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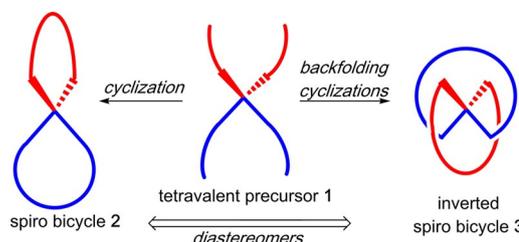Link to publication

▌**Spiro Compounds**

Template-Directed Synthesis of an Inverted Spiro Architecture

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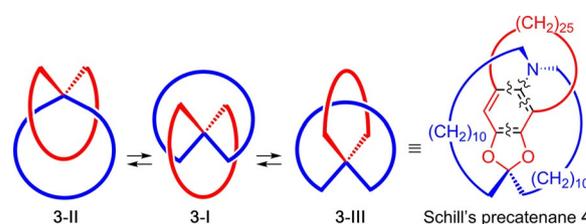
Abstract: The regular bicyclic spiro motif is highly abundant given its synthetic accessibility while the diastereomer—virtually obtained through inversion at the central atom—is almost unknown. We have developed methodology to access the elusive inverted spiro architecture by employing a covalent template-directed approach. Comparison with the regular spiro bicycle analog unequivocally established the diastereomeric relationship, providing insight into the fascinating stereochemical and structural properties.

Scheme 1. Sketches of both spirocyclic diastereomers and their mutual linear precursor.

Scheme 2. Possible conformations of an inverted spiro bicycle **3** and comparison with Schill's precatenane **4**.

The bicyclic spiro geometry can be considered as a molecular 3D equivalent of the Figure-of-eight, typified by connection of two rings to the same tetrahedral core atom. The inherent three dimensionality combined with rigidity makes spiro bicycles privileged molecular scaffolds.[1] Spirocyclic motifs are generally found in natural products and synthetic drug molecules,[2] as well as hole transport materials[3] and microporous polymers.[4] Thus the synthesis of spirocycles is well established, given its ubiquity across chemical disciplines. As depicted in Scheme 1, the archetypical spiro compound **2** can be obtained after connecting the reactive termini of the precursor compound **1**, bearing four molecular chains connected at the same tetrahedral atom. Conversely, two consecutive backfolding cyclizations may be envisioned from **1** to afford the inverted spiro diastereomer **3**.

Inversion of the central ring-connecting atom in the C_2-symmetric spiro geometry **2** results in diastereomer **3** instead of the enantiomeric mirror image, yielding a fundamentally new stereochemical feature not found in other organic molecules. Compared to the classic spiro bicycle **2**, the inverted spiro geometry **3** exhibits molecular compactness. In addition, several conformations may be envisioned (Scheme 2) making this

unique class of bicyclic molecules interesting for further studies.

Schill and Lüttringhaus described the first targeted synthesis of a [2]catenane using covalent templating in their historic paper in 1964, utilizing the inverted spiro multicycle **4** as the key precatenane intermediate (Scheme 2).[5] Three possible conformations **3I-III** exist, featuring the bicyclic inverted spiro geometry. Virtual cleavage of the C—N bond and three bonds within the phenyl moiety of Schill's multicyclic precatenane **4**, reveals the inverted spiro conformer with similarity to **3-III**.

An important design element in Schill's elegant [2]catenane synthesis is the rigid perpendicular arrangement enforced by the ketal moiety to direct backfolding cyclizations from both planes of the phenyl via bisalkylation of the aniline by the bis(12-bromododecyl)ketal precursor.

In our endeavors to develop a novel methodology towards entangled molecules, for which the current supramolecular approaches[6] fall short, we recently disclosed a covalent approach towards inverted spiro multicycles, also named as quasi[1]catenanes.[7] However, these inverted macrocyclic spiro compounds still contained a central tetrahedral carbon atom that is part also of a five-membered fluorene-centered cyclopentadiene[7a] or ketal,[7b] similar to Schill's precatenane **4**. In this communication we describe the successful targeted synthesis of the truly bicyclic inverted spiro [27,27]-membered bi-

