Synthesis of Dithiane-Based Photolabile Molecular Systems

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Dedicated to Howard E. Zimmerman on the occasion of his 75th birthday

Abstract: Synthesis of photolabile molecular systems based on lithiodithiane addition to carbonyl compounds is described. Dithianes of the spiro structure, e.g., 2,4,8,10-tetrathiaspiro[5.5]undecane and 2,4-dithia-8,10-dioxaspiro[5.5]undecane are utilized as tethers, thus allowing for a modular approach to building a diverse set of photocleavable molecules. A variety of carbonyl compounds ranging from simple substituted benzaldehydes to formylated benzocrown ethers, carbohydrates or calixarenes are found to be suitable for this chemistry.

Key words: photolabile molecular hosts, photoinduced electron transfer, dithiane, 2,4,8,10-tetrathiaspiro[5.5]undecane, 2,4-dithia-8,10-dioxaspiro[5.5]undecane, calix[4]arene, benzocrown ether, ribofuranose, glucopyranose, galactopyranose

Recently we reported1 an efficient photoinduced C-C bond cleavage in α-hydroxyalkyl-1,3-dithianes (Corey–Seebach dithiane-carbonyl adducts2). The mechanism of this reaction involves photochemically induced single electron transfer from the dithiane moiety to the excited molecule of ET-photosensitizer (benzophenone), accompanied by mesolytic C-C cleavage in the generated cation-radical, which is assisted by the anion-radical of benzophenone.

In view of the remarkable efficiency for both lithiodithiane addition to substituted benzaldehydes and photo-fragmentation of such dithiane adducts, we have been investigating the applicability of these systems as molecular latches that could be used to attach various molecular and macromolecular blocks and, at the same time, could be selectively unfastened on demand.3 One of the many potential applications for these systems could be in assembling photocleavable molecular hosts capable of releasing guest molecules upon irradiation. Our specific strategy was to tether two formylated macromolecular blocks with spiro-bis-dithiane 1 (Scheme 2) or dithiane-bis-methanol 2 (Scheme 3) to produce a photolabile system equipped with one or two photocleavable C-C bonds. A variety of compounds having a benzaldehyde fragment in their structure are suitable for such assembly. In this paper we report the synthesis of the linkers 1 and 2, approaches to several dithiane-bearing molecular building blocks and, finally, joining these blocks together to furnish photolabile molecular systems.

Synthesis of linkers 1 and 2: The novel spiro-bis-
87% of the corresponding tetrathioacetate 4 (Scheme 4). However, attempts to deacetylate 4 under basic conditions (MeONa/MeOH) produced the target tetra-thiol that was considerably contaminated by thietanes (Scheme 5). We rationalized that intramolecular nucleophilic displacement in this sterically hindered environment can be a significant channel to partially relieve steric strain. An alternative approach – combining both thioacetate hydrolysis and thioacetal formation in one step under acid-catalyzed conditions – was successful and the target spiro-bisdithiane 1 was obtained in 76% isolated yield.

Dimethanol 2 was synthesized from commercially available 2,2-bis(bromomethyl)-1,3-propanediol (5), which was first protected via cyclic acetal formation with formaldehyde to give 6, and then reacted with potassium thioacetate. The critical feature of this synthetic sequence was that during the next, acid-catalyzed step no extra formaldehyde was added and therefore the deprotection of the diol and formation of the dithiane ring occurred via methylenic transfer from oxygens to sulfurs (59% yield).

**Scheme 4**

More complex systems can be assembled using monoformylated calix[4]arene 9 as a building block (R = EtOCH$_2$CH$_2$). Its reaction with dilithiated 1 in THF furnished bis-calixarene 10 in 71% yield.

Bis-adducts 8 and 10 are photolabile molecular systems. They cleave quantitatively, regenerating benzaldehyde or calixarene 9 respectively, upon irradiation in the presence of benzophenone in acetonitrile.

Utilizing essentially the same conditions, we assembled crown ether-based hosts 11 and 12, starting from monoformylated dibenz-24-crown-8 and benzo-18-crown-6 ethers, respectively.
Complexation properties and photophysics of these and other molecular hosts described in this paper will be discussed elsewhere.

