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Nanoscale Molecular Rods with a New Building Block for Solubility Enhancement

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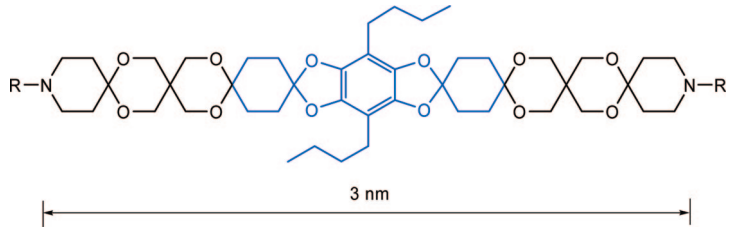
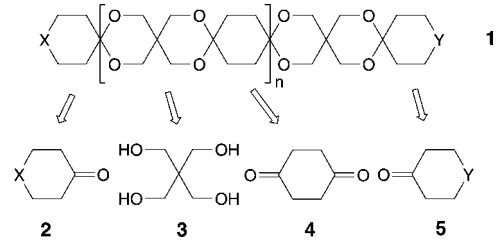


A new building block bearing a [1,3]dioxolo[4,5-*f*][1,3]benzodioxole core was developed to enhance the solubility of molecular rods by lateral alkyl chains. On incorporation in molecular rods with oligospiroketal structure, the straight geometry is retained, which was concluded from the X-ray crystal structure analysis of one of the rods. The determination of the solubility of a collection of rods bearing this building block revealed that already a butyl group efficiently hinders the aggregation of the rods and consequently causes a considerable enhancement of the solubility. Piperidine rings are located at the ends of the rods, which offer the opportunity for versatile functionalization. Thus, an *N*,*N*′-bis(azidoacetyl)-functionalized rod was prepared, which could serve as rigid linkage, initiated by a "Click" reaction.

Introduction

The imitation of the fascinating functional diversity of biological systems by synthetically generated molecules is one of the pivotal objectives of current chemical research. In this context, the rational and selective construction of well-defined three-dimensional assemblies is a great challenge. While nature goes back to a variety of biopolymers (proteins, nucleic acids, carbohydrates, etc.) to solve this problem, chemists need a versatile "construction kit" containing basic shapes such as balls, rings, plates or rods. Therefore, the development of molecular rods, i.e., relatively rigid molecules with a large aspect ratio, has been an intensively treated research area for several years.[1] Recently, we reported on the synthesis and properties of a new type of molecular rods whose backbone structure is based on oligospiroketals.[2] These rods (**1**) are assembled of tetrols such as pentaerythritol **3**, diones such as cyclohexan-1,4-dione **4** and terminal modules **2** and **5** bearing different functionalities X, Y (Scheme 1). These building blocks are connected by ketal

SCHEME 1



formation, for which we developed a new mild and highly selective method.[2]

The backbone of molecular rods of type **1** shows rather hydrophobic behavior, despite the numerous oxygen atoms of the ketal moieties. This can be explained by an effective steric shielding of these atoms by the adjacent methylene groups. Not unexpectedly, the solubility of oligospiroketals **1** consisting of seven or more rings is dramatically diminished if X and Y are "normal" functional groups (e.g., N atoms with conventional protective groups). This fact strongly impedes the handling of these compounds and could be standing in the way of their application. In our recent publication,[2] we solved this problem by introduction of terminal solubility-enhancing groups (SEGs) in the X- and Y-positions. Besides previously known groups

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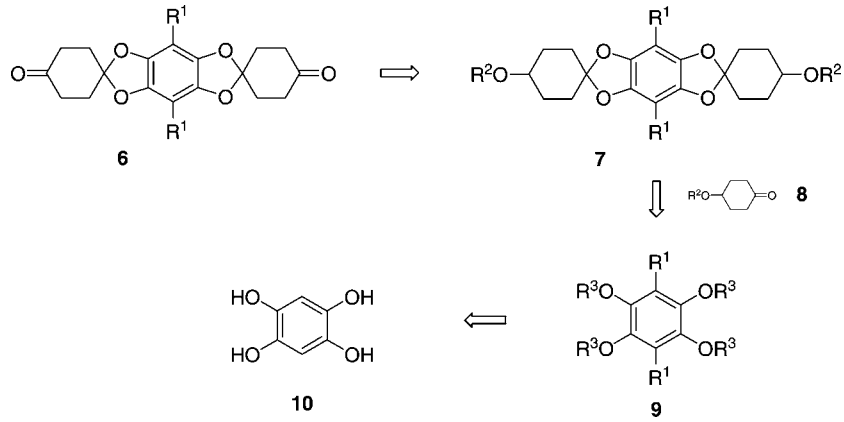
SCHEME 2



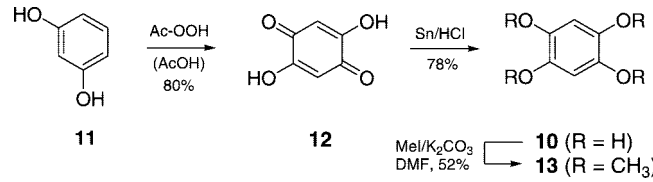
(e.g., 2-ethylhexyloxycarbonyl, EHOC[3]), we developed new modified Fmoc groups (MIO-Fmoc and DIO-Fmoc[4]), mainly to have base-labile protective groups in hand that are compatible with the acid-labile oligospiroketal skeleton.[5] Although the introduction of SEGs in a terminal position of the molecular rods is very convenient to solve the solubility problem, this approach certainly proved to be a hindrance if other functional groups are needed at the ends of the rods. Such cases ultimately require the introduction of *lateral* SEGs in the architecture of oligospiroketals **1**. Herein we wish to report on the development of new building blocks with lateral SEGs for solubility enhancement in organic solvents as well as their successful application on the synthesis of nanoscale molecular rods.