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cycle **3**, that is, where the central carbon atom is the sole linkage between macrocycles (Scheme 3). To achieve this goal, we have developed a covalent template-mediated strategy to direct the required highly disfavored, consecutive-backfolding macrocyclizations.[8] For comparative reasons the related regular spiro macrobicyclic diastereomer **2** was prepared from the same tetrahedral precursor.
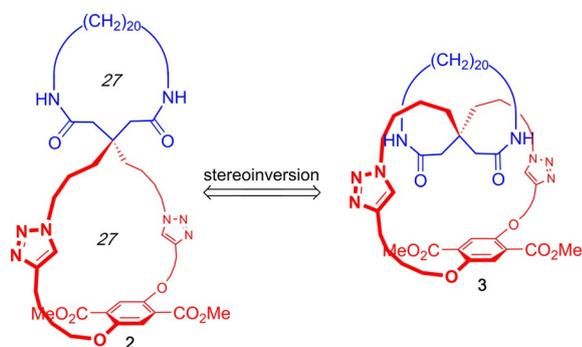
Scheme 3. Molecular structure of the target regular spiro macrobicycle **2** and inverted analog **3**.

Scheme 4 outlines the synthetic strategy, starting with the temporary connection of a tetravalent, bond-tethering template **5** to two of the four linear ring-precursors in the tetrahedral starting compound **1**.
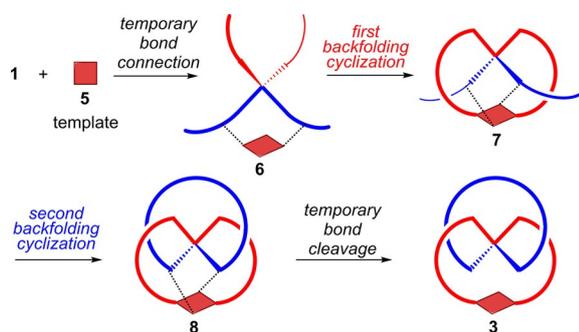

Scheme 4. Outline of the template-directed strategy to direct the backfolding cyclizations.

Molecule **6** is now preorganized for the first backfolding macrocyclization, facilitated by reaction of the remaining two template valencies within **6** to the termini of the other two (red) ring-precursor chains affording the cage-type intermediate **7**. The first cyclization is forced to proceed in a perpendicular and backfolded fashion as a consequence of the tetrahedral geometry of the central atom. The final backfolding macrocyclization is performed by connection of the termini of the remaining two (blue) ring-precursor chains in **7** to afford the inverted spiro connectivity in **8**, with cleavage of the bond-tethering template liberates the inverted spiro macrobicycle **3**. Taking into account that the synthesis of the regular spiro bicycle from **1** entails two macrocyclization steps, the approach to

the inverted geometry only requires two steps more: making and breaking the temporary covalent linkages to the template.

To access the inverted spiro bicycle **3** and its regular spiro diastereomer **2** (Scheme 3) through a bond-tethering template strategy (Scheme 4) the tetrahedral starting compound **1** and template **5**[7a] were synthesized (Scheme 5).
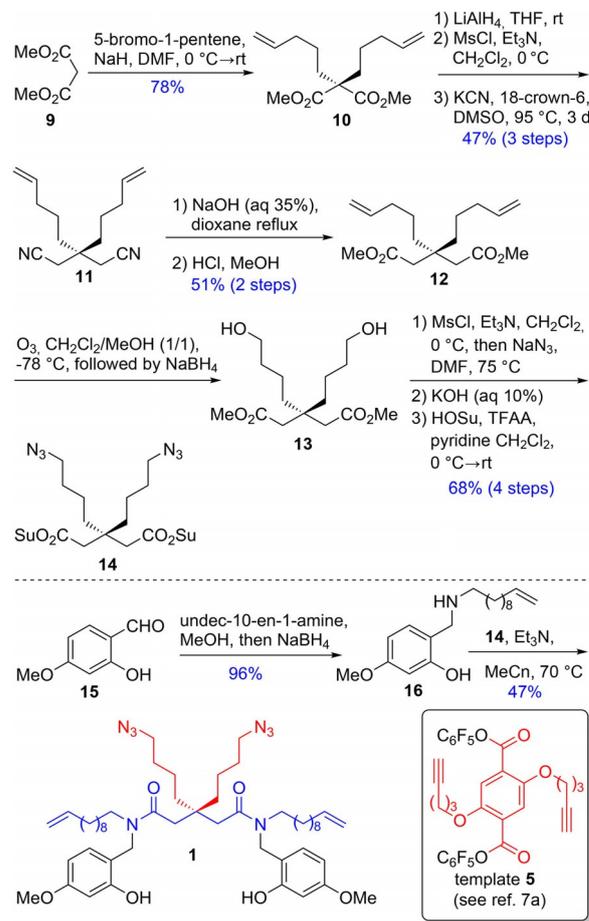
Scheme 5. Synthesis of the linear macrocyclization precursor **1** and structure of the template **5** (Su = succinimide).