**Monoadducts as building blocks for non-symmetric assemblies:** In order to diversify the series of photocleavable molecular hosts containing our dithiane-based photolatching device, we synthesized a series of mono-adducts of 1 and monoacetals of 2, which were utilized in the subsequent steps for coupling with various formyl-bearing blocks:

Thus, on reacting formyl-substituted benzo crown ethers or calix[4]arene with mono-lithiated spiro-bis-dithiane 1, we synthesized 13–16.

Bidentate precursors 17–19 were prepared from mono-lithiated 1 and bis-formylated dibenzocrowns⁶ or calix[4]arene.⁵

Similar monodithiane-containing systems can be readily obtained from diol 2 via acetal formation. The simplest illustration of this approach is the benzaldehyde acetal 20, which upon treatment with butyl lithium and quenching with another mole of benzaldehyde produces photocleavable molecule 21.
We utilized this coupling mode in order to introduce chiral auxiliary groups into the building blocks, specifically, in conjunction with carbohydrate-based formylated systems. There are several readily available formyl-bearing pyranoses or furanoses, with fully protected hydroxy groups, which are suitable for Corey–Seebach chemistry. For example, treating furanose 22 with 2 under acid-catalyzed conditions furnished acetal 23 in 72% yield (Scheme 10). A similar synthetic sequence starting from D-galactose derivative 24 produced a D-galactopyranosyl-bearing dithiane 25, although the overall yield was only 38% (Scheme 11).
Glycosidation of phenols bearing formyl or dithiane moieties offered yet another approach to chiral building blocks. We coupled tetramethyl glucopyranose 26 with 5-(p-hydroxyphenyl)-1,3-dithiane 27 to furnish dithiane-bearing permethylated glucopyranoside 28.

Various carbohydrate fragments can also be introduced in the form of glycosides of p-hydroxybenzaldehyde. For example, glycosidation with tetraacetylated glucopyranosyl bromide produced 29, which we utilized as a carbonyl component.

Building a diverse series of photolabile molecular objects: Having such a diverse assortment of precursors, we then coupled them with aromatic aldehydes, ranging in complexity from unpretentious benzaldehyde, to formylated benzocrown ethers, to calixarenes. Figure 7 shows the photolabile (hybrid) systems that were synthesized by joining dissimilar dithiane and formyl-bearing components. Details on experimental procedures can be found in the experimental section.

In conclusion, we have shown that the classic dithiane-carbonyl chemistry can be successfully adopted to assemble a diverse set of organic macromolecules, which are capable of photochemically induced disassembly in the presence of electron-transfer sensitizers.

Common reagents were purchased from Aldrich Chemical Co. and used without additional purification. THF was refluxed over and distilled from potassium benzophenone ketyl prior to use. 1H and 13C NMR spectra were recorded at 25 °C on a Varian Mercury 400 MHz instrument. TMS was used as an internal standard. Column chromatography was performed on silica gel, 70–230 mesh ASTM, using EtOAc–hexane mixtures (gradient from 1:20 to 1:2), unless specified. HP 6890 with MSD detector was used to analyze the compounds.

5,5-Bis(bromomethyl)-[1,3]dioxane (6)
To a solution of 2,2-bis(bromomethyl)-1,3-propanediol (5, 5 g, 19.1 mmol) in formalin (7.0 mL) was added concd HCl (4 mL) at r.t. The mixture was refluxed overnight with stirring. After being cooled to r.t., it was extracted twice with CH2Cl2 (2/15 mL). The organic phases were combined and washed with sat. Na2CO3 (30 mL), dried (MgSO4), and solvent was then removed under reduced pressure to afford the crude acetal 6 (5.0 g, 96%). It was used without further purification.

1H NMR (CDCl3): δ = 4.79 (s, 2H), 3.83 (s, 4H), 3.58 (s, 4H).
13C NMR (CDCl3): δ = 94.4, 71.5, 38.1, 35.2.
MS (EI): m/z (%): 273 (M+ , 5), 244 (15), 214 (90), 163 (50), 133 (60), 53 (100).