Results and Discussion

Synthesis of the Solubility-Enhancing Building Block 6. First, we considered the introduction of alkyl chains either in pentaerythritol **3** or in cyclohexan-1,4-dione **4**. Besides the probably cumbersome synthesis of those derivatives, the stereochemical situation would become highly complicated owing to the newly generated chirality centers. Therefore, we decided to prepare the building block **6** bearing a [1,3]dioxolo[4,5-*f*][1,3]benzodioxole core and lateral solubility-enhancing groups R^1. A retrosynthetic analysis of compounds **6** is outlined in Scheme 2. The keto groups in **6** should be resulting from protected hydroxyl groups in **7**. This compound could be prepared from 3,6-disubstituted 1,2,4,5-tetrahydroxybenzene **9** (R^3 = H) or its tetratrimethylsilylether (R^3 = TMS) and protected 4-hydroxycyclohexanone **8** by common acetalization methods. Compounds **9** could be traced to the literature-known 1,2,4,5-tetrahydroxybenzene **10**.

Our synthesis began with the oxidation of resorcinol **11** to 2,5-dihydroxy-1,4-benzoquinone **12** with peracetic acid.[6] While this method provided **12** with good yields, an also reported route from 1,4-hydroquinone proved to be less reproducible and gave **12** only in very low yields.[7] Several methods were reported for the reduction of quinone **12** to 1,2,4,5-tetrahydroxybenzene **10**

SCHEME 3



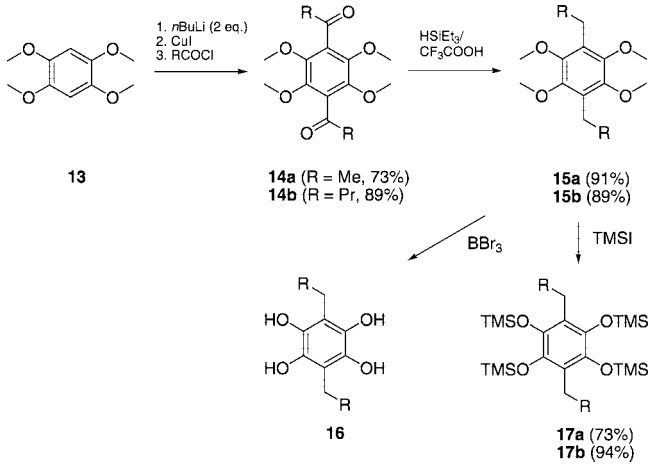
(Sn/HCl,[7,8a] PtO_2/H_2,[8b] $Pd/C/H_2$[8c]). We performed this step with Sn/HCl and obtained the tetraphenol **10** with a yield of 78%. In view of the next target structure (**7**), **10** could now already be coupled with the protected 4-hydroxycyclohexanone **8**, but unfortunately, we found that the resulting spiroketal moiety is too labile for the steps required for the introduction of side chains R^1 (see below). Therefore, we protected the tetraphenol **10** as the relatively tough tetramethylether **13**[8b] (Scheme 3).

The introduction of the side chains in the 3- and 6-positions of **13** turned out to be difficult. The classical Friedel−Crafts acylation failed due to the migration tendency of the methyl groups under these conditions. The bismetalation with *n*BuLi followed by treatment with acid chlorides or Weinreb amides did not afford the desired products. Finally, the reaction between 3,6-biscuprates of **13**, prepared by bismetalation and subsequent treatment with CuI, and acid chlorides according to Bringmann[9] was crowned with success. The reduction of the keto groups could be smoothly accomblished with $HSiEt_3/CF_3COOH$ reagent.[10] The deprotection of tetraethers **15** to tetraphenols **16** with BBr_3[11] succeeded, but compounds **16** have proven to be less suitable for the preparation of target compounds **7** due to their extreme oxidation lability. The conversion of **15** into the tetra(trimethylsilyl) ethers **17** with trimethylsilyl iodide[12] is much more favorable. Compounds **17** are air-stable and could even be purified by flash chromatography (Scheme 4).

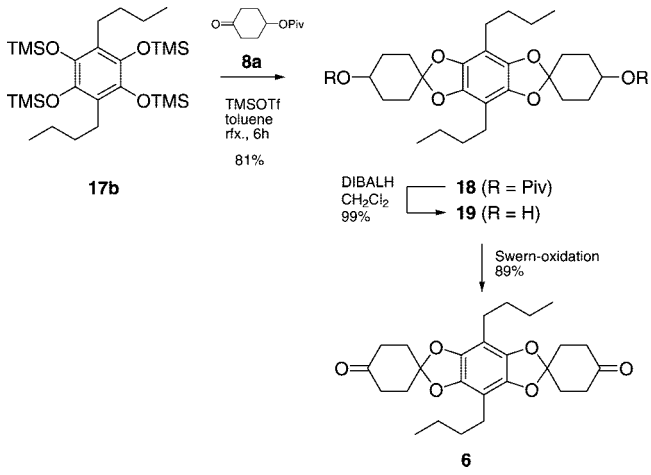
The last steps to the building block **6** were performed only with dibutyl derivative **17b** because we suspected that the ethyl chains in **17a** are too short for an efficient enhancement of the