As all main reactions towards the inverted spiro geometry involve potentially difficult macrocyclizations, we enlisted the use of consecutive, high-yielding reactions including lactonization,[9] Cu-catalyzed azide-alkyne cycloaddition[10] (CuAAC) and ring-closing metathesis[11] (RCM). Furthermore, these reactions possess orthogonal reactivities, obviating the need for protective groups. We utilized our previous bond-tethering template **5**, featuring ester and electron-rich benzylic linkages to ensure reliable cleavage via consecutive transesterification and acidolysis.[12]

The reaction sequence towards **1** commenced by a double alkylation of dimethyl malonate (**9**) by 5-bromo-1-pentene to afford dialkyl malonate ester **10** in 78% yield (Scheme 5). Compound **10** was reduced using LiAlH4 followed by conversion to the corresponding mesylate diester using mesyl chloride and nucleophilic displacement with KCN giving dinitrile **11** in a 47% yield over three steps. Hydrolysis of nitrile **11** with aque-

ous NaOH provided the corresponding carboxylic acid analogue, which was directly converted into the corresponding methyl diester **12** in a 51% yield over two steps. Ozonolysis of the terminal alkenes and reductive work-up using NaBH$_4$ provided diol **13**. Introduction of the azide functionalities was accomplished after conversion of the alcohols to the corresponding mesylates followed by treatment with NaN$_3$. The ester moieties of the azide derivative were saponified using 10% aqueous NaOH. Treatment of the carboxylic acids with an excess of TFAA and *N*-hydroxysuccinimide gave activated diester **14** in 85% isolated yield (Scheme 5; Su=succinimide). Amine **16** was easily prepared from aldehyde **15** and undec-10-en-1-amine, using a standard reductive amination procedure with NaBH$_4$. For the preparation of **1**, di-OSu-activated ester **14** was subsequently reacted with two equivalents of amine **16**, which afforded **1** in 47% yield.

With the tetrahedral cyclization precursor **1** and template **5** available the scene was set for the final four key steps to arrive at the bicyclic inverted spiro geometry (Scheme 6). Macrolactonization at high dilution (MeCN, 1 mM) between the phenolic hydroxyl groups of **1** and pentafluorophenyl-activated template **5** using Cs$_2$CO$_3$ as a base in the presence of molecular sieves to remove any traces of water gave the 21-membered macrocycle **6** in an isolated yield of 92%. At this stage, product characterization via ^{1}H NMR was severely hampered due to the presence of rotamers. A double CuAAC reaction was then executed (CH$_2$Cl$_2$, 1 mM) for the first backfolding macrocyclizations employing [Cu(CH$_3$CN)$_4$]BF$_4$ (20 mol%) and TBTA (20 mol%) as the catalyst system to access the cage-type compound **7** in 65% yield.[13] FT-IR spectroscopy and LC-MS analysis confirmed successful conversion of the azides and clean formation of a product with the expected molecular mass. The final backfolding macrocyclization by RCM was performed with the 2nd generation Grubbs catalyst (20 mol%) at high dilution (CH$_2$Cl$_2$, 2 mM) and a slightly elevated temperature of 40 °C to give **8** in a moderate 47% yield. Removal of the benzylic tethers was accomplished by methoxide-mediated lactone opening followed

by methanolic HCl treatment to cleave the benzylic bonds giving the 27+27-membered inverted spiro bicycle in 75% yield over the last two steps. Catalytic hydrogenation of the *E/Z*-alkene mixture produced pure **3**, which was fully characterized by NMR (vide infra). The regular spiro macrobicycle was made from the common cage-type precursor **7**. Treatment of **7** with K$_2$CO$_3$ in MeOH induced transesterification under mild conditions resulting in ring-opening of the lactones followed by immediate conformational relaxation by unwinding of the intermediate quasi[1]rotaxane to give monocycle **17** in essentially quantitative yield. The ^{1}H NMR spectrum features the singlet at 3.71 ppm demonstrating successful transesterification, with the other signals appearing highly resolved, indicative of complete unfolding of the first ring fragment from the template moiety. Acidolytic removal of the benzylic tether remnants to afford **18** was followed by the final macrocyclization step via RCM providing the regular spiro bicycle **19**. Subsequent catalytic hydrogenation of the alkene furnished the classical spiro bicycle **2** in 44% yield over three steps. The diastereomeric relationship between **2** and **3** was already obvious in regular TLC with different retentions (R_f = 0.29 vs. 0.42, EtOAc/MeOH = 9:1) observed, and confirmed by reversed-phase LC-MS. The inverted spiro bicycle **3** experiences significant retention compared to the regular spiro bicycle **2** pointing to a higher polarity of the latter compound.