Pentaerythritol tetrathioacetate (4)
Potassium thioacetate (31.8 g, 278 mmol) was dissolved in DMF (150 mL) and pentaerythrityl tetrabromide (3, 12.1 g, 31 mmol) was added to this solution. The reaction mixture was stirred under N2 atm for 60 h at 25 °C, the solvent was then removed under vacuum. The residue was dissolved in CH2Cl2 (150 mL) and washed thrice with H2O (3/100 mL). The organic phase was dried (MgSO4) and concentrated. The crude product was recrystallized from MeOH to give the title compound (10.1 g, 87%).

1H NMR (CDCl3): δ = 3.04 (s, 8H), 2.36 (s, 12H)
13C NMR (CDCl3): δ = 194.0, 42.7, 34.9, 30.7.
MS (EI): m/z (%): 325 ([M – CH3CO]+, 100), 283 (40), 241 (90), 223 (45), 119 (30).

5,5-Bis(acetylthiomethyl)-[1,3]dioxane (7)
Potassium thioacetate (6,25 g, 54.7 mmol) was dissolved in DMF (40 mL) and 5,5-bis(bromomethyl)-[1,3]dioxane (6, 5.0 g, 18.3 mmol) was added to this solution. The reaction mixture was stirred for one day at r.t. The solvent was removed under vacuum. The residue was dissolved in CH2Cl2 (50 mL), washed with H2O (50 mL), brine (50 mL), and dried (MgSO4). The organic layer was concentrated to afford the crude product 7 (4.0 g, 82%). It was used without further purification.

1H NMR (CDCl3): δ = 4.78 (s, 2H), 3.66 (s, 4H), 3.09 (s, 4H), 2.36 (s, 6H).
13C NMR (CDCl3): δ = 194.4, 94.1, 72.5, 37.7, 31.4, 30.7.

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MS (EI): m/z (%) = 264 (M^+, 2), 221 (100), 191 (10), 179 (10), 131 (15), 117 (20), 99 (14), 85 (22).

2,4,8,10-Tetrathiaspiro[5.5]undecane (1)
Pentaerythrityl tetrathioacetate (4, 3 g, 8.15 mmol) was suspended in a formalin–HCl mixture (53 mL of 40% formalin, 8 mL of 37% HCl) and the reaction mixture was refluxed for 16 h. It was neutralized with sat. Na₂CO₃ after being cooled to r.t. The product was extracted with CH₂Cl₂ (50 mL), the organic layer was dried (MgSO₄), and concentrated. Crude product was recrystallized from a CHCl₃–MeOH mixture. Decolorization when boiling with activated carbon in CHCl₃–MeOH (70:30) for 1 h gave white crystals 1 (1.39 g, 76%), mp 163–164 °C.

¹H NMR (CDCl₃): δ = 3.66 (s, 4H), 2.95 (s, 8H).

¹³C NMR (CDCl₃): δ = 38.6, 32.2, 24.9.

MS (EI): m/z (%) = 224 (M^+, 100), 177 (30), 131 (40), 99 (60), 85 (50).


5,5-Bis(hydroxymethyl)-[1,3]dithiane (2)
To a solution of 2 N HCl (20 mL) was added dithioacetate (7, 1 g, 3.8 mmol), and the reaction mixture was refluxed for one day. The dark oil residue was discarded. The reaction mixture was cooled, neutralized with Na₂CO₃, then extracted with CH₂Cl₂ (4 × 30 mL). The organic layer was dried (MgSO₄), and concentrated to give crude product 2 (0.40 g, 59%). Recrystallization from CHCl₃ afforded pure compound as white crystals, mp 100.5–101 °C.

¹H NMR (CDCl₃): δ = 3.90 (s, 4H), 3.77 (s, 1H), 3.69 (s, 2H), 2.96 (s, 1H), 2.72 (s, 4H).

¹³C NMR (CDCl₃): δ = 67.6, 67.3, 44.4, 34.6, 33.4, 32.1.

