GlucoSiFA and LactoSiFA: New Types of Carbohydrate-Tagged Silicon-Based Fluoride Acceptors for ¹⁸F-Positron Emission Tomography (PET)

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Abstract
GlucoSiFA derivatives bearing an azide or alkynyl side chain were obtained from peracetyl- D-glucose using as key step a tosylation substitution by a SiFA thiolate obtained from 4-(di-tert-butylfluorsi- lyl)benzenethiol. In analogy, two-fold SiFA-substituted maltose and lactose derivatives were synthesized via bistosylates. Introduction of an acetal-protecting group in β-D-azidolactose allowed the synthesis of a LactoSiFA derivative bearing only one SiFA moiety.

Key words carbohydrates, silicon-based fluoride acceptors, nucleophilic substitution, tosylation, regioselectivity

The introduction of positron emission tomography (PET) as a non-invasive method for medical diagnostic in vivo imaging has become an indispensable tool in precision medicine development. PET not only helps to understand the complex interplay between biological targets such as receptors and enzymes and their cognate ligands but furthermore assists devising new therapeutic regimens based on non-invasive biological target validation. Besides PET, a straightforward example for diagnostic imaging is the use of X-rays that has revolutionized medicine. However, this method only yields anatomic/structural information whereas PET and related radioisotope-based imaging methodologies look directly at dynamic biological processes without interference. PET, in addition to magnetic resonance imaging (MRI) and computed tomography (CT), has proved to be an elegant and non-invasive method to elucidate in vivo biochemistry. It allows metabolic tracking of bioactive compounds and quantification of biochemical and/or enzymatic processes in living organisms. Among commonly used radioactive isotopes such as ¹³C, ¹⁵N, ¹⁸O, ¹⁸F, ⁶⁴Cu, and ⁶⁸Ga, the use of fluorine-18 has become rather popular due to its favorable physical properties such as a half-life of 109.7 minutes that allows for longer synthesis times and remote shipment to local imaging facilities and a low positron energy leading to PET images of highest resolution.

There are different strategies for incorporating ¹⁸F into radiopharmaceuticals. On the one hand, fluorination at carbon atoms in both aromatic and aliphatic compounds can be achieved by electrophilic as well as nucleophilic reactions and a variety of appropriate reagents has been developed for this purpose. Alternatively, ¹⁸F can also be bound via isotopic exchange to non-carbon elements such as boron, aluminum, silicon, and phosphorus. These non-canonical labeling concepts got momentum in the last two decades although some of the labeling principles have already been introduced to the literature as early as 1958 but remained dormant for many years. The progress achieved in these types of chemistry was regularly summarized in review articles. Aryldialkylsilicon fluorides, ArR₂SiF, in which the silicon atom is sufficiently protected with R = isopropyl6 or tert-butyl7a substituents are stable under physiological conditions and undergo ¹⁹F to ¹⁸F isotopic exchange with good radiochemical yields. The tert-butyl-
isotopes of iodine and copper-64. A variety of different radionuclides such as carbon-11, fluorine-18, gallium-68, different radioisotopes of iodine and copper-64. With this in mind and the intention to increase the water-solubility of the SiFA moiety, herein we report the synthesis and characterization of SiFA-substituted sugar de-
derivatives that also contain a variety of functional groups that hold potential for subsequent protein conjugation by click-type chemistry.

Our synthesis of the β-D-azido-substituted GlucoSiFA derivative 5 (Scheme 1) started with peracetyl-D-glucose (1; mixture of anomers), which was first brominated at the anomeric center with HBr/AcOH. The resulting α-D-glycosyl bromide underwent clean substitution with sodium azide to afford β-D-glycosyl azide 2. Both steps proceeded in excellent yield, as did the subsequent deprotection with sodium methoxide. A selective monotosylation at the primary hydroxy group of the unprotected β-D-azidoglucose gave the difunctionalized monosaccharide 3 in 72% yield. Finally, the desired GlucoSiFA derivative 5 was obtained in 74% yield (51% over 5 steps) by nucleophilic substitution of the tosylate with deprotonated 4-(di-tert-butylfluorosilyl)benzenethiol (4). Due to the pronounced base sensitivity of SiFA derivatives, this step has to be carried out with bulky, less nucleophilic bases. In the event, potassium tert-butoxide in DMSO gave the best results.

