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Preparation of Fully Substituted Anilines for the Synthesis of Functionalized Indoles

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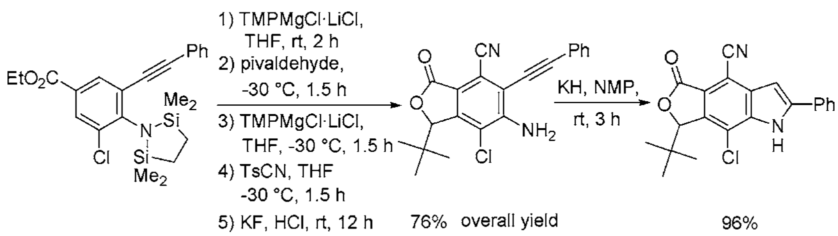
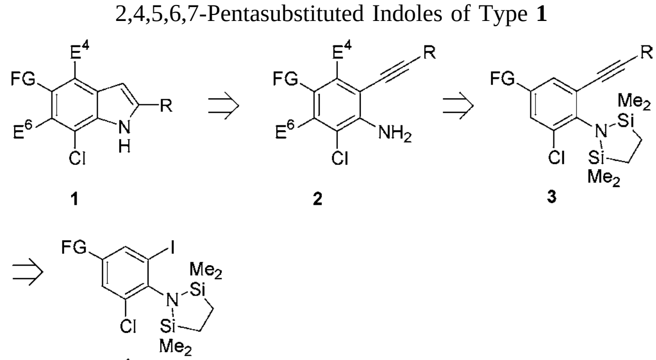
ABSTRACT



A wide range of highly functionalized indoles were prepared by the successive magnesiation of readily available *o*-alkynyl protected anilines using TMPMgCl·LiCl or LDA, followed by a KH-mediated cyclization reaction.

The indole skeleton is present in numerous bioactive natural products, pharmaceuticals, or agrochemicals,[1] and a range of synthetic methods has been developed[2] for the preparation of these heterocycles. Most methods rely on the incorporation of functionality prior to indole ring construction,[3] but directed metalations of indole scaffolds also provide access to functionalized indoles.[4] Recently, we have reported several methods for the preparation of arylmagnesium compounds by either Br/Mg-exchange reactions[5] or direct metalation through deprotonation[6] and have applied them to heterocycle synthesis. Herein, we report a new approach for the synthesis of 2,4,5,6,7-pentasubstituted indoles **1** via the use of highly substituted anilines prepared by regioselective metalations (Scheme 1).

Scheme 1. Retrosynthetic Analysis for the Preparation of 2,4,5,6,7-Pentasubstituted Indoles of Type **1**



We have envisioned that indoles of type **1** could be prepared from anilines of type **2** via an anionic cyclization.[3b,i,7] The polyfunctionalized anilines **2** will be prepared by selective metalation of the protected anilines **3**, which are obtained by Negishi cross-coupling[8] using selectively halogenated aniline building blocks **4**. The preparation of **4** was achieved in three steps (Scheme 2).

(1) (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (c) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761. For recent references on the total synthesis of indole alkaloids, see: (d) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342. (e) Baran, P. S.; Guerrero, C. A.; Hafensteiner, B. D.; Ambhaikar, N. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3892. (f) Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 15038.

(2) For recent reviews, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.

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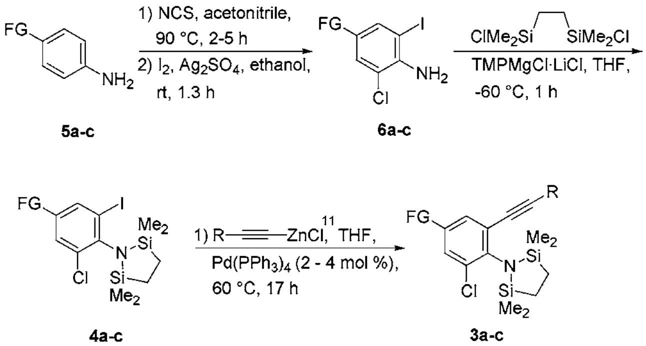
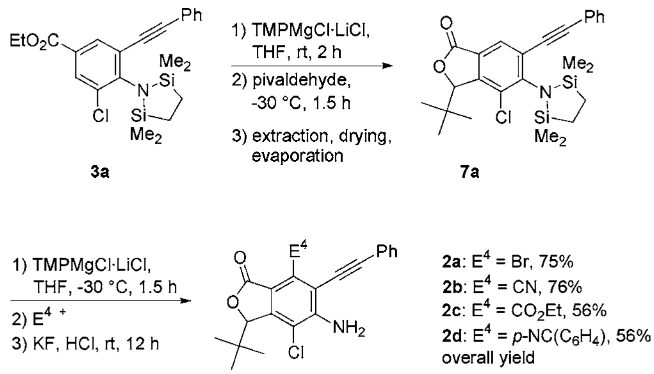
Scheme 2. Selective Halogenation and Protection of Para-Functionalized Anilines of Type **5** Followed by Negishi Cross-Coupling