MS (EI): m/z (%) = 180 (M^+, 95), 115 (30), 85 (100), 71 (45), 57 (60).


Acetal Preparation with 2:3-Phenyl-2,4-dioxa-8,10-dithiaspiro[5.5]undecane (20); Typical Procedure
To a solution of benzaldehyde (106 mg, 1.0 mmol) and 5,5-bis-(hydroxymethyl)-[1,3]dithiane (2, 180 mg, 1.0 mmol) in benzene (20 mL) was added toluene sulfonic acid monohydrate (20 mg). H₂O was removed by azeotrope formation during 3 h. The reaction mixture was cooled to r.t. and washed with sat. NaHCO₃ (20 mL). The aqueous layer was extracted twice with benzene (2 × 20 mL), the organic phases were combined, dried (MgSO₄), and concentrated to give 20 (256 mg, 96%).

¹H NMR (CDCl₃): δ = 7.50–7.44 (m, 2H), 7.40–7.32 (m, 3H), 5.43 (s, 1H), 4.53 (d, 2H, J = 12 Hz), 3.70 (s, 2H), 3.66 (d, 2H, J = 12 Hz), 3.16 (s, 2H), 2.50 (s, 2H).

¹³C NMR (CDCl₃): δ = 137.6, 128.9, 128.2, 125.9, 102.3, 73.9, 34.7, 34.6, 32.4, 28.4.

MS (EI): m/z (%) = 268 (M^+, 100), 132 (50), 99 (55), 85 (55).

Figure 7 Photolabile hybrids assembled by coupling different dithiane- and formyl-bearing building blocks
3-(6-Methoxy-2,2-dimethyl-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2,4-dioxo-8,10-dithiaspiro[5,5]undecane (23)
Methyl 2,3-O-isopropylidene-5-aldehyde-β-d-ribofuranoside(8) (22, 500 mg, 2.5 mmol) and TsOH·H₂O (30 mg) in benzene were reacted, as described above for 20, to give 646 mg (72%) of 23.

1H NMR (CDCl₃): δ = 5.00 (s, 1H), 4.80 (d, 1H, J = 5 Hz), 4.53 (d, 1H, J = 5 Hz), 4.45 (d, 2H, J = 12 Hz, 4.37 (d, 1H, J = 8 Hz), 4.11 (d, 1H, J = 8 Hz), 3.67 (s, 2H), 3.42 (d, 2H, J = 12 Hz), 3.34 (s, 3H), 3.05 (s, 2H), 2.42 (s, 2H), 1.48 (s, 3H), 1.32 (s, 3H).

13C NMR (CDCl₃): δ = 112.5, 108.9, 101.2, 86.8, 88.4, 80.9, 79.3, 73.3, 54.7, 34.5, 34.4, 32.3, 28.5, 26.5, 25.2.


5-(2,4-Dioxo-8,10-dithiaspiro[5,5]undec-3-yl)-2,2,7,7-tetramethyl-tetrahydro-bis[1,3]dioxol[4,5-b;4',5'-d]pyrran (25)
1.2:3,4-Di-O-isopropylidene-6-aldehyde-α-D-galactopyranose(8,10) (24, 997 mg, 3.8 mmol) and TsOH·H₂O (40 mg) in benzene were reacted as described above and purified by column chromatography (silica gel; EtOAc–hexane) (620 mg, 38%).

1H NMR (CDCl₃): δ = 5.56 (d, 1H, J = 5 Hz), 4.66 (d, 1H, J = 7 Hz), 4.60 (dd, 1H, J = 12, 2 Hz), 4.58 (dd, 1H, J = 8, 2 Hz), 4.37 (dd, 1H, J = 12, 2 Hz), 4.29 (dd, 1H, J = 5, 2 Hz), 4.27 (dd, 1H, J = 12, 2 Hz), 3.76–3.74 (m, 2H), 3.67 (d, 1H, J = 14 Hz), 3.49 (dd, 1H, J = 12, 8 Hz), 3.13 (d, 1H, J = 14 Hz), 2.96 (d, 1H, J = 14 Hz), 2.48 (d, 1H, J = 14 Hz), 2.37 (d, 1H, J = 14 Hz), 1.54 (s, 3H), 1.46 (s, 3H), 1.35(s, 3H), 1.32 (s, 3H).

