Cyclotrimerization approach to unnatural structural modifications of pancratistatin and other amaryllidaceae constituents — Synthesis and biological evaluation

Tomas Hudlicky, Michael Moser, Scott C. Banfield, Uwe Rinner, Jean-Charles Chapuis, and George R. Pettit

Abstract: The phenanthridone core of pancratistatin lacking all aromatic oxygenation was prepared by cyclotrimerization of acetylene-containing scaffolds 30 and 41, reflecting the natural and the C-1 epi configuration, respectively, of the amino inositol moiety. The cobalt-catalyzed formation of the aromatic core led to bisTMS derivatives 39 and 48, as well as bisacetyl derivative 51. The effectiveness of cyclotrimerization of the natural or trans series was compared with that of the cis series. In addition, the yields of cyclotrimerization were compared for propargylic amines and propargylic amides. Eleven derivatives, including the fully hydroxylated phenantridone 39, were tested against seven cancer cell lines. Three of the compounds displayed activities only an order of magnitude less than those of 7-deoxypancratistatin. Full experimental and spectral details are provided for all key compounds and future projections for the preparation of unnatural analogs of Amaryllidaceae constituents are advanced, along with some new insight into the minimum pharmacophore of pancratistatin.

Key words: cyclotrimerization, alkaloids, cobalt catalyst.

Introduction

Pancratistatin (1) and its congeners (Fig. 1) have been at the forefront of activities in both synthetic and medicinal communities (1). All four naturally occurring constituents have been synthesized by many creative approaches (2–5), and significant effort has been devoted to the investigation of the mode of action (6), active pharmacophore (7), and more bioavailable agents (8). To date many truncated versions of the key constituents have been prepared (9) and evaluated for activities against several cancer cell lines. From the results of these evaluations, several generalizations
have emerged with regard to the structural elements essential to activity. First, the hydroxyphenanthridone moiety is thought to be essential to high activity of pancratistatin and narciclasine; its deletion, as in 7-deoxypancratistatin and lycoridine, leads to a significant drop in activity (10). Second, the amino inositol motif is also essential, save for small changes at C-1 and C-2; deletion of the hydroxyls at these positions or altering substitution patterns at C-1 does not altogether eliminate activity (7, 11). Various unnatural derivatives with specific deletions in the hydroxylated ring have been tested. A recent article established that the minimum requirement for activity is the 2,3,4-triol pattern found in all active constituents (11). Third, deletion of some of the aromatic oxygenation lowers activity significantly (12). Fourth, recently synthesized lactone mimics 5 and 6, in both configurations at C-4, were found inactive, suggesting that the phenanthridone unit is essential for retention of activity (13). Finally, an indole mimic of pancratistatin (7) recently prepared in our laboratory possessed borderline activity against one cell line (Table 1) (14).

These observations, as well as the bioavailability studies, indicate that the greatest opportunity for structural alterations exists in modifications of the aromatic core of the natural product. To prepare a large number of derivatives, a diversity-oriented synthesis strategy (DOS) is the most efficient way to generate libraries of compounds for testing. Rather than synthesize uniquely functionalized aryl residues for eventual attachment to the amino inositol unit, we have chosen the cyclotrimerization approach portrayed in Fig. 2, which is based on acetylene- and nitrile-containing scaffolds and their cobalt-catalyzed trimerization to aromatic (15) and heteroaromatic (16) variants of the pancratistatin type. This unique transformation was discovered in 1864 by Berthelot (17), who prepared benzene by passing acetylene over hot copper. We note that Berthelot’s paper, published in 1866, is usually cited as the event of original discovery (17b, 17c). This is not the correct citation and for historical interest we include the original description of his 1864 experiment here:

Il est un cas de condensation de l’acétylène naissant très-remarquable et qui mérite un examen particulier, bien que la démonstration en soit plutôt vraisemblable que rigoureusement établie: c’est la condensation de l’acétylène en benzine. Entre la formule de l’acétylène, $C_4H_2$, et celle de la benzine $C_{12}H_6$, c’est-à-dire entre les poids de ces deux corps ramenés à l’état gazeux et au même volume, il existe une relation très-simple; la deuxième formule est triple de la première:

$$3 \; C_4H_2 = C_{12}H_6.$$ 

Or cette relation n’existe pas seulement entre les formules des deux corps; mais on peut admettre que, dans certaines circonstances que nous allons signaler, l’acétylène naissant se transforme réellement en benzine. Voici ces circonstances.