![Scheme 1 Synthesis of β-D-azido-substituted GlucoSiFA derivative 5](image)

Starting point of the synthesis of the β-D-alkynyl-substituted GlucoSiFA derivative 8 (Scheme 2) was the Lewis acid catalyzed substitution of the anomeric acetyl group of peracetyl-D-glucose (1) with propargyl alcohol, which provided β-D-glycoside 6 in 76% yield. The following steps via monotosylate 7 proceeded as before and gave target molecule 8 in 33% yield over four steps.

![Scheme 2 Synthesis of β-D-alkynyl-substituted GlucoSiFA derivative 8](image)

In order to further increase the hydrophilicity of carbohydrate-tagged SiFA derivatives, we next used disaccharides as starting material. Here, serious reactivity and selectivity issues were encountered. For example, even though β-D-azidogalactose can be monotosylated selectively at the primary hydroxy group, all attempts of a monotosylation of β-D-azidomelibiose (which also contains only one primary hydroxy group) failed and provided either mixtures of bistosylated products at low yield, or no product at all. We then shifted our attention to maltose and lactose as starting disaccharides and first prepared two-fold SiFA-substituted derivatives (Scheme 3).

Whereas the tosylation of β-azido-D-maltose (9a) with pTsCl in pyridine proceeded rather sluggishly, the reactivity was strongly increased in the presence of zinc bromide. Under these conditions, complete conversion was observed after 1 hour at −20 °C, and the bistosylate 10a was isolated in 50% yield. Both leaving groups could be replaced with SiFA moieties under standard conditions using 4 and tBuOK to afford the target molecule 11a in 67% yield. The corresponding SiFA-tagged β-alkynyl-D-maltose 11b was obtained in the same manner from 9b via bistosylate 10b in 31% and 55% yield, respectively.

Similar to the maltose derivatives, the corresponding β-azido- and alkynyl-substituted D-lactoses 12a/b could not be selectively monotosylated at one of the two primary hydroxy groups. Rather, the bistosylates 13a/b were obtained in 44% and 36% yield, which were converted into the two-fold SiFA-modified lactoses 14a/b in moderate yields (33/36%).

It is evident from these results that a protection of one of the two primary hydroxy groups is required for the synthesis of a disaccharide bearing only one SiFA unit. Gratifyingly, the presence of an axial OH group in the galactose ring of β-D-azidolactose 12a allows a selective acetalization to afford product 15 in 74% yield (Scheme 4). For this substrate, the selectivity of the tosylation was examined in detail (Table 1).

With 4 equivalents of zinc bromide and 5 equivalents of tosyl chloride in pyridine at −20 °C, a mixture of the desired monotosylate 16 (41% yield) and the bistosylate 17 (21% yield) was obtained after 10 minutes (Table 1, entry 1). Thus, not only the primary, but also the secondary hydroxy group at C-4′ are reactive under these conditions. As expected, increasing the reaction time up to 40 minutes fa...
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The formation of the bistosylate 17 (entries 2–4); the best yield of the monotosylate 16 (49%) was obtained after 30 minutes and decreased to 30% after 40 minutes. Smaller amounts of pTsCl afforded a higher selectivity in favor of the monotosylate 16 (entries 5 and 6), which was isolated as the sole product in the presence of 1.3 equivalents of pTsCl (entry 6), albeit in a low yield of 30%. Interestingly, the tosylation of the corresponding lactose derivative bearing a propargyl glycoside instead of the azido group gave only a bistosylate bearing the tosyl groups at the 2-CH2 group and C-4. At this point, it is not clear which factors govern the regioselectivity of these transformations. Unfortunately, attempts to introduce other leaving groups (mesylate, 4-bromophenylsulfonate, bromide) failed.

The structural assignment of tosylation products 16 and 17 is based on extensive NMR studies. Moreover, both products were isolated in crystalline form and characterized by single crystal X-ray diffraction analysis. The quality of the crystals of monotosylate 16 was rather low and allowed only the structural assignment of the constitution, but not of the absolute stereochemistry of the acetal stereocenter. In contrast to this, the acetal stereocenter of the major isomer (87%) of bistosylate 17 (Figure 1) shows S-configuration as estimated by the twin law of the measured crystal. The X-ray diffraction analysis also proved the presence of the two tosyl groups at the 2-CH2 and 4′ positions.