(3) Ball, D. F.; Goggin, P. L.; McKaen, D. C.; Woodward, L. A. *Spectrochim. Acta* **1960**, *16*, 1358–1367.
(4) Wessig, P.; Czapla, S.; Möllnitz, K.; Schwarz, J. *Synlett* **2006**, 2235–2238.
(5) The stability of the spiroketal moieties towards acid environment proved to be higher than expected for the moment, probably due to the mentioned steric shielding of the oxygen atoms.
(6) Barltrop, J. A.; Burstall, M. L. *J. Chem. Soc.* **1959**, 2183–2186.
(7) Weider, P. R.; Hegedus, L. S.; Asada, H.; Dandreq, S. V. *J. Org. Chem.* **1985**, *50*, 4276–4281.
(8) (a) Aldridge, S.; Calder, R. J.; Cunningham, M. H.; Malik, K. M. A.; Steed, J. W. *J. Organomet. Chem.* **2000**, *614*−*615*, 188–194. (b) Keegstra, E. M. D.; Huisman, B. H.; Paardekooper, E. M.; Hoogesteger, F. J.; Zwikker, J. W.; Jenneskens, L. W.; Kooijman, H.; Schouten, A.; Veldman, N.; Spek, A. L. *J. Chem. Soc., Perkin Trans. 2* **1996**, 229–240. (c) Reddy, T. J.; Iwama, T.; Halpern, H. J.; Rawal, V. H. *J. Org. Chem.* **2002**, *67*, 4635–4639.
(9) Bringmann, G.; Geuder, T.; Harmsen, S. *Synthesis* **1994**, 1143–1145.
(10) Kursanov, D. N.; Parnes, Z. N.; Bassova, G. I.; Loim, N. M.; Zdanovich, V. I. *Tetrahedron* **1967**, *23*, 2235–2242.
(11) McOmie, J. F. W.; West, D. E. *Organic Synthesis*; Wiley: New York, 1973; *Collect. Vol. V*, p 412.
(12) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761–374.

SCHEME 4



SCHEME 5



solubility. The reactivity of **17b** toward ketones **8** is remarkably low, and all previously successfully applied acetalization methods[2] failed. After numerous attempts, we found that the reaction of **17b** with pivaloyl protected ketone **8a** in refluxing toluene in the presence of trimethylsilyl triflate provides the desired product **18** with satisfactory yields. While the deprotection of **18** to the diol **19** with DIBALH proceeds smoothly and with nearly quantitative yields, the otherwise very mild and convenient Dess−Martin oxidation[13] gave the dione **6** only in very low yields, even if $NaHCO_3$ is added as buffer. On the other hand, we obtained **6** with good yields employing the Swern oxidation (DMSO, $(COCl)_2$, Et_3N) (Scheme 5).

Synthesis and Properties of Molecular Rods Bearing 6. To examine the usability of the new building block **6** in the synthesis of longer molecular rods of type **1**, we needed various diols, preferably with different functional groups at the end of the rods. In this connection we turned special attention to base-labile protective groups, which are fully compatible with the oligospirane skeleton. In Scheme 6, the route to various 1,5-dioxa-9-azaspiro[5.5]undecane-3,3-dimethanols **23** is summarized. We have chosen the protective groups trifluoroacetyl (**23a**, removable with NaOMe), chloroacetyl (**23b**, removable with

SCHEME 6

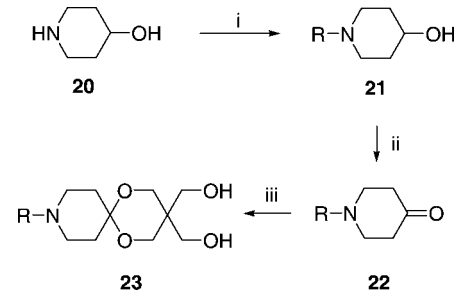


TABLE 1

	R	yield **21** (%)	yield **22** (%)	yield **23** (%)
a	CF_3CO	46[a]	95[b]	31
b	$ClCH_2CO$	64[c]	83[d]	
c	TEOC[e]	31[f]	84[d]	72
d	Fmoc	99[g,i]	94[d,i]	
e	Cbz	96[h,i]	94[d,i]	58[i]

[a] $(CF_3CO)_2O$, dioxane, Et_3N. [b] Swern oxidation ($(COCl)_2$,Et_3N). [c] $ClCH_2COCl$, K_2CO_3, AcOEt/H_2O. [d] Dess−Martin oxidation.[13] **22b** was mentioned in literature but without experimental details and characterization.[16] **22c** is described in ref 17 but prepared by another method. [e] TEOC = 2-(trimethylsilyl)ethoxycarbonyl. [f] TEOC-Cl, K_2CO_3, dioxin, H_2O. [g] FmocOSu. [h] Cbz-Cl. [i] Reference 2.

o-phenylendiamine[14a] or thiourea[14b]), 2-(trimethylsilyl)ethoxycarbonyl (**23c**, removable with fluoride[15]), and 9-fluorenylmethoxycarbonyl (**23d**, removable with piperidine/DMF). The acylation of 4-hydroxypiperidine **20** to compounds **21** proceeded smoothly in all cases, though the yield of **21c** was only moderate. By oxidation (Swern or Dess−Martin) we obtained the ketones **22**, which then were treated with pentaerythritol under classic conditions (DMF/benzene, reflux) to prepare diols **23**. Unfortunately, the acetalization only succeeded with **22a** and **22c**, and the yield of the former was only 31% (Scheme 6, Table 1).