Fortunately, the ^{1}H NMR spectra of **2** and **3** both demonstrated sharp, well resolved signals allowing full characterization of the molecular structures (Figure 1). Strikingly, the regular spiro compound **2** demonstrates all methylene-type protons attached to the same carbon atoms next to hetero-atoms as a single multiplet, while for the inverted spiro bicycle **3** each proton gives an isolated multiplet. The broken symmetry within the densely packed inverted spiro geometry **3** affords greater difference in the chemical environment around these methylene protons, emerging from restricted rotation of the cyclophane-type terephthalic phenyl ring over the C−O single bonds due to steric clashes between the methyl esters and
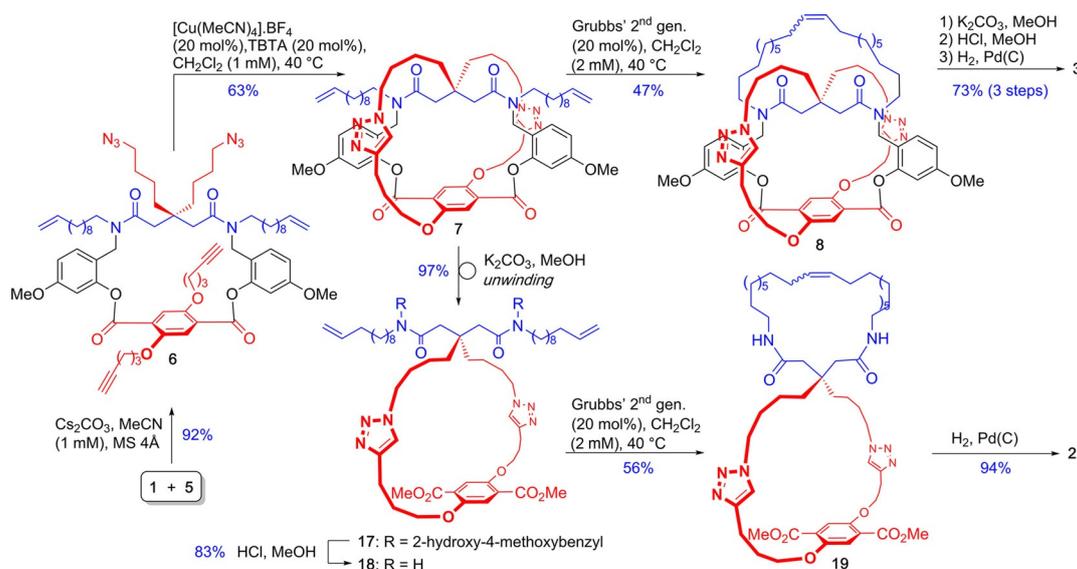
Scheme 6. Endgame towards the regular spiro bicycle **2** and inverted spiro bicycle **3**.
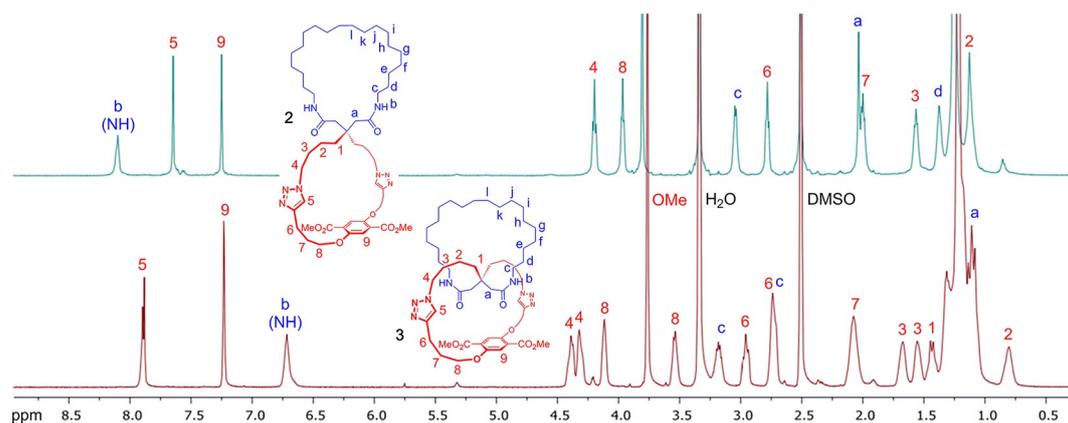
Figure 1. ^{1}H NMR spectra and peak assignments of regular spiro bicycle **2** and inverted spiro bicycle **3**.