13C NMR (CDCl₃): δ = 109.2, 108.7, 107.0, 100.0, 96.3, 74.0, 72.7, 70.6, 70.5, 70.3, 68.8, 34.6, 34.5, 32.4, 28.6, 26.3, 26.1, 25.0, 24.6.

HRMS: m/z calcd for C₂₂H₂₃O₁₁S₂ [M⁺]: 421.1355. Found: 421.1299.

Dithiane–Carbonyl Adducts: Phenyl-3-phenyl-2,4-dioxo-8,10-dithiaspiro[5,5]undec-9-y]methanol (21); Typical Procedure
A solution of 3-phenyl-2,4-dioxo-8,10-dithia-spiro[5,5]undecane (20, 244 mg, 0.91 mmol) in freshly distilled THF (10 mL) was cooled to −25 °C under N₂. Then n-ButLi (1.6 M solution in hexanes, 0.56 mmol, 0.30 mL) was added drop-wise with stirring. The resulting mixture was stirred for 2 h at −25 °C to complete lithiation. The resulting solution of the anion was cooled to −78 °C, and a solution of benzaldehyde (155 mg, 1.46 mmol) in THF (2 mL) was added drop-wise with stirring. The reaction mixture was stirred for 1 h at this temperature and then stored in a freezer at −25 °C overnight. It was quenched with a sat. NH₄Cl solution, extracted twice with Et₂O, added drop-wise with stirring. The reaction mixture was stirred for 2 h at −25 °C and reacted as described above for 21 with 5-formyl-25,26,27,28-tetraspiro(2-ethoxyethoxy)calix[4]arene (9, 330 mg, 0.45 mmol). After column separation, the title compound was obtained (270 mg, 71%).

1H NMR (CDCl₃): δ = 6.70–6.74 (m, 22H), 4.52–4.39 (m, 10H), 4.18–4.04 (m, 16H), 3.93–3.87 (m, 2H), 3.86–3.80 (m, 16H), 3.57–3.49 (m, 16H), 3.18–3.06 (m, 10H), 2.90–2.57 (m, 6H), 2.02–1.92 (m, 2H), 1.25–1.15 (m, 24H).


Mono-adduct of 1 with Calixarene; Compound 13
A solution of 1 (430 mg, 1.92 mmol) in THF (20 mL) was treated with n-ButLi (1.6 M solution in hexanes, 1.92 mmol, 1.20 mL) and reacted with 5-formyl-25,26,27,28-tetraspiro(2-ethoxyethoxy)calix[4]arene (375 mg, 0.50 mmol) as described above for 21. After column separation (silica gel; CHCl₃–MeOH; 19:1), the title compound was obtained (512 mg, 86%).

1H NMR (CDCl₃): δ = 6.96–6.78 (m, 7H), 4.77 (d, 1H, J = 7 Hz), 4.24–4.12 (m, 8H), 4.06–3.96 (m, 9H), 3.62 (s, 2H), 3.26–2.64 (m, 9H).

Anal. Calcd for C₉₀H₁₁₂O₅S₄: C, 64.70; H, 7.10. Found: C, 64.83; H, 7.24.

Mono-adduct of 1 with 4-formyldibenzo-18-crown-6; Compound 14
A solution of 1 (462 mg, 2.06 mmol) in THF (50 mL) was treated with n-ButLi (1.6 M solution in hexanes, 6.19 mmol, 3.87 mL) and reacted with 4-formyldibenzo-18-crown-6(370 mg, 0.55 mmol) as described above for 21. After column separation (silica gel; CHCl₃–MeOH; 19:1), the title compound was obtained (512 mg, 81%).

1H NMR (CDCl₃): δ = 7.06–7.14 (m, 11H), 4.53–4.56 (m, 5H), 4.17–4.05 (m, 8H), 3.94 (d, 1H, J = 7 Hz), 3.86–3.81 (m, 8H), 3.64 (s, 2H), 3.58–3.51 (m, 8H), 3.18–2.66 (m, 12H), 2.02 (s, 1H), 1.25–1.16 (m, 12H).