To find access to compounds **23b,d** nevertheless, we have made a detour. Starting from the previously described Cbz-protected diol **21e**,[2] we prepared the free amine **24** in nearly quantitative yield by hydrogenation. The acylation of **24** either with 4-nitrophenyl-chloroacetate or with FmocOSu afforded **23b** and **23d**, respectively, in excellent yields. Furthermore, we were interested in the *N*-azidoacetyl derivative **23f** (vide infra), which could be easily obtained by treatment of **23b** with NaN_3 in DMF (Scheme 7).

With diols **23** in hand we attended to the synthesis of nanoscale molecular rods using our previously developed double-activation method.[2] To investigate the coupling reaction and the solubility properties of the rods without the influence of terminal functional groups, we first performed a coupling of **6** with the literature-known 1,5-dioxaspiro[5.5]undecane-3,3-

(13) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(14) (a) Holley, R. W.; Holley, A. D. *J. Am. Chem. Soc.* **1952**, *74*, 3069. (b) Masaki, M.; Kitahara, T.; Kurita, H.; Ohta, M. *J. Am. Chem. Soc.* **1968**, *90*, 4508.

(15) (a) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358. (b) Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.

(16) Padmanilayam, M.; Scorneaux, B.; Dong, Y. X.; Chollet, J.; Matile, H.; Charman, S. A.; Creek, D. J.; Charman, W. N.; Tomas, J. S.; Scheurer, C.; Wittlin, S.; Brun, R.; Vennerstrom, J. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5542.

(17) Levell, J.; Astles, P.; Eastwood, P.; Cairns, J.; Houille, O.; Aldous, S.; Merriman, G.; Whiteley, B.; Pribish, J.; Czekaj, M.; Liang, G. Y.; Maignan, S.; Guilloteau, J. P.; Dupuy, A.; Davidson, J.; Harrison, T.; Morley, A.; Watson, S.; Fenton, G.; McCarthy, C.; Romano, J.; Mathew, R.; Engers, D.; Gardyan, M.; Sides, K.; Kwong, J.; Tsay, J.; Rebello, S.; Shen, L. D.; Wang, J.; Luo, Y. Y.; Giardino, O.; Lim, H. K.; Smith, K.; Pauls, H. *Bioorg. Med. Chem.* **2005**, *13*, 2859.

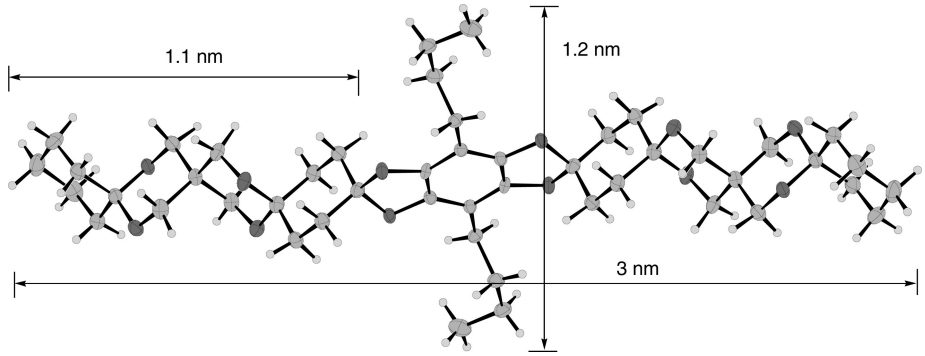


FIGURE 1. Crystal structure of **26a**.