Nous avons vu précédemment (p. 286) qu’en faisant passer un courant de vapeur de formène trichloré (chloroforme), $C_2HCl_3$, sur du cuivre chauffé au rouge, le chlore est absorbé et l’acétylène prend naissance. Rêpons cette expérience avec le formène tribromé (bromoforme), $C_2HBBr_3$, nous obtiendrons de la benzine. Nous sommes donc autorisés à penser que 3 molécules d’acétylène naissant peuvent se condenser en une seule molécule de benzine: la benzine serait alors du triacétylène.

This is an example of condensation of the nascent acetylene that is very remarkable and deserves a close examination, even though the demonstration is rather plausible then rigorously established: it is the condensation of the acetylene into benzene. There is a very simple relationship between the formula of acetylene, $C_4H_2$, and the formula of benzene, $C_{12}H_6$, specifically between the weight of equal volumes of those two bodies in the gas state: the second formula is triple of the first:

$$3 \; C_4H_2 = C_{12}H_6.$$ 

Now such relation does not just exist between the formulas of the two bodies; but we can admit that under certain particular circumstances that we may point to, nascent acetylene is actually transformed to benzene. We have already seen (p. 286) that by passing a stream of gaseous trichlorinated formene (chloroform), $C_2HCl_3$, over red-hot copper, chlorine is absorbed and acetylene is generated. By repeating this experience with tribrominated formene (bromoform), $C_2HBBr_3$, we would obtain some benzene. This leads us to think that three molecules of nascent acetylene could combine to form a single molecule of benzene. Thus benzene would be a triacetylene.

The reaction enjoyed moderate attention and, indeed, exhibited moderate yields in most of the documented examples in the literature, including recent applications (18). An ex-

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**Fig. 1.** Amaryllidaceae constituents (1–4) and some recently synthesized unnatural mimics (5–7).

- Pancratistatin (1)
- Narciclasine (2)
- 7-Deoxypancratistatin (3)
- Lycoridine (4)
- Lactone narciclasine mimic, $X = OH$
- Lactone lycoridine mimic, $X = H$
- 6 Lactone lycoridine mimic, $X = H$
- 7 β-Carboline-1-one mimic

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ception to such critique is found in the classic application of cyclotrimerization to the total synthesis of estrone by Funk and Vollhardt in 1977 (19), shown in Fig. 3. Despite the attention this synthesis received, only once more was this technique featured in a total synthesis effort — an approach to morphine also disclosed by Vollhardt and co-workers (20) (Fig. 3). In the estrone synthesis, the initial cyclization furnished a low yield of $^{13}$ in addition to the intermediate benzocyclobutane, which, under the conditions of the reaction, underwent $[4+2]$ cyclization to $^{13}$ in a total yield of 71%. In the approach to morphine, benzofuran $^{15}$ yielded the tetracyclic morphine skeleton as a single diastereomer with C-5, C-9, and C-13 correctly set, indicating the potential for adjustment to the total synthesis of morphine itself, once appropriate substitution parameters for the incipient quaternary center at C-13 were designed. The emphasis on multicomponent reactions and cascade processes, so prevalent in the last decade or so (21, 22), seemed in sharp contrast to the apparent underutilization of cyclotrimerization techniques that satisfy both of these criteria. We reasoned that the modest yields reported in most of the applications could be addressed through appropriate reaction engineering and optimization of conditions. The benefits that would be harvested in the area of structure and activity relationships (SAR) for the analogs of the pancratistatin group of compounds seemed to outweigh the uncertainty and expectations of moderate yields in the construction of aromatic nuclei of the analogs.

In this manuscript we report the successful synthesis of several pancratistatin analogs by a high-yielding cyclotrimerization strategy to furnish all the aromatic nuclei and the tetracyclic morphine core in a single synthetic step. The compounds were evaluated for their antiproliferative activity against a panel of human cancer cell lines and in murine P388 lymphocytic leukemia. The results are summarized in Table 1.

