rinse), and concentrated *in vacuo* to give **7** (86 mg, 0.394 mmol, 96%) as a colorless oil: IR (neat) 2955, 1729, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, J = 1.8 Hz, 1H), 3.62 (t, J = 6.1 Hz, 2H), 2.33-2.41 (m, 1H), 1.75-1.80 (m, 1H), 1.54-1.62 (m, 2H), 1.42-1.49 (m, 1H), 1.11 (d, J = 6.9 Hz, 3H), 0.96 (t, J = 8.0 Hz, 9H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 62.7, 46.3, 30.3, 27.1, 13.6, 7.0, 4.6; HRMS (FAB+) calcd. for $C_{12}H_{25}O_2Si$ (M-H) 229.1624, found 229.1623.



A **7** **21**

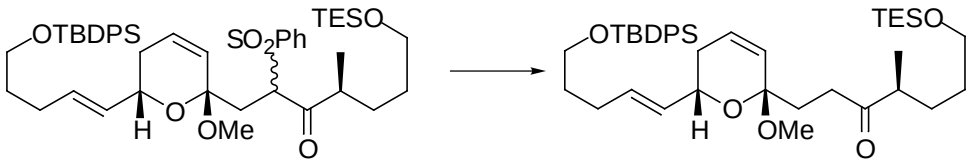
Hydroxy Sulfone 21: To a stirred solution of **A** (166 mg, 0.275 mmol) in THF (1.5 mL) at -78°C was added LDA[2] (310µL, 0.31 mmol, 1 M in THF / hexanes) dropwise *via* a syringe. After 20 min, a precooled solution of the aldehyde **16** (75 mg, 0.344 mmol) in THF (0.3 mL) was added rapidly *via* cannula to the yellow sulfone solution. After 25 min, the reaction was removed from the cooling bath. After an additional 2 min, the reaction was quenched with sat. aq. NH_4Cl (25 mL) and extracted with EtOAc (4 X 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-28% EtOAc / hexanes, to give **21** (182 mg, 0.0.22 mmol, 81%) as a colorless oil.