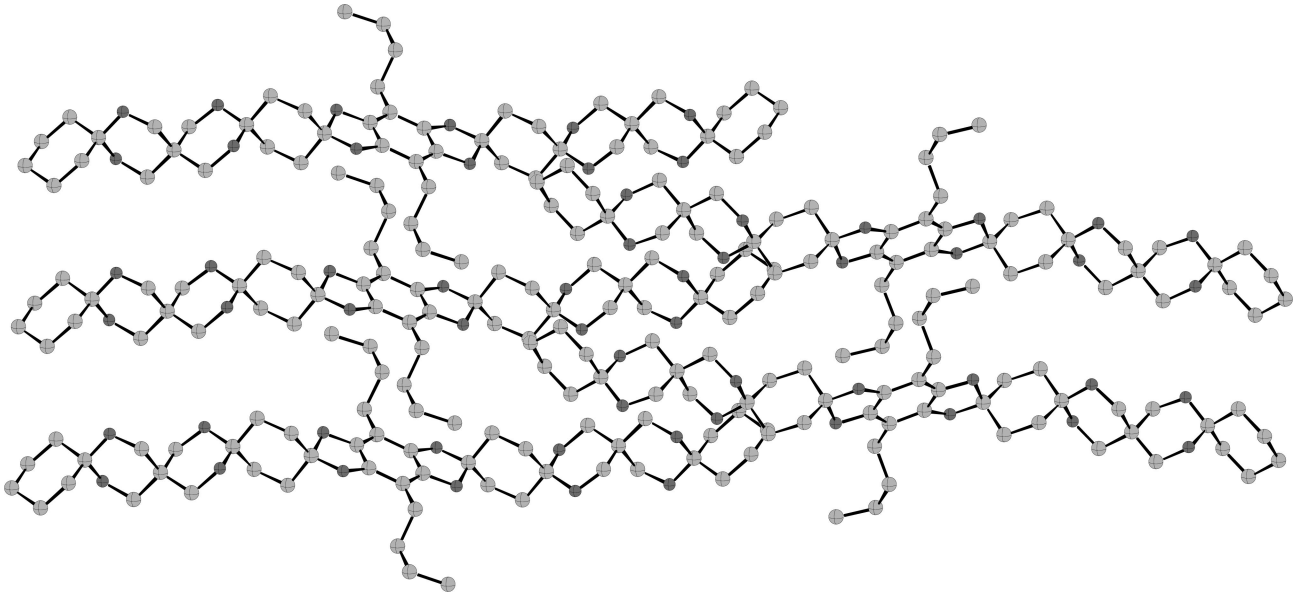
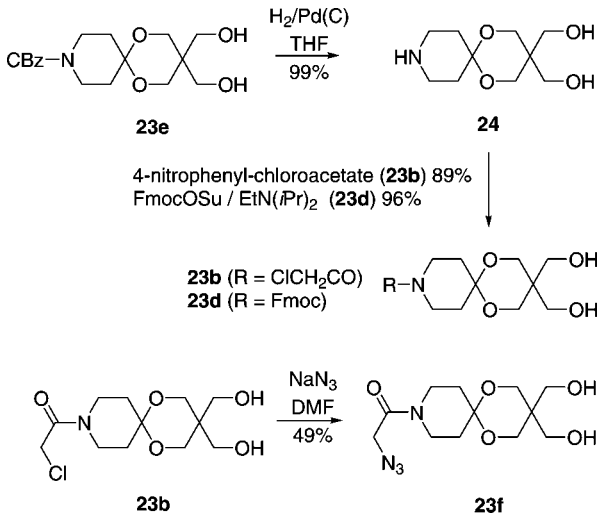


FIGURE 2. Crystal packing of **26a**.

SCHEME 7



dimethanol **25**[18] and obtained the desired rod **26a** with up to 41% yield. The structure of **26a** was unambiguously proven by MALDI-MS and X-ray crystal structure analysis.[19] Figure 1 shows the molecular structure of **26a** as well as some distances clarifying the size of the molecule. It is clearly discernible that **26a** adopts a straight geometry and all saturated six-membered rings have a chairlike conformation (Figure 1). It is also instructive to take a look at the crystal packing of **26a**. In Figure 2, five molecules of **26a** within the elemental cell are depicted. One can see that the rods are tightly packed but that the aromatic rings do not form π-stacks, though they are coplanar. In fact, they are laterally displaced against one another and the three terminal carbon atoms of the butyl groups are located nearly perpendicular above the aromatic rings at a distance of about 3.5 Å. This results in a stairs-like arrangement of the rods as seen in Figure 3, showing a side view of three molecules in the direction of the rod axis (the saturated six-membered rings are omitted). Obviously, the length of the butyl group is sufficient to disturb a close contact of the rods (which is also reflected in the enhanced solubility, see below) but makes a dense packing of the rods not yet impossible.

To our delight, the yields of rods **26b**−**f** bearing N-protected piperidine rings at the ends are considerably higher than that of **26a**. Besides **26** we isolated the shortened rods **27** in some cases, arising from a reaction of **6** with only 1 equiv of diol **23** (Scheme 8, Table 2). It is worth noting that the azidoacetyl-substituted rod **26f** opens up versatile applications because it

(18) (a) Schaeffer, J. R.; Stevens, R. *E J. Org. Chem.* **1973**, *38*, 1241. (b) Murguia, M. C.; Grau, R. J. *Synlett* **2001**, 1229.

(19) Details of the structure investigation are available on request from the Cambridge Crystallographic Data Centre, on quoting the depository number CCDC 676130.

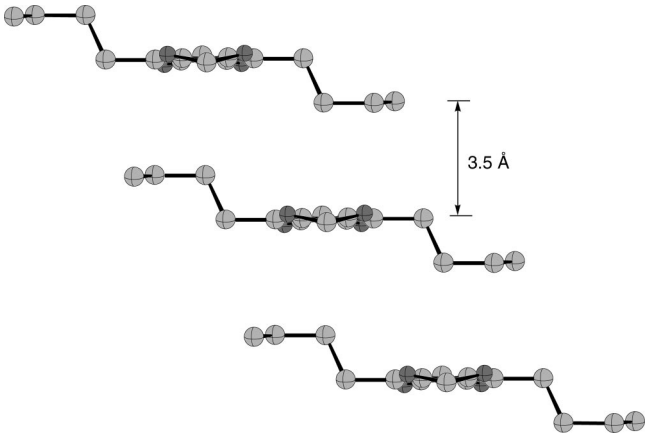


FIGURE 3. Side view of three molecules in the crystal packing of **26a**. Saturated six-membered rings are omitted.