Bidentate Precursor 19: Typical Procedure

A solution of 1 (1.2 g, 5.33 mmol) in freshly distilled THF (20 mL) was cooled to –78 °C under N₂. Then n-BuLi (1.6 M solution in hexanes, 5.76 mmol, 3.6 mL) was added drop-wise with stirring. The resulting mixture was allowed to stand for 2 h at –20 °C. Then 5,17-diformyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene (0.62 g, 0.8 mmol) was added and the reaction mixture was stirred overnight at rt. The reaction mixture was quenched with sat. NH₄Cl, evaporated, and extracted with CHCl₃. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane, 2:3) to afford 0.484 g of 19 (49.7%).

Calixarene Bidentate Precursor 19

1H NMR (CDCl₃) δ = 6.29–6.86 (m, 10H), 4.46–4.52 (m, 4H), 4.34–4.39 (m, 2H), 4.18–4.21 (m, 4H), 4.00–4.07 (m, 4H), 3.78–3.89 (m, 10H), 3.63 (s, 2H), 3.49–3.58 (m, 8H), 2.67–3.17 (m, 20H), 2.04 (s, 2H), 1.14–1.23 (m, 12H).


Dibenzo-24-crown-8 based Bidentate Precursor 18

13C NMR (CDCl₃): δ = 74.0–74.6 (m, 8H), 73.9 (m, 8H), 73.3 (m, 8H), 72.9, 71.6, 70.9, 69.2, 68.3, 67.6, 66.9, 66.3, 65.6, 64.8, 64.0, 63.2, 62.5, 61.8, 60.9, 59.1. 1H NMR (CDCl₃): δ = 7.09 (d, 2H, J = 8 Hz), 6.97 (d, 2H, J = 8 Hz), 4.80 (d, 1H, J = 7 Hz), 4.09 (d, 1H, J = 14 Hz), 3.67–3.64 (m, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 3.59–3.55 (m, 1H), 3.55 (s, 3H), 3.49–3.39 (m, 2H), 3.38 (s, 3H), 3.30–3.20 (m, 3H), 3.16–3.08 (m, 1H), 3.05–3.05 (m, 2H), 2.82–2.75 (m, 2H).

Adduct of 23 with Benzaldehyde: Compound 31

A solution of 23 (287 mg, 0.79 mmol), n-BuLi (1.6 M solution in hexanes, 0.71 mmol, 0.44 mL), and benzaldehyde (75 mg, 0.71 mmol) was reacted as described above for 21. Purification by column chromatography (EtOAc–hexane, 1:3) afforded 0.445 g (51.90% of 21).

2-(4-[1,3]Dithian-5-yl-phenoxy)-6-methoxymethyl-3,4,5-trimethoxy-tetrahydropyran (28)

To a stirred solution of 2,3,4,5-tetra-O-methyl-d-glucopyranose 26 (400 mg, 1.69 mmol) and 4-[1,3]dithian-5-yl-phenol (27, 358 mg, 1.69 mmol) in THF (6 mL) at 0 °C were added Ph₃P (443 mg, 1.69 mmol) and a solution of diethyl azodicarboxylate (294 mg, 1.69 mmol) in THF (3 mL). The mixture was stirred at rt. overnight. It was concentrated and the product was isolated by column chromatography to afford 28 (510 mg, 70%). 1H NMR (CDCl₃): δ = 7.09 (d, 2H, J = 8 Hz), 6.97 (d, 2H, J = 8 Hz), 4.80 (d, 1H, J = 7 Hz), 4.09 (d, 1H, J = 14 Hz), 3.67–3.64 (m, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 3.59–3.55 (m, 1H), 3.55 (s, 3H), 3.49–3.39 (m, 2H), 3.38 (s, 3H), 3.30–3.20 (m, 3H), 3.16–3.08 (m, 1H), 3.05–3.05 (m, 2H), 2.82–2.75 (m, 2H).