The protected monotosylated β-azido-ᴅ- lactose derivative 16 obtained in 49% yield under the conditions of Table

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**Scheme 3** Synthesis of two-fold SiFA-substituted maltose and lactose derivatives 11 and 14

**Scheme 4** Synthesis of β-ᴅ-azido-substituted LactoSiFA derivative 19

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The protected monotosylated β-ᴅ-azido-ᴅ- lactose derivative 16 obtained in 49% yield under the conditions of Table
procedures for the monofunctionalization of suitable carbohydrates, as well as, the synthesis of carbohydrate-tagged SiFA derivatives bearing different handles for protein conjugation.

Reactions were carried out under argon atmosphere using oven- or flame-dried glassware. Air- and moisture-sensitive reagents were transferred via syringe. All reagents were obtained commercially and used without further purification. THF, Et₂O, CH₂Cl₂, and MeCN were dried using a MB-SPS-800 system (M. Braun). Reactions were monitored by TLC using silica gel 60 plates provided by Merck and Macherey-Nagel. Visualization was accomplished with UV light (254 nm), ceric ammonium molybdate, KMnO₄, or anisaldehyde.

1H, 13C, 19F, and 26Si NMR spectra were recorded with Bruker Avance III HD (400–600 MHz) and calibrated against residual solvent peaks. IR spectra were obtained with a PerkinElmer Spectrum Two UATR spectrophotometer. Mass spectra were recorded with a Thermo Fisher Scientific TSQ (LCMS-ESI) and a Thermo Electron LTQ Orbitrap spectrometer (HPLC-ESI).

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>ZnBr₂·2 H₂O (equiv)</th>
<th>PtCl (equiv)</th>
<th>Time (min)</th>
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<td>30</td>
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</table>

* In pyridine at −20 °C.

Figure 1

X-ray crystal structure of bistosylate 17

1, entry 3, was treated with the thiolate formed by deprotonation of 4-(di-tert-butylfluorosilyl)benzenethiol (4) with tBuOK. The SiFA-tagged lactose derivative 18 was isolated in 61% yield. Finally, acetal cleavage was achieved by heating 18 with 80% aqueous acetic acid to 70 °C for 4 hours. This afforded the desired β-α-azido-substituted LactoSiFA derivative 19 in 64% yield (14% over 4 steps from 12a) (Scheme 4).

In conclusion, this work demonstrates the utility of carbohydrates for the synthesis of hydrophilic SiFA derivatives. The GlucoSiFA derivatives 5 and 8 bearing an azide or alkyn handle for peptide and protein conjugation via 1,3-dipolar cycloaddition were obtained in a straightforward manner from peracetyl-D-glucose in 51% and 36% overall yield, respectively. The key step is the substitution of a tosylate by a SiFA thiolate obtained from 4-(di-tert-butylfluorosilyl)benzenethiol (4). In analogy, the two-fold SiFA-substituted maltose and lactose derivatives 11 and 14 are readily accessible in overall yields between 13% and 34%. Introduction of an acetal protecting group in β-D-azidolactose 12a allowed the synthesis of the LactoSiFA derivative 19 in 14% overall yield. Further work is devoted to improved
A solution of (2R,3S,4R,5R,6R)-2-azido-3,4,5-trihydroxytetrahydro-2H-pyran-3-yl)methyl 4-Methylbenzolsulfonate (3)

A solution of (2R,3S,4R,5R,6R)-2-azido-3,4,5-triol (585 mg, 2.85 mmol, 1.0 equiv) in anhyd pyridine (7 mL) was cooled to 0 °C and treated with pTsCl (962 mg, 5.05 mmol, 1.3 equiv) in anhyd pyridine (3 mL). The mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, EtOAc); yield: 1.22 g (84%); colorless solid.

IR (ATR): 3347, 3293, 2934, 2859, 1582, 1470, 1387, 1365, 1262, 1180, 1066, 1007, 824, 811, 740, 715, 645 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.78 (d, J = 8.3 Hz, 2 H, ArH), 7.45 (d, J = 8.1 Hz, 2 H, ArH), 4.37 (d, J = 7.8 Hz, 1 H, β-H), 4.34 (dd, J = 10.9 Hz, J₂ = 1.8 Hz, 1 H, 2H), 4.29–4.26 (m, 1 H, 4H), 4.21 (s, 1 H, 4H), 4.19–4.15 (m, 1 H, 3H), 3.32–3.23 (m, 1 H, 3H), 3.34 (dd, J = 9.2 Hz, J₂ = 7.9 Hz, 1 H, 2H), 2.43 (s, 3 H, ArCH₃).