SCHEME 8

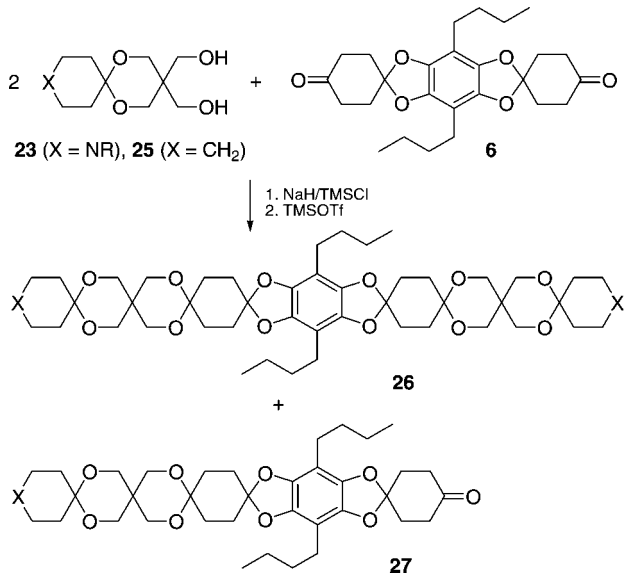


TABLE 2

	X	yield **26** (%)	yield **27** (%)
a	CH_2	35 − 41 [a]	
b	CF_3CO-N	76	15
c	TEOC-N	77	
d	Fmoc-N	42	
e	Cbz-N	52	9
f	N_3CH_2CO-N	74	9

[a] The reaction is accompanied by the formation of oligomers,which were not further characterized

can easily be coupled with other molecules bearing a terminal alkyne moiety by using the well-established "Click" reaction.[20]

To prove that the terminal N-protecting groups could be removed, we treated the Cbz-protected rod **26e** with hydrogen in the presence of catalytic amounts of Pd(C) and obtained the diamine **28** with good yields (Scheme 9).

Finally, we investigated the solubility of rods **26a,b,d,e,f** and **28** in dichloromethane. To our delight, already the rod **26a**

(20) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (c) Bock, V. D.; Hiemstra, H.; Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.

SCHEME 9

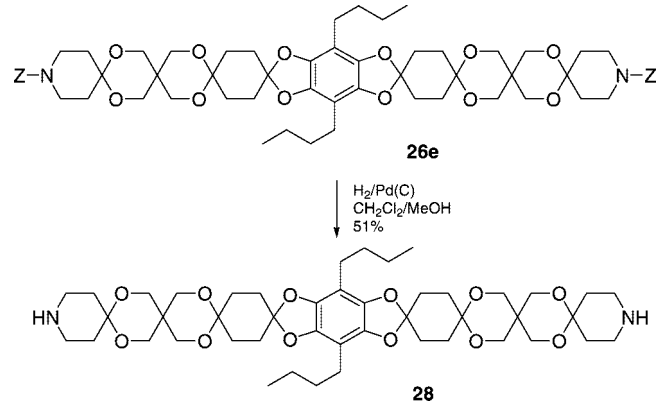


TABLE 3

	X[a]	solubility [g/L][b]
26a	CH_2	20 ± 4
26b	CF_3CO-N	419 ± 40
26d	Fmoc-N	30 ± 6
26e	Cbz-N	294 ± 23
26f	N_3CH_2CO-N	144 ± 16

[a] See Scheme 8. [b] In CH_2Cl_2.

without terminal functional groups exhibits a considerable solubility of 20 g/L (Table 3). The rods **26b**, **26e** and **26f**, bearing trifluoroacetyl, Cbz and azidoacetyl groups at the termini, are extremely soluble, suggesting a synergistic effect of the lateral and terminal groups. On the other hand, the Fmoc groups in **26d** have only a marginal influence on the solubility. Although **28** is very scarcely soluble in dichloromethane, its solubility in water is surprisingly high (1.8 ± 0.5 g/L).

Conclusion

In summary, we succeeded in the synthesis of molecular rods with a length of about 3 nm (without consideration of the terminal functional groups) by implementation of a new approach for solubility enhancement. Although the introduction of SEGs in *terminal* positions is tried and tested, *lateral* SEGs are inevitably required if other functional groups have to be installed at the ends of the rods. To this end, we developed the new building block **6** bearing a [1,3]dioxolo[4,5-*f*][1,3]benzodioxole moiety as core element. If integrated in molecular rods with oligospirane skeleton, the straight rod-like geometry is not altered due to the topology of this element. In contrast to terminal SEGs, the relatively short butyl groups already cause a very satisfactory solubility enhancement. The coupling of **6** with various diols (**23**, **25**) using our previously established acetalization method[2] proceeded smoothly and provided the resulting molecular rods **26** mostly in good yields. Compounds **26** are, despite the very electron-rich aromatic core, sufficiently stable and could be handled without special precautions. The efficiency of our concept is impressively demonstrated by the solubility of the rods **26**. Even the rods **26a** and **26d** bearing no solubility-enhancing groups at the ends have satisfactory solubilities of 20−30 g/L, whereas the other rods are extremely soluble.

Having principally solved the problems related with scarce solubility of rods **1**, either by *terminal*[2] or *lateral* SEGs, right now we are developing applications in material and biochemical sciences and will report on interesting results soon.