nearby atoms of the opposing macrocycle. After heating at 120 °C the individual methylene protons in **3** coalesced into single peaks. The downfield shift of 1.24 ppm of the triazole CH and upfield shift of 1.39 ppm of the amide NH in the inverted spiro bicycle are also noteworthy. Similarly, in the ^{13}C NMR spectrum the triazole–CH carbon atom showed a slight shift of 122.0 ppm in **2** to 124.3 ppm in **3** with other signals experience no perturbation of chemical shift. These observations are most probably caused by the presence of a hydrogen bond between the amide carbonyl and the triazole-CH in **3**.[14] This would match, using the same ring colors for the structures in both Schemes 2 and 3, for conformations **3-I** or **3-II**. Semi-empirical calculations (PM6) supported these observations, showing an energy difference of 2 kcal mol^{-1} only between the **3-I** and **3-II** inverted spiro conformation, with a slight preference for the latter. Conformation **3-III** was not found in the calculations (see Supporting Information), potentially due to the reduced conformational freedom in the triazole- and phthalate-containing macrocycle, It is worth mentioning that these calculations reveal very little energy difference (3 kcal mol^{-1}) between **2** and **3** (conformation **3-I**) indicating that no van der Waals interaction or ring strain is present within the 27 + 27-membered inverted spiro macrobicyclic architecture. Calculations support the blocked rotation within the inverted spiro compound **3** over the C–O single bonds at the cyclophane-type terephthalic phenyl ring thereby introducing planar chirality. Attempts to separate these enantiomers of **3** by chiral-HPLC analysis were unsuccessful and only a single broad peak was observed.

In summary, we report the targeted synthesis of both a spiro bicycle and its inverted diastereomer using covalent template-induced backfolding macrocyclizations. This enables fundamental studies on the new stereochemistry and the unique packing of the inverted spiro bicycle architecture.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

[1] Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673 – 3682.
[2] L. K. Smith, I. R. Baxendale, *Org. Biomol. Chem.* **2015**, *13*, 9907 – 9933.
[3] S. Fantacci, F. De Angelis, M. K. Nazeeruddin, M. Grätzel, *J. Phys. Chem. C* **2011**, *115*, 23126 – 23133.
[4] P. M. Budd, B. S. Ghanem, S. Makhseed, N. B. McKeown, K. J. Msayib, C. E. Tattershall, *Chem. Commun.* **2004**, *2*, 230 – 231.
[5] G. Schill, A. Lüttringhaus, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 546 – 547; *Angew. Chem.* **1964**, *76*, 567 – 568.
[6] *The Nature of the Mechanical Bond: from Molecules to Machines*; C. J. Bruns, J. F. Stoddart, Wiley, Hoboken, **2016**.
[7] a) L. Steemers, M. J. Wanner, M. Lutz, H. Hiemstra, J. H. Van Maarseveen, *Nat. Commun.* **2017**, *8*, 15392; b) L. Steemers, M. J. Wanner, B. R. C. van Leeuwen, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2017**, 874 – 878.
[8] V. Martí-Centelles, M. D. Pandey, M. I. Burguete, S. V. Luis, *Chem. Rev.* **2015**, *115*, 8736 – 8834.
[9] A. Parenty, X. Moreau, G. Niel, J. M. Campagne, *Chem. Rev.* **2013**, *113*, PR1 – PR40.
[10] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599; *Angew. Chem.* **2002**, *114*, 2708 – 2711; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057 – 3064.
[11] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18 – 29.
[12] L. C. Packman, *Tetrahedron Lett.* **1995**, *36*, 7523 – 7526.
[13] a) G. Chouhan, K. James, *Org. Lett.* **2011**, *13*, 2754 – 2757; b) T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853 – 2855.
[14] Y. Hua, A. H. Flood, *Chem. Soc. Rev.* **2010**, *39*, 1262 – 1271.