### Table 1. Evaluation of the activities of aromatic deoxygenated TMS derivatives of 7-deoxypancratistatin.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Murine P388 lymphocytic leukemia</th>
<th>Pancreas BXPC-3</th>
<th>Breast MCF-7</th>
<th>CNS SF-268</th>
<th>Lung NCI-H460</th>
<th>Colon KM20L2</th>
<th>Prostate DU-145</th>
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<td>0.29</td>
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<tr>
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<td><img src="image2" alt="Compound 3" /></td>
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<td>0.026</td>
<td>0.019</td>
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<tr>
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<tr>
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<td><img src="image4" alt="Compound 5" /></td>
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<td>4.9</td>
<td>4.4</td>
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<tr>
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merization protocol from fully functionalized scaffolds of type 9 (23). The biological evaluation of the analogs, also reported herein, provided some surprising results and cast some uncertainty on the previously held views regarding some of the structural features deemed essential for biological function.

Results and discussion

The original intent of our study was the investigation of a de novo approach to pancratistatin (1) from scaffold 9 in which the acetylene partners would provide a triply silylated arene that could be converted to the fully oxygenated core of pancratistatin. Portrayed in Scheme 1 are the results of this particular approach, which met with abject failure because of the steric issues associated with multiply silylated sites or perhaps random desilylation processes similar to those observed when Rainier used an iron-based catalyst (24). Only the cobalt-coordinated tetracycle 20 was isolated in low yield from the reactions of bisacetylene 19 (Scheme 1). The final cycloaddition of bis(trimethylsilyl)acetylene (BTMSA) did not lead to the fully silylated arene 21, presumably because of steric crowding.

When Ni(COD)$_2$ was employed as a catalyst, the cyclo-trimerization of 22 gave an interesting dimeric product (23) in 47% yield. The use of a zirconium catalyst (25) did not lead to dimeric 23 and gave other products.

Adjustments in the strategic plan led to the construction of simpler scaffolds unencumbered by TMS groups and cyclotrimerization attempts to attain a 7-deoxypancratistatin

<table>
<thead>
<tr>
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<td>1.6</td>
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<tr>
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<td>1.7</td>
<td>1.7</td>
<td>1.6</td>
<td>1.7</td>
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<td>1.8</td>
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<tr>
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<td><img src="image.png" alt="Image" /></td>
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</tr>
</tbody>
</table>

Note: Compounds 36, 37, 38, 39, 44, and 48 are marginally inactive to completely inactive in the p388 leukemia cell lines.

3 The exposure of propargyl amide 22 to a zirconium-based catalyst led to some unusual results. The propargyl amide was lost and tosylamide 18 was recovered, in addition to an unusual structure, tentatively identified as cyclic allene A, which may result in an ene reaction between the propargyl group and the hydrogen at 10b.

A ([1R,2S,6R]-4,4-Dimethyl-12-methylene-14-(4-methylphenylsulfonyl)-11-trimethylsilyl-3,5-dioxa-14-azatricyclo-[7.5.0.0^2,6]tetradeca-7,9,10-trien-13-one): [α]$_D^{25}$ +79.0 (c 0.95, CHCl$_3$), R$_f$ 0.81 (hexanes – ethyl acetate, 4:1). IR (CHCl$_3$, cm$^{-1}$): 3683, 3020, 2962, 2932, 2401, 2167, 1736, 1660, 1598, 1598, 1598, 1374, 1308, 1278, 1251, 1216, 1189, 1176, 1091, 1063, 950, 908, 847, 757, 669, 582. $^1$H NMR (300 MHz, CDCl$_3$, ppm): 8.00 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.11 (s, 1H), 5.80 (dd, J = 9.9, 3.1 Hz, 1H), 5.64 (d, J = 10.2 Hz, 1H), 4.71 (t, J = 5.0 Hz, 1H), 4.63 (d, J = 4.8 Hz, 1H), 4.40 (m, 1H), 2.43 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H). $^1$H NMR (75 MHz, CDCl$_