21 **15**

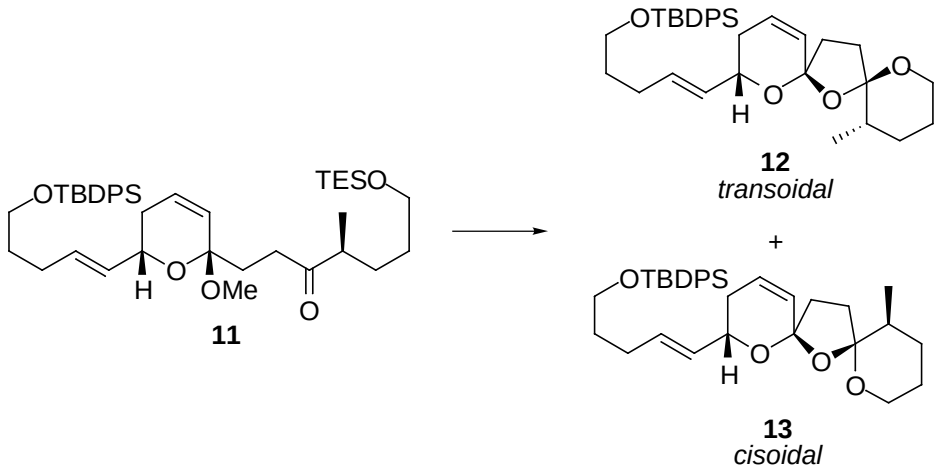
Keto sulfone 15: To a stirred solution of **21** (40.0 mg, 0.0487 mmol) in CH_2Cl_2 (0.8 mL) with powdered 4 Å mol. sieves (≈ 200 mg) was sequentially added NMO (13 mg, 0.11 mmol) and TPAP (6.8 mg, 0.019 mmol) at r.t. An additional portion of TPAP (6 mg, 0.017 mmol) was added during the course of the reaction. After 1.5 h, the reaction was diluted with 30% EtOAc / hexanes (10 mL), filtered through a small plug of silica gel (30% EtOAc / hexanes rinse), and concentrated *in vacuo*. The resultant oil was purified by chromatography over silica gel, eluting with 5-20% EtOAc / hexanes, to give **15** (29 mg, 0.035 mmol, 73%) as a colorless oil: $[\alpha]_D^{23}$ +17.3° (c 3.45, $CHCl_3$); IR (neat) 3070, 2952, 17.16, 1310, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.76 (d, J = 7.5 Hz, 2H), 7.65-7.68 (m, 5H), 7.51-7.59 (m, 2H), 7.36-7.46 (m, 6H), 6.01-6.08 (m, 1H of a diastereomer), 5.01-5.96 (m, 1H of a diastereomer), 5.31-5.64 (m, 3H), 4.61 (dd, J - 3.4, 3.4 Hz, 1H of a diastereomer), 4.47 (d, J = 9.0 Hz, 1H of a diastereomer), 4.12-4.22 (m, 1H) 3.57-3.68 (m, 4H), 3.11 (s, 3H of a diastereomer), 3.06 (s, 3H of a diastereomer), 2.92-3.03 (m, 1H), 2.60 (dd, J = 10.0, 13.8 Hz, 1H of a diastereomer), 2.27 - 2.38 (m, 1H of a diastereomer), 2.25 (d, J = 6.2 Hz, 1H), 1.80-2.20 (m, 7H), 1.50-1.68 (m, 3H), 1.17 (d, J = 6.7 Hz, 3H of a diastereomer), 1.11 (d J = 7.2 Hz, 3H of a diastereomer), 1.06 (s, 9H of a diastereomer), 1.05 (s, 9H of a diastereomer), 0.93-0.98 (m, 9H), 0.55-0.65 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 204.6, 136.7, 135.8, 134.4, 134.3, 132.8, 132.3, 130.3, 129.8, 139.6, 129.2, 129.1, 127.9, 127.8, 127.7, 97.4, 96.5, 69.8, 69.3, 69.1, 68.8,

63.4, 63.0, 62.8, 49.4, 48.0, 47.6, 34.7, 34.2, 32.2, 32.1, 30.8, 30.5, 30.3, 29.9, 28.9, 28.8, 28.7, 27.1, 19.4, 16.4, 14.9, 7.1, 4.6.