Adduct of 28 with Benzaldehyde: Compound 30

A solution of glycoside 28 (190 mg, 0.44 mmol), n-BuLi (1.6 M solution in hexanes, 0.71 mmol, 0.44 mL), and benzaldehyde (75 mg, 0.71 mmol) was reacted as described above for 21. The product was purified by column chromatography. (76 mg, 32%).

Adduct of 29 with Dithiane: Compound 32

A solution of 1,3-dithiane (100 mg, 0.83 mmol) in THF (15 mL) was cooled to –25 °C under N₂. Then n-BuLi (1.6 M solution in hexanes, 1.0 mmol, 0.63 mL) was added drop-wise with stirring. The resulting mixture was stirred for 2 h at –25 °C. It was then added slowly into a solution of 4-O-[meta-O-acetyl-[β-D-glucopyranosyl]benzaldehyde 29a (377 mg, 0.83 mmol) in THF (20 mL) at –78 °C with vigorous stirring. The reaction mixture was stirred for 1 h at this temperature and then stored in a freezer at –25 °C overnight. The work-up procedure was the same as for 21. The product was purified by column chromatography (250 mg, 52%).

Adduct of 30 with Dithiane: Compound 33

A solution of 1,3-dithiane (100 mg, 0.83 mmol) in THF (15 mL) was cooled to –25 °C under N₂. Then n-BuLi (1.6 M solution in hexanes, 1.0 mmol, 0.63 mL) was added drop-wise with stirring. The resulting mixture was stirred for 2 h at –25 °C. It was then added slowly into a solution of 4-O-[meta-O-acetyl-[β-D-glucopyranosyl]benzaldehyde 29a (377 mg, 0.83 mmol) in THF (20 mL) at –78 °C with vigorous stirring. The reaction mixture was stirred for 1 h at this temperature and then stored in a freezer at –25 °C overnight. The work-up procedure was the same as for 21. The product was purified by column chromatography (250 mg, 52%).
The combined organic extracts were dried (MgSO₄), and the solvent was then removed under vacuum. The residue was purified by column chromatography (gradient elution with CHCl₃–CH₂OH, 100:0 to 95:5) to give 11 (1.2 g, 61%).

1H NMR (CDCl₃): δ = 6.82–7.02 (m, 3H), 5.00–5.08 (m, 1H), 4.31–4.46 (m, 3H), 4.12–4.21 (m, 2H), 3.91–4.05 (m, 2H), 3.83–3.90 (m, 3H), 3.57–3.78 (m, 14H), 2.59–3.10 (m, 8H).


**Monoadduct of 1 with 3-Formylbenzo-18-crown-6;** Compound 11

Yield = 46%.

A solution of 1 (353 mg, 1.57 mmol) in THF (50 mL) was treated with n-BuLi (1.6 M solution in hexanes, 3.76 mmol, 2.4 mL) and reacted with 4-formylbenzo-24-crown-8 [16] (1.6 g, 3.36 mmol in 25 mL of THF) as described above for 21. The reaction mixture was quenched with sat. NH₄Cl and extracted twice with Et₂O (2 × 10 mL). The combined organic extracts were dried (MgSO₄), and the solvent was then removed under vacuum. The residue was purified by column chromatography (gradient elution with CHCl₃–CH₂OH, 100:0 to 97:3) to give 11 (1.2 g, 61%).

1H NMR (CDCl₃): δ = 7.04–6.78 (m, 14H), 4.86–4.74 (m, 2H), 4.24–4.06 (m, 16H), 4.04–3.96 (m, 2H), 3.96–3.70 (m, 32H), 3.15–2.58 (m, 8H).

HRMS (characterized in a form of mono-sodium molecular ion): m/z calcd for C₁₂₆H₁₆₀O₂₆S₈Na⁺: 2454.9. Found: 2455.9.

**Bis-adduct of 1 with 4-Formylbifentibenz-18-crown-6;** Compound 12

Yield = 46%.

1H NMR (CDCl₃): δ = 6.81–7.01 (m, 6H), 5.00–5.09 (m, 2H), 4.25–4.48 (m, 6H), 4.12–4.19 (m, 4H), 3.57–4.02 (m, 34H), 2.56–3.24 (m, 8H).