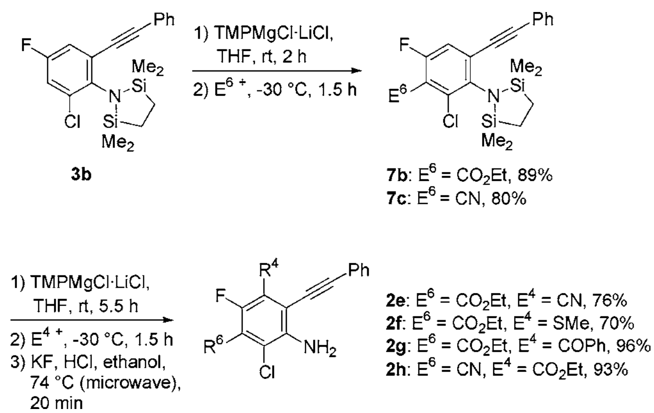
aniline of type **5**	FG	product of type **6**, yield [%]	product of type **4**, yield [%]	product of type **3**, R, yield [%]
5a	CO_2Et	**6a**, 83	**4a**, 83	**3a**, R = Ph, 97
5b	F	**6b**, 65	**4b**, 81	**3b**, R = Ph, 96
5c	CN	**6c**, 88	**4c**, 98	**3c**, R = Bu, 70

Thus, the sequential halogenation of para-substituted anilines **5** first, with NCS[9] (1-chloro-2,5-pyrrolidinedione, 1.0 equiv, 90 °C, 2−5 h) followed by iodine in the presence of silver sulfate[7a] (1.0 equiv, rt, 1.3 h), led to the corresponding 2-chloro-6-iodoanilines bearing functional groups such as an ester **6a** (83%), a fluoride **6b** (65%), or a nitrile **6c** (88%). Additional nitrogen protection using the protecting group $(ClMe_2SiCH_2)_2$ (1.0 equiv, −60 °C)[10] in the presence of TMPMgCl·LiCl (magnesium 2,2,6,6-tetramethylpiperidide−lithium chloride, 2.0 equiv, −60 °C, 1 h) provided the expected building blocks **4a** (83%), **4b** (81%), and **4c** (98%) (Scheme 2). The Negishi cross-couplings of alkynylzinc chlorides (R = Ph, Bu)[11] with an aryl iodide of type **4** [Pd$(PPh_3)_4$ (2−4 mol %), 60 °C, 17 h] afforded the expected *o*-alkynylanilines **3a** (97%), **3b** (96%), and **3c** (70%). These protected anilines **3** undergo smoothly successive metalations using TMPMgCl·LiCl and provide after trapping with different electrophiles fully functionalized anilines of type

Scheme 3. One-Pot Procedure for the Polyfunctionalization and Deprotection of Aniline Derivative **3a**



Scheme 4. Polyfunctionalization and Deprotection of *p*-Fluoro-Substituted Aniline **3b**



(3) (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. (b) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355. (c) Beller, M.; Breindl, C.; Riermeier, T. H.; Eichberger, M;, Trauthwein, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3389. (d) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507. (e) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501. (f) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2757. (g) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc*. **2000**, *122*, 5662. (h) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 10251. (i) Rodriguez, A. L.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (j) Köhling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett*. **2003**, *5*, 3213. (k) Knepper, K.; Bräse, S. *Org. Lett*. **2003**, *5*, 2829. (l) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295. (m) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1881.