Experimental Section

1-[2,3,5,6-Tetramethoxy-4-(1-oxobutyl)phenyl]-1-butanone (14b). To a solution of **13** (2.00 g, 10.11 mmol) in dry THF (75 mL) was added dropwise at 0 °C *n*-BuLi (16.0 mL, 1.6 M in hexane, 25.60 mmol, 2.5 equiv). The resulting orange suspension was stirred for 4 h at room temperature. CuI (4.80 g, 25.23 mmol, 2.5 equiv) and butyryl chloride (8.40 mL, 80.89 mmol, 8.0 equiv) was added slowly. The reaction mixture was stirred for 1 h, then diluted with Et_2O and washed with saturated aqueous NH_4Cl solution and brine. The organic layer was dried, evaporated and purified by flash chromatography (PE/EtOAc 10:1) yielding **14b** as a white solid (3.04 g, 8.98 mmol, 89%). R_f = 0.4 (PE/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) σ 0.98 (CH_3, 6H, t, ^3J = 7.4 Hz), 1.68−1.75 (CH_2CH_3, 4H, m), 2.72 (C(O)CH_2, 4H, t, ^3J = 7.2 Hz), 3.80 (OCH_3, 12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) σ 13.6 (CH_3), 16.8 (CH_2CH_3), 46.9 (C(O)CH_2), 61.7 (OCH_3), 132.6 (CCO), 144.9 ($COCH_3$), 203.3 (CO); mp 66−67 °C; IR 2968, 2941, 1702, 1459, 1400, 1052 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{26}O_6Na$ [M + Na^+] 361.1627, found 361.1622.

1,4-Dibutyl-2,3,5,6-tetramethoxy-benzene (15b). To a solution of **14b** (3.04 g, 8.98 mmol) in CF_3COOH (14 mL) was added dropwise $HSiEt_3$ (7.10 mL, 44.90 mmol, 5.0 equiv) and the mixture was stirred until complete conversion of **14b** was indicated by TLC. Water and $NaHCO_3$ solution were added until gas evolution ceased and the resulting mixture was extracted two times with CH_2Cl_2. The combined organic layers were dried, evaporated and purified by flash chromatography (PE/EtOAc 100:5) yielding **15b** as a white solid (2.47 g, 7.94 mmol, 89%). R_f = 0.6 (PE/EtOAc 100:5); ^{1}H NMR (300 MHz, $CDCl_3$) σ 0.97 (CH_3, 6H, t, ^3J = 7.1 Hz), 1.37−1.52 ((CH_2)$_2CH_3$, 8H, m), 2.60 ($C_{Ar}CH_2$, 4H, t, ^3J = 7.8 Hz), 3.83 (OCH_3, 12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) σ 14.0 (CH_3), 23.2 ((CH_2)$_3CH_3$), 24.3 ((CH_2)$_3CH_3$), 33.3 ((CH_2)$_3CH_3$), 60.5 (OCH_3), 127.9 ($C_{Ar}CH_2$), 147.3 ($COCH_3$); mp 55−56 °C; IR 2952, 2930, 1459, 1408, 1109, 1038 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{30}O_4$ [M^+] 310.2144, found 310.2144.

[2,5-Dibutyl-3,4,6-tris[(trimethylsilyl)oxy]phenoxy]trimethylsilane (17b). To a solution of **15b** (2.47 g, 7.94 mmol) in CCl_4 (25 mL) was added TMSI (6.80 mL, 49.96 mmol, 6.3 equiv) and the mixture was stirred overnight at 70 °C. The solvent was evaporated and the resulting residue was purified by flash chromatography (PE/CH_2Cl_2 5:1) yielding **17b** as a white solid (3.83 g, 7.06 mmol, 89%). R_f = 0.4 (PE); ^{1}H NMR (300 MHz, $CDCl_3$) σ 0.17 ($Si(CH_3)_3$, 36H), 0.91 (CH_3, 6H, t, ^3J = 7.3 Hz), 1.20−1.32 ((CH_2)$_3CH_3$, 4H, m), 1.44−1.53 ((CH_2)$_3CH_3$, 4H, m), 2.50 ((CH_2)$_3CH_3$, 4H, t, ^3J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) σ 0.67 ($Si(CH_3)_3$), 14.0 (CH_3), 22.4 ((CH_2)$_3CH_3$), 25.8 ((CH_2)$_3CH_3$), 30.8 ((CH_2)$_3CH_3$), 123.9 ($C_{Ar}CH_2$), 139.6 ($COSi(CH_3)_3$); mp 40−41 °C; IR 2957, 1438, 1248, 852, 838 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{54}O_4Si_4$ [M^+] 542.3099, found 542.3099.

4,4″-Bis(pivaloyloxy)-dispiro[cyclohexane-1,2′-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6′,1″-cyclohexane (18). To a solution of **17b** (3.82 g, 7.06 mmol) and **8a** (2.89 g, 14.56 mmol, 2.0 equiv) in dry toluene (130 mL) was added TMSOTf (130 μL, 0.71 mmol, 0.1 equiv). The reaction mixture was refluxed until complete conversion of **17b** and **8a** was observed by TLC. The solvent was evaporated and the resulting residue was purified by flash chromatography (PE/EtOAc 30:1) yielding **18** as a white solid (3.50 g, 5.69 mmol, 81%). R_f = 0.4 (PE/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) σ 0.90−0.97 ((CH_2)$_n$$CH_3$, 6H, m), 1.24 ($C(CH_3)_3$, 18H, s), 1.30−1.42 ($CH_2CH_3$, 4H, m), 1.52−1.65 ($CH_2CH_2CH_3$, 4H, m), 1.86−2.10 (($CH_2$)$_2$CH, 16H, m), 2.47−2.56 ($C_{Ar}CH_2$, 4H, m), 4.96−4.98 (CH, 2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) σ 13.9 ((CH_2)$_n$$CH_3$), 22.2 ($CH_2CH_3$), 23.7 ($C_{Ar}CH_2$), 27.2 ($C(CH_3)_3$), 27.5 (($CH_2$)$_2$CH), 30.7 (($CH_2CH_2$)$_2$CH), 31.0 ($CH_2CH_2CH_3$), 38.9 ($C(CH_3)_3$), 68.7 (CH), 106.2 ($C_{Ar}CH_2$), 116.2 (C($CH_2CH_2$)$_2$CH), 138.5 ($C_{Ar}O$), 177.9 (CO); mp 159−163 °C; IR 2962, 2872, 1720, 1443, 1175, 1124 cm^{-1}; HRMS (ESI) calcd for $C_{36}H_{55}O_8$ [M + H^+] 615.3898, found 615.3891.