IR (ATR): 3354, 3290, 2115, 1347, 1248, 1188, 1167, 1106, 1064, 1011, 969, 936, 836, 824, 811, 740, 715, 646, 599 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 7.52 (d, J = 8.1 Hz, 2 H, ArH), 7.39 (d, J = 8.1 Hz, 2 H, ArH), 4.59 (d, J = 8.4 Hz, 1 H, β-H), 3.69–3.66 (m, 1 H), 3.59–3.48 (m, 4 H), 3.34 (t, J = 8.5 Hz, 1 H), 3.31 (dd, J₁ = 14.1 Hz, J₂ = 7.8 Hz, 1 H), 1.05 [s, 18 H, 2 × C(CH₃)₃].

13C NMR (150 MHz, CDCl₃): δ = 138.4 (s, Ar), 134.5 (d, J = 4.1 Hz, Ar), 130.8 (s, J = 13.8 Hz, Ar), 127.2 (d, Ar), 90.0 (d, CH₃N), 76.9, 76.4, 73.5, 72.5 (4 d, CH₄), 34.5 (t, CH₃S), 27.3 [q, C(CH₃)₃], 20.3 [s, J = 12.4 Hz, C(CH₃)₃].

HRMS (ESI): m/z calcd for C₂₀H₃₃FN₃O₄SSi [M + H]+: 458.19396; found: 458.19396;

[(2R,3S,4S,5R,6R)-3,4,5-Trihydroxy-6-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran-2-yl]methyl 4-Methylbenzolsulfonate (7)

A solution of (2R,3S,4S,5R,6R)-3,4,5-triol (847 mg, 3.88 mmol, 1.0 equiv) in anhyd pyridine (7 mL) was cooled to 0 °C and treated with pTsCl (706 mg, 3.71 mmol, 1.0 equiv) in anhyd pyridine (3 mL). The mixture was stirred at rt for 24 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, EtOAc); yield: 1.12 g (65%); colorless solid.

IR (ATR): 3354, 3290, 2115, 1347, 1248, 1188, 1167, 1079, 1057, 1012, 967, 894, 813, 781, 705, 663, 552, 505 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 5.95 (s, J = 15.7 Hz, 1 H, β-H), 5.32 (d, J = 8.7 Hz, 1 H, CHO), 4.51 (d, J = 8.7 Hz, 1 H, β-H), 2.42 (d, J₁ = 10.8 Hz, J₂ = 1.7 Hz, 1 H), 3.52 (dd, J₁ = 9.8 Hz, J₂ = 6.5 Hz, 1 H), 3.16 (dd, J₁ = 8.9 Hz, J₂ = 5.2 Hz, 1 H), 3.04 (td, J₁ = 9.4 Hz, J₂ = 5.6 Hz, 1 H), 2.95 (td, J₁ = 8.8 Hz, J₂ = 5.6 Hz, 1 H), 2.45 (s, 3 H, ArCH₃).

13C NMR (150 MHz, DMSO-d₆): δ = 136.2 (s, ipso-Ar), 130.6, 128.1 (2 d, Ar), 90.1 (d, CHN), 76.5 (d, CH₃CH₃), 75.7, 73.5, 70.3 (3 d, CHO), 69.5 (t, CHOCH₂), 21.8 (q, ArCH₃).

HRMS (ESI): m/z calcd for C₂₉H₄₁FN₃O₄SSi [M + Na]+: 495.07711; found: 495.07710.


A solution of 4 (50 mg, 0.18 mmol, 1.2 equiv) in anhyd DMSO (1 mL) was treated with BuOK (20 mg, 0.18 mmol, 1.2 equiv). The mixture was stirred at 50 °C for 30 min. After the addition of 7 (56 mg, 0.15 mmol, 1 equiv) in anhyd DMSO (1 mL), the mixture was stirred at 50 °C for 24 h. Cooling to rt was followed by addition of excessaq 1 M HCl. The mixture was dissolved in Et₂O and washed withaq 1 M HCl (3 × 20 mL) and H₂O (3 × 20 mL). After drying (MgSO₄), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel) using a gradient starting withpentane/Et₂O (15:1) and ending with Et₂O/MeOH (20:1); yield: 36.8 g (52%); colorless powder.