(4) (a) Gribble, G. W. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 1, p 43. (b) Greenhill, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 497. (c) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. (d) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899. (e) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757. (f) Kondo, Y.; Yoshida, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331. (g) Schlosser, M.; Ginanneschi, A.; Leroux, F. *Eur. J. Org. Chem.* **2006**, 2956, and refs cited therein. (h) Yang, X.; Althammer, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 1665.

(5) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 156.

(6) (a) Krasovskiy, A;, Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P.; *Org. Lett.* **2006**, *8*, 5673. (c) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. For pioneer work using magnesium amides, see: (d) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016.

(7) (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Org. Chem.* **2005**, *70*, 6213. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Adv. Synth. Catal.* **2006**, *348*, 1301.

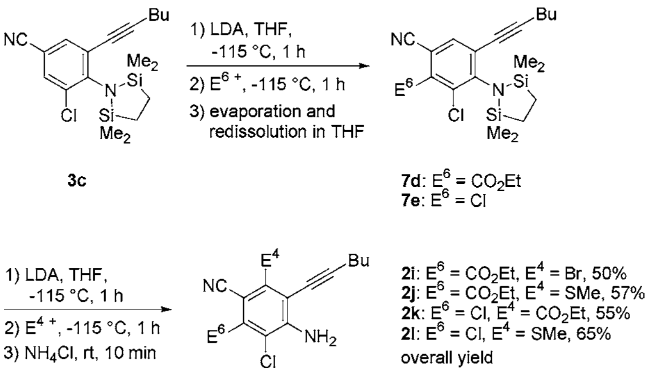
(8) (a) Negishi, E. *Acc. Chem. Res*. **1982**, *15*, 340. (b) King, A. O.; Okukado, N.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358. (c) Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957. (d) Qian, M.; Negishi, E. *Tetrahedron Lett.* **2005**, *46*, 2927. (e) Métay, E.; Hu, Q.; Negishi, E. *Org. Lett.* **2006**, *8*, 5773.

(9) Lazar, C.; Kluczyk, A.; Kiyota, T.; Konishi, Y. *J. Med. Chem.* **2004**, *47*, 6973.

(10) (a) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787. (b) Grega, K. C.; Barbachyn, M. R.; Brickner, S. J.; Mizsak, S. A. *J. Org. Chem.* **1995**, *60*, 5255.

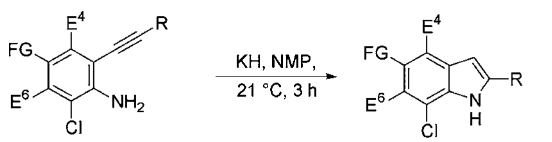
(11) The corresponding alkynylzinc chlorides (R = Ph, Bu) were prepared by first metalation with *i*-PrMgCl·LiCl or *n*-BuLi (21 °C, 0.5 − 1 h) followed by a transmetalation reaction with $ZnCl_2$ (1.0 equiv, c = 1.0 mol/L in THF, -30 °C, 30 min); see the Supporting Information.

Scheme 5. One-Pot Procedure for the Polyfunctionalization and Deprotection of Aniline Derivative **3c**



2 (Scheme 3). Thus, the *N*-protected aniline derivative **3a** led, after magnesiation with TMPMgCl·LiCl (1.1 equiv, rt, 2 h) and trapping with pivaldehyde (1.2 equiv, −30 °C, 1.5 h), to the expected magnesium alcoholate that cyclizes spontaneously to the crude lactone **7a**. After a short workup (see the Supporting Information), the lactone **7a** was again magnesiated with TMPMgCl·LiCl (1.2 equiv, −30 °C, 1.5 h). Successive trapping with several electrophiles such as $(BrCl_2C)_2$, TsCN, or $NCCO_2Et$ (−30 °C, 1.5 h) followed by

Scheme 6. Potassium Hydride Mediated Cyclization Reaction for the Preparation of Highly Functionalized Indoles **1a−l**