15 **11**

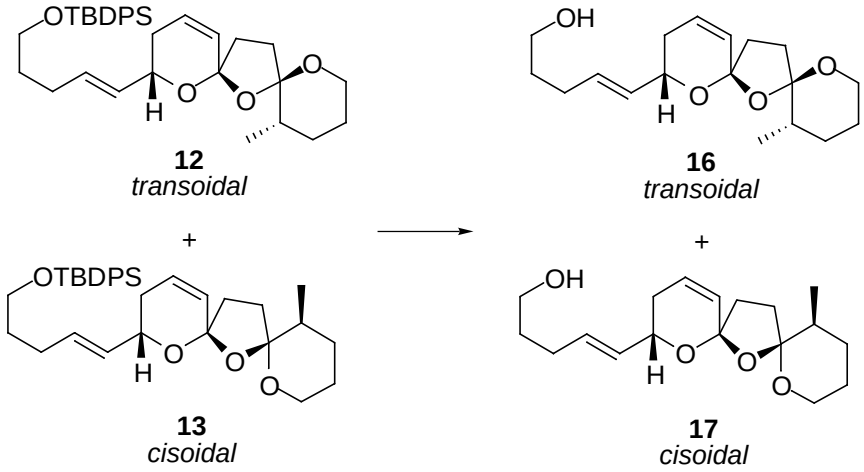
Ketone 11: To a stirred solution of **15** (86 mg, 0.103 mmol) in THF (0.6 mL) and MeOH (1.8 mL) at -10°C was added Na_2HPO_4 (70.6 mg, 0.493 mmol) followed by Na / Hg (330 mg, 0.712 mmol, 5% Na). After 75 min, the reaction was diluted with 35% EtOAc / hexanes (10 mL), filtered through a small plug of silica gel (35% EtOAc / hexanes rinse), and concentrated *in vacuo* to give crude **11** (0.103 mmol) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 0.9 ,6.2 Hz, 4H), 7.36-7.45 (m, 6H), 5.96-6.02 (m, 1H), 5.69 (dt, J = 6.5, 15.5 Hz, 1H), 5. 63 (d, J = 9.9 Hz, 1H), 5.52 (dd, J = 6.6, 15.5 Hz, 1H), 4.22-4.29 (m, 1H), 3.67 (t, J = 6.2 Hz, 2H), 3.58 (t, J = 5.8 Hz, 2H), 2.40-2.60 (m, 2H), 1.80-2.15 (m, 6H), 1.52-1.70 (m, 5H), 1.30-1.50 (m, 2H), 1.05-1.08 (m, 12H), 0.95 (t, J = 7.9 Hz, 9H), 0.58 (q, J = 7.9 Hz, 6H); HRMS (FAB+) calcd. for $C_{40}H_{61}O_4Si_2$ (M+-MeOH) 661.4108, found 661.4124 .



Spirocycles 12 and 13: To a stirred solution of crude **11** (0.103 mmol) in PhMe (7 mL) and t-BuOH (7 mL) was added CSA (123 mg, 0.529 mmol). After 19 h, the reaction was quenched with solid $NaHCO_3$ (500 mg). After 10 min, the solution was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with Et_2O (4 X 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 3-12% EtOAc / hexanes, to give more polar **12** and less polar **13** (38 mg, 0.070 mmol, 68% over the 2 steps) as colorless oils.

12: $[\alpha]_D^{23}$ -13.0° (c 0.185, $CHCl_3$); IR (neat) 2931, 2858, 1428, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.65-7.68 (m, 4H), 7.34-7.43 (m, 6H), 5.94-6.0 (m, 1H), 5.62-5.72 (m, 2H), 5.50 (dd, J = 6.0, 15.4 Hz, 1H), 4.36-4.43 (m, 1H), 3.92 (ddd, J = 3.0, 11.6, 11.6 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 3.57 (dt, J = 4.3, 11.2 Hz, 1H), 1.83-2.20 (m, 10H), 1.56-1.79 (m, 5H), 1.04 (s, 9H), 1.01 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 134.2, 132.3, 130.7, 129.7, 128.2, 127.8, 110.0, 104.4, 69.0, 63.4, 62.8, 37.1, 36.5, 32.6, 32.1, 30.3, 28.9, 27.5, 27.0, 21.5, 19.4, 15.6; HRMS (FAB+) calcd. for $C_{34}H_{47}O_4Si$ (M+H) 547.3244, found 547.3228.

13: $[\alpha]_D^{23}$ -65.3° (c 0.19, $CHCl_3$); IR (neat) 2960, 2930, 2855, 1467, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.64-7.68 (m, 4H), 7.34-7.45 (m, 6H), 5.94-6.00 (m, 1H), 5.53-5.75 (m, 3H), 4.42-4.49 (m, 1H), 3.84 (ddd, J = 2.2, 11.1, 11.1 Hz, 1H), 3.60-3.67 (m, 1H), 3.66 (t, J = 6.2 Hz, 2H), 1.83-2.26 (m, 10H), 1.47-1.72 (m, 5H), 1.04 (s, 9H), 0.87 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 134.2, 132.4, 130.6, 129.7, 128.8, 128.0, 127.8, 109.6, 105.3, 70.1, 63.5, 62.0, 37.8, 37.5, 35.5, 32.1, 30.2, 28.9, 28.6, 27.0, 19.4, 16.8; HRMS (FAB+) calcd. for $C_{34}H_{47}O_4Si$ (M+H) 547.3244, found 547.3252.