IR (ATR): 3347, 3293, 2934, 2859, 1582, 1470, 1387, 1365, 1218, 1106, 1007, 824, 811, 740, 715, 645, 599 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.57–7.49 (m, 2 H, ArH), 7.39–7.36 (m, 2 H, ArH), 4.50 (d, J = 7.3 Hz, 1 H, β-H), 4.36 (dd, J₁ = 15.7 Hz, J₂ = 2.4 Hz, 1 H), 4.25 (dd, J₁ = 15.9 Hz, J₂ = 2.2 Hz, 1 H), 3.61–3.48 (m, 4 H, 3H), 3.46–3.41 (m, 1 H), 3.17 (dd, J₁ = 14.2 Hz, J₂ = 7.3 Hz, 1 H), 2.48 (t, J = 2.4 Hz, 1 H), 1.60 (br s, 3 H, CHOH). 1.05 [s, 18 H, 2 × C(CH₃)₃].
A solution of 9a (100 mg, 0.27 mmol, 1.0 equiv) in anhyd pyridine (2.4 mL) was cooled to −20 °C and treated with ZnBr₂·2H₂O (243 mg, 1.08 mmol, 4.0 equiv) and then with pTsCl (257 mg, 1.35 mmol, 5.0 equiv) in anhyd pyridine (1 mL). The mixture was stirred at −20 °C for 1 h. The reaction was carried out three times in separate flasks. The reaction mixtures were combined, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, EtOAc): yield = 367 mg (50%); colorless solid.

IR (ATR): 3705, 3363, 1722, 1450, 1353, 1242, 1165, 1107, 1062, 921, 812, 660, 551, 504 cm⁻¹.

HRMS (ESI): m/z calc for C₂₉H₉₂F₆N₂O₈S₂Si₂Na [M + Na⁺]: 1258.7; found: 1226.7 (M⁻).

13C NMR (100 MHz, CDCl₃): δ = 138.8 (s, Ar), 134.1 (d, Ar), 130.4 (s, Ar), 127.1 (d, Ar), 100.1 (d, CH₂C₆H₅), 77.2 (s, C(CH₃)₃), 76.3 (d, CH), 75.4 (s, C(C₆H₅)₃), 75.3, 73.6, 72.9 (3 d, CH₃), 55.9 (t, CH₃C₆H₅), 34.5 (t, CH₂S), 27.3 (q, CH₂C₆H₅), 20.3 [s, J = 12.5 Hz, CH₃(CH₂)₃].

19F NMR (565 MHz, CDCl₃): δ = −188.9 (d, J = 297.6 Hz).

29Si NMR (119 MHz, CDCl₃): δ = 15.3 (d, J = 297.8 Hz).

HRMS (ESI): m/z calc for C₂₉H₉₂F₆N₂O₈S₂Si₂Na [M + Na⁺]: 894.36449; found: 894.36446.

A solution of 12a (100 mg, 0.22 mmol, 1.0 equiv) in anhyd pyridine (2.4 mL) was cooled to –20 °C and treated with ZnBr₂·2 H₂O (237 mg, 1.08 mmol, 4.0 equiv) and then with pTsCl (257 mg, 1.35 mmol, 5.0 equiv) in anhyd pyridine (1 mL). The mixture was stirred at –20 °C for 48 h. Cooling to rt was followed by addition of excess aq 1 M HCl (3 × 20 mL) and H₂O (3 × 20 mL). After drying (MgSO₄), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel) using a gradient starting with cyclohexane/EtOAc (3:1) and ending with EtOAc; yield: 160 mg (89.0%); HRMS (ESI): m/z calcd for C₂₉H₃₇O₁₅S₂Na [M + Na]⁺: 872.36359; found: 872.36441.

A solution of 12b (100 mg, 0.26 mmol, 1.0 equiv) in anhyd pyridine (2.3 mL) was cooled to –20 °C and treated with ZnBr₂·2 H₂O (237 mg, 1.05 mmol, 4.0 equiv) and then with pTsCl (251 mg, 1.33 mmol, 5.0 equiv) in anhyd pyridine (1 mL). The mixture was stirred at –20 °C for 90 min. The reaction was carried out twice in separate flasks. The re-action mixtures were combined, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel), using a gradient starting with EtOAc/cyclohexane (30:1) and ending with EtOAc/MeOH (10:1); yield: 160 mg (44%); colorless solid.