**Calixarene Adduct with 4-Formyl-benzidene-24-crown-8;** Compound 35

Yield = 27%. A solution of 9 (387 mg, 0.4 mmol) in freshly distilled THF (20 mL) was cooled to –78 °C under N₂. n-BuLi (1.6 M solution in hexanes, 0.88 mmol, 0.55 mL) was added drop-wise with stirring. The resulting mixture was allowed to stand for 2 h at –20 °C. 4-Formylbifentibenz-18-crown-6 (105 mg, 0.27 mmol) was added and reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched with sat. NH₄Cl, concentrated by evaporation, and extracted with CHCl₃. The solvent was removed in vacuum and the residue was purified by column chromatography, eluting first with CHCl₃–MeCN (1:1) to remove starting materials and then with CHCl₃–MeOH (98:2) to afford 35 (198 mg, 54%).

1H NMR (CDCl₃): δ = 6.93–6.80 (m, 7H), 6.70–6.45 (m, 11H), 4.80–4.74 (m, 1H), 4.52–4.46 (m, 4H), 4.45–4.41 (m, 1H), 4.20–4.00 (m, 24H), 4.00–3.95 (m, 1H), 3.94–3.87 (m, 1H), 3.84–3.80 (m, 8H), 3.57–3.49 (m, 8H), 3.18–2.60 (m, 12H), 2.00–1.94 (m, 1H), 1.17–1.28 (m, 12H).

MS [Na⁺]: m/z = 1374.9, 1375.9, 1376.9 (in agreement with isotope pattern calculated for C₇₃H₉₀O₂₆S₄Na: m/z = 1374.5, 1375.5, 1376.5.)

**Calixarene Adduct with 4-Formyl-dibenz-24-crown-8;** Compound 36

Yield = 58%.

1H NMR (CDCl₃): δ = 6.91–6.78 (m, 6H), 6.70–6.45 (m, 11H), 4.80–4.73 (m, 4H), 4.52–4.45 (m, 4H), 4.45–4.42 (m, 4H), 4.18–4.04 (m, 16H), 4.02–3.94 (m, 1H), 3.93–3.88 (m, 9H), 3.86–3.80 (m, 16H), 3.57–3.49 (m, 8H), 3.18–2.60 (m, 12H), 1.98–1.92 (m, 1H), 1.28–1.17 (m, 12H).

MS [Na⁺]: m/z = 1462.9, 1463.9, 1464.9 (in agreement with isotope pattern calculated for C₇₇H₁₀₀O₁₈S₄Na: m/z = 1462.6, 1463.6, 1464.6.)

**Bis-Calixarene Adduct with 4,4'-Diformylbifenzo-18-crown-6;** Compound 33

Yield = 18%.

A solution of the appropriate [9-(hydroxy-phenyl-methyl)-2,4,8,10-tetrathiaspiro[5,5]undec-3-yl]-phenyl-methanediol (8 mg, 0.02 mmol) and benzophenone (7 mg, 0.04 mmol), in CD₃CN (0.6 mL) was degassed by freeze-pump-thaw cycles and sealed in a Pyrex NMR tube. Irradiations were carried out in a carousel Rayonet photoreactor, with reaction progress monitored by NMR by disappearance of the starting material and appearance of the aldehyde signal. After 1 h of irradiation the conversion was about 80%.

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References and Notes

(2) For a review, see: Gröbel, B.-T.; Seebach, D. Synthesis 1977, 357.
(4) The product is a mixture of diastereomers; while 1 itself is of C₂ symmetry, its disubstituted derivatives have allenic-type chirality. Combined with (in general) two new stereogenic centers at former carbonyls, it accounts for four pairs of diastereomers. Due to the macromolecular nature of most of the adducts described in this paper, we did not separate the individual diastereomers (unless otherwise stated in the experimental part). Reactions of bis-lithiated 1 with symmetric ketones produced a single (racemic) product.
(11) Liu, B. Youji Huaxue 1990, 10, 255.