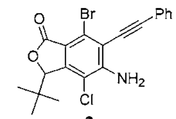
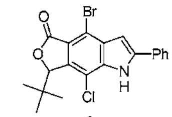
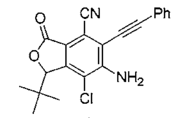
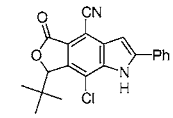
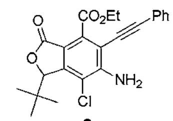
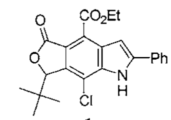
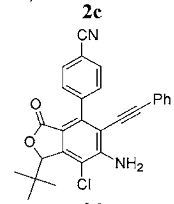
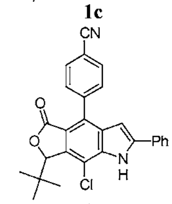
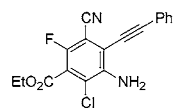
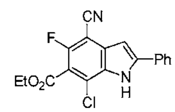
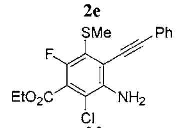
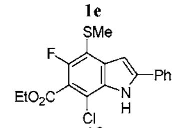
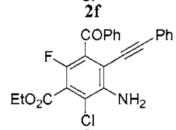
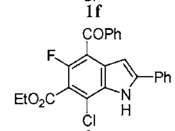
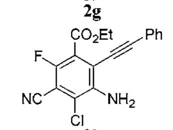
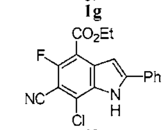
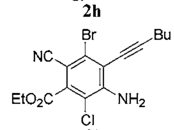
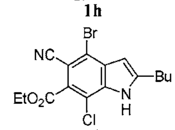
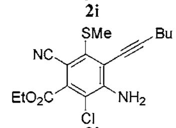
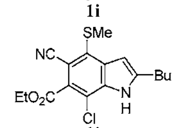
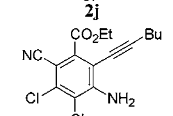
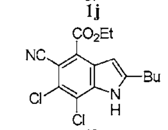
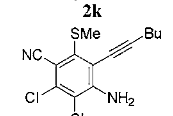
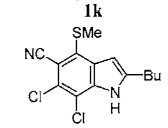


2a-l → **1a-l**: 62-98%

treatment with an acidic KF solution (ca. 3 equiv, rt, 12 h) afforded the corresponding fully functionalized anilines **2a** (75%), **2b** (76%), and **2c** (56%). After the transmetalation of **7a** with $ZnCl_2$ (1.3 equiv, −30 °C, 30 min), a $Pd(PPh_3)_4$-catalyzed Negishi cross-coupling reaction with 4-iodobenzonitrile (1.5 equiv, 60 °C, 35 h) provided the corresponding aniline **2d** in 56% overall yield (Scheme 3). Furthermore, we have extended this magnesiation procedure for the functionalization of the *p*-fluoro-substituted aniline derivative **3b** (Scheme 4). After deprotonation of **3b** with TMPMgCl·LiCl (1.1 equiv, rt, 2 h), the resulting magnesium intermediate was reacted with electrophiles such as $NCCO_2Et$ or TsCN leading to the expected products **7b** (89%) and **7c** (80%). Further treatment with TMPMgCl·LiCl (1.2 equiv, rt, 5.5 h) followed by the addition of TsCN, $PhSO_2SMe$,[12] PhCOCl,[13] or $NCCO_2Et$ led, after deprotection in the presence of an acidic KF solution (4.5 equiv, 74 °C, 20 min, microwave), to fully functionalized anilines **2e** (76%), **2f**

(12) Stoll, A. H.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 606.

Table 1. Potassium Hydride Mediated Preparation of Highly Functionalized Indoles of Type **1**

entry	aniline of type **2**	product of type **1**	yield (%)[a]
1	 **2a**	 **1a**	98
2	 **2b**	 **1b**	96
3	 **2c**	 **1c**	91
4	 **2d**	 **1d**	86
5	 **2e**	 **1e**	93
6	 **2f**	 **1f**	98
7	 **2g**	 **1g**	62
8	 **2h**	 **1h**	75
9	 **2i**	 **1i**	98
10	 **2j**	 **1j**	92
11	 **2k**	 **1k**	91
12	 **2l**	 **1l**	93

[a] Isolated yield of analytically pure compounds.