IR (ATR): 3369, 2912, 2116, 1728, 1598, 1451, 1352, 1255, 1173, 1060, 971, 811, 769, 689, 662, 550 cm⁻¹.

IR (ATR): 3343, 2912, 2712, 1598, 1451, 1352, 1173, 1049, 1019, 971, 931, 836, 819, 769, 691, 661, 551 cm⁻¹.

IR (ATR): 3343, 2912, 1728, 1598, 1451, 1352, 1173, 1049, 1019, 971, 931, 836, 819, 769, 691, 661, 551 cm⁻¹.
A solution of 15 (100 mg, 0.22 mmol, 1.0 equiv) in anhyd pyridine (2 ml) was cooled to −20 °C and treated with ZnBr₂·H₂O (198 mg, 0.88 mmol, 4.0 equiv) and then with pTsCl (209 mg, 1.1 mmol, 5.0 equiv) in anhyd pyridine (1 ml). The mixture was stirred at −20 °C for 30 min. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel) using a gradient starting with EtOAc/cyclohexane (1:1, +1 Et₂N) and ending with EtOAc/MeOH (3:1, +1 Et₂N). Yield: 66 mg (49%); colorless solid.

1H NMR (600 MHz, DMSO-d₆): δ = 7.76 (d, J = 8.1 Hz, 2 H, ArH), 7.44 (dd, J₁ = 6.1 Hz, J₂ = 2.4 Hz, 2 H, ArH), 7.41–7.35 (m, 5 H, ArH), 5.74 (d, J = 5.6 Hz, 1 H, OH), 5.56 (s, 1 H), 5.19 (d, J = 4.1 Hz, 1 H, OH), 5.06–4.99 (m, 2 H, OH), 4.63–4.56 (m, 2 H), 4.33 (d, J = 7.4 Hz, 1 H), 4.13 (dd, J₁ = 11.0 Hz, J₂ = 7.2 Hz, 1 H), 4.09–4.05 (m, 2 H, ArH), 3.96 (d, J = 12.2 Hz, 1 H), 3.79 (t, J = 8.3 Hz, 1 H), 3.58 (s, 1 H), 3.48–3.39 (m, 3 H), 3.36 (d, J = 9.5 Hz, 1 H), 3.03 (dd, J₁ = 8.6 Hz, J₂ = 5.8 Hz, 1 H), 2.38 (s, 3 H, ArCH₃).

IR (ATR): 3486, 3037, 2875, 2116, 1729, 1598, 1357, 1246, 1103, 1043, 963, 905, 868, 812, 697, 669, 552 cm⁻¹.

HRMS (ESI): m/z calcd for C₄₀H₃₂N₂O₃S₆Na [M + Na⁺]: 876.16; found: 876.32.

X-ray Crystal Data

Intensity data for the colorless crystal of compound 17 were collected on a D8 Venture Bruker Diffractometer, SC-KRD using Cu-Kα radiation at 173(2) K. The molecular structure was solved with direct methods using SHELXS-2014/7 or SHELXTL-2014/7 and refinements were carried out against F² by using SHELXL-2014/7 or OLEX2. The data obtained by the measurement were treated in the refinement procedure as a 2-component twin. Applying the TwinRotMat option in the program PLATON revealed a twin law (BASF 0.13258).

A solution of 4 (110 mg, 0.41 mmol, 1.2 equiv) in anhyd DMSO (3 ml) was treated with rBuOK (45.8 mg, 0.41 mmol, 1.2 equiv). The mixture was stirred at 50 °C for 30 min. After the addition of 16 (207 mg, 0.34 mmol, 1 equiv) in anhyd DMSO (1 ml), the mixture was stirred at 50 °C for 2 d. Cooling to rt was followed by addition of excess aq 1 M HCl. The mixture was dissolved in Et₂O and washed with aq 1 M HCl (3 × 20 ml) and H₂O (3 × 20 ml). After drying (MgSO₄), the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel) using a gradient starting with cyclohexane/EtOAc (2:1) and ending with EtOAc; yield: 146 mg (61%); colorless solid.
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611656.

References

(11) CCDC 1866515 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.