Spirocycles 16 and 17: To a stirred solution of **12** and **13** (38 mg, 0.070 mmol) in THF (0.5 mL) was added TBAF (2 mL, 2.0 mmol, 1.0 M in THF). After 90 min, the reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (4 X 75 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-40% EtOAc / hexanes, to give sequentially **16** (9.0 mg, 0.032 mmol, 46 %) followed by **17** (9.0 mg, 0.032 mmol, 46%) as colorless oils.

16: $[\alpha]_D^{23}$ -34.4° (c 0.39, $CHCl_3$); IR (neat) 3419, 2927, 2855, 1455, 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94-6.00 (m, 1H), 5.60-5.75 (m, 2H), 5.54 (dd, J = 6.1, 15.7

Hz, 1H), 4.37-4.44 (m, 1H), 3.91 (ddd, J = 3.0, 11.2, 11.2 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.57 (ddd, J = 4.4, 4.4, 11.0 Hz, 1H), 1.83-2.18 (m, 10H), 1.62-1.80 (m, 5H), 1.38 (bs, OH), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 131.1, 129.7, 128.2, 110.0, 104.4, 68.9, 62.8, 62.6, 37.2, 36.5, 32.4, 32.1, 30.4, 28.9, 27.5, 21.5, 15.6; HRMS (FAB+) calcd. for $C_{18}H_{27}O_3$ (M-H) 291.1960, found 291.1959.

17: $[\alpha]_D^{23}$ -118.0° (c 0.405, $CHCl_3$); IR (neat) 3440, 2964, 2927, 1226, 990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95-6.00 (m 1H), 5.75 (dt, J = 6.6, 15.4 Hz, 1H), 5.59-5.65 (m, 2H), 4.43-4.50 (m, 1H), 3.86 (dd, J = 11.3, 11.3 Hz, 1H), 3.65 (t, J = 6.5 Hz, 2H), 3.62-3.67 (m, 1H), 1.82-2.27 (m, 10H), 1.49-1.71 (m, 5H), 0.86 (d, J = 6. 4 Hz, 3H); 13C NMR (75 MHz, $CDCl_3$); δ 132.1, 131.0, 128.8, 128.0, 109.7, 105.3, 70.0, 62.6, 62.1, 37.8, 37.5, 35.5, 32.1, 30.2, 29.0, 28.6, 26.3,16.9; HRMS (FAB+) calcd. for $C_{18}H_{27}O_3$ (M-H) 291.1960, found 291.1964.

Equilibration of Cisoidal 17: To a stirred solution of **17** (3.9 mg, 0.0127 mmol) in PhMe (0.85 mL) and *t*-BuOH (0.85 mL) was added CSA (15.5 mg, 0.0667 mmol). After 16 h, the reaction was quenched with solid $NaHCO_3$ (100 mg). After 5 min, the reaction was diluted with 35% EtOAc / hexanes (10 mL), filtered through a small plug of silica gel (35% EtOAc / hexanes rinse), concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-40% EtOAc / hexanes, to give sequentially **16** (1.8 mg, 0.0058 mmol, 44 %) followed by **17** (2.0 mg, 0.032 mmol, 50%) as a colorless oils.

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(1) This protocol is an adaptation of a literature protocol. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(2) The 1.0 M LDA solution was prepared fresh immediately prior to use: To a stirred solution of *N*, *N*-diispropyl amine (404 mg, 560 µL, 4.0 mmol) in THF (1.84 mL) at -78°C was added *n*-BuLi (1.6 mL, 4.0 mmol, 2.5 M in hexanes) dropwise. After 5 min, the white suspension was warmed to -10°C. After 30 min, the solution was employed in the relevant reaction.