4,4″-Dihydroxy-dispiro[cyclohexane-1,2′-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6′,1″-cyclohexane (19). To a solution of **18** (3.44 g, 5.60 mmol) in dry CH_2Cl_2 (90 mL) was added dropwise at −78 °C DIBALH (28.5 mL, 1.0 M in hexane, 28.50 mmol, 5.1 equiv) and the mixture was stirred until complete conversion of **18** was observed by TLC. MeOH was added until gas evolution ceased. CH_2Cl_2 was added and the organic layer was washed with aqueous tartaric acid. The solvent was evaporated and the resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH 100:3) yielding **19** as a white solid (2.48 g, 5.55 mmol, 99%). R_f = 0.3 (CH_2Cl_2/MeOH 100:3); ^{1}H NMR (300 MHz, $CDCl_3$) σ 0.89−0.95 (CH_3, 6H, m), 1.27−1.41 (CH_2CH_3, 4H, m), 1.51−1.65 ($CH_2CH_2CH_3$, 4H, m), 1.77−1.88 ((CH_2)$_2$CH + OH, 10H, m), 1.92−1.98 ((CH_2)$_2$CH, 4H, m), 2.08−2.16 ((CH_2)$_2$CH, 4H, m), 2.45−2.55 ($C_{Ar}CH_2$, 4H, m), 3.89−3.91 (CH, 2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) σ 13.8 (CH_3), 22.1 (CH_2CH_3), 23.6 ($C_{Ar}CH_2$), 30.8 ((CH_2CH_2)$_2$CH), 31.1 ($CH_2CH_2CH_3$ + (CH_2)$_2$CH), 67.6 (CH), 106.1 ($C_{Ar}CH_2$), 116.3 (C(CH_2CH_2)$_2$CH), 138.5 ($C_{Ar}O$); mp 159−163 °C; IR 3407, 2952, 2867, 1440, 1122, 1082 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{39}O_6$ [M + H^+] 447.2748, found 447.2741.

Dispiro[cyclohexane-1,2′-[1,3]dioxolo[4,5-*f*][1,3]benzodioxole-6′,1″-cyclohexan-4,4′dione (6). To a solution of DMSO (1.50 mL, 21.14 mmol, 4.1 equiv) in dry CH_2Cl_2 (60 mL) was added dropwise at −78 °C oxalyl dichloride (1.40 mL, 16.28 mmol, 3.1 equiv). After 30 min of stirring, **18** (2.32 g, 5.20 mmol) dissolved in dry CH_2Cl_2 (15 mL) was added and the mixture was stirred for 30 min. The reaction mixture was treated with NEt_3 (7.4 mL, 53.09 mmol, 10.2 equiv) and stirred for 15 min while warming up to room temperature. CH_2Cl_2 was added and the organic layer was washed with aqueous tartaric acid, the solvent was evaporated and the resulting residue was purified by flash chromatography (PE/EtOAc 10:1) yielding **6** as a pale yellow solid (2.05 g, 4.64 mmol, 89%). R_f = 0.2 (PE/EtOAc 10:1); ^{1}H NMR (300 MHz, $CDCl_3$) σ 0.93 (CH_3, 6H, t, ^3J = 7.3 Hz), 1.30−1.43 (CH_2CH_3, 4H, m), 1.55−1.65 ($CH_2CH_2CH_3$, 4H, m), 2.32 ((CH_2)$_2$CO, 8H, t, ^3J = 7.0 Hz), 2.55 ($C_{Ar}CH_2$, 4H, t, ^3J = 7.4 Hz), 2.63 ((CH_2)$_2$CO, 8H, t, ^3J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) σ 13.8 (CH_3), 22.2 (CH_2CH_3), 23.7 ($C_{Ar}CH_2$), 30.9 ($CH_2CH_2CH_3$), 33.5 ((CH2)$_2$CO), 37.3 ((CH2)$_2$CO), 106.6 ($C_{Ar}CH_2$), 115.0 (C(CH_2CH_2)$_2$CO), 138.6 ($C_{Ar}O$), 209.0 (CO); mp 146−147 °C; IR 2952, 2930, 2862, 1717, 1437, 1124 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{35}O_6$ [M + H^+] 443.2434, found 443.2428.

General Procedure for Preparation of Octaspiranes 26. An ice-cooled solution of **6** in Et_2O was treated with NaH (2.0 equiv) and TMSCl (2.0 equiv) and stirred for 1 h. The corresponding diol **25** or **26** (2.0 equiv) and TMSOTf (0.1 equiv) were added and the reaction mixture was stirred at room temperature until complete conversion was indicated by TLC. The solvent was evaporated and the resulting residue was purified by flash chromatography.

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Supporting Information Available: Experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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