(70%), **2g** (96%), and **2h** (93%). Moreover, the *p*-cyano-substituted aniline **3c** could also be metalated. The magnesiation with TMPMgCl·LiCl did not occur to a reasonable extent, so that we have performed the direct lithiation of compound **3c** using LDA (1.05 equiv, −115 °C, 1 h, Scheme 5). Neither attack on the nitrile group nor aryne formation were observed. Quenching with electrophiles such as $NCCO_2$-Et or FCl_2CCClF_2[14] provided the expected products **7d** and **7e**. After evaporation and redissolution in THF, the mixture was again reacted with LDA (1.05 equiv, −115 °C, 1 h) to give the corresponding lithiated intermediates. Trapping with $(BrCl_2C)_2$, $PhSO_2SMe$,[12] or $NCCO_2Et$ (−115 °C, 1 h) followed by acidic workup with saturated NH_4Cl (rt, 10 min) led to the completely functionalized unprotected anilines **2i** (50%), **2j** (57%), **2k** (55%) and **2l** (65%) through a convenient three-step, one-pot protocol.

Finally, the fully functionalized anilines of type **2** were transformed to the corresponding indoles of type **1** in the presence of KH (2.0−3.5 equiv). After the mild reaction at 21 °C for 3 h, the highly functionalized indoles **1a−l** were obtained in 62−98% yield (Scheme 6, Table 1, entries 1−12).

In summary, we have shown that the successive metalation of *o*-alkyl- or arylalkynylanilines provides a convenient, straightforward access to fully substituted anilines of type **2**.[15] Functional groups such as esters, nitriles, or halogenides are tolerated even using strong lithium amide bases such as LDA. Furthermore, we have transformed these anilines to various new highly functionalized unprotected indoles in excellent yields. In comparison to directed indole metalations, this approach provides an easy access for the functionalization of the positions 4, 5, 6, and 7 of the adjacent benzene ring.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The benzoylation reaction providing compound **2g** was performed by first a transmetalation to the corresponding copper intermediate using CuCN·2LiCl (1.2 equiv, −30 °C, 30 min) followed by the addition of PhCOCl (1.3 equiv, −30 °C, 1.5 h); for the use CuCN·2LiCl, see: Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(14) Marzi, E.; Bobbio, C.; Cottet, F.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 2116.

(15) **Typical Procedure. Preparation of 5-Amino-7-bromo-3-*tert*-butyl-4-chloro-6-phenylethynyl-3*H*-isobenzofuran-1-one (2a).** A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with the aniline derivative **3a** (1.33 g, 3.00 mmol) and THF (2.5 mL). After the addition of TMPMgCl·LiCl (2.75 mL, c = 1.20 mol/L) at 21 °C, the reaction mixture was stirred for 2 h and then cooled to −30 °C. Pivaldehyde (0.40 mL, 3.60 mmol) was added dropwise with a syringe, and the mixture was stirred for 1.5 h at this temperature. The completion of the reaction was checked by GC analysis of reaction aliquots treated with satd aqueous NH_4Cl solution. Quenching with a mixture of ice−water/NH_4Cl 2/1, extraction with diethyl ether, drying over Na_2SO_4, and concentration in vacuo provided the sensitive compound **7a** that was immediately used in the next step without further purification. After redissolution in THF (2.5 mL) and cooling to −30 °C, TMPMgCl·LiCl (3.00 mL, c = 1.20 mol/L) was added. The mixture was stirred for 1.5 h at −30 °C followed by the dropwise addition of 1,2-dibromo-1,1,2,2-tetrachloroethane (1.27 g, 3.90 mmol, solution in THF). After being stirred for a further 1.5 h, the cooling device was removed, allowing the reaction mixture to warm to 21 °C. Aqueous HCl (10 mL, c = 2 mol/L) was added followed by KF (0.46 g, 8.0 mmol) and HCl (0.15 mL, 38% in H_2O). The mixture was stirred vigorously at 21 °C over night (12 h) and neutralized with satd aqueous Na_2CO_3. After extraction with CH_2Cl_2, drying over Na_2SO_4, and concentration in vacuo, purification by column chromatography (eluant: pentane/ethyl acetate, 3:1) afforded **2a** (943 mg, 75%) as a light yellow solid (mp 210.4−212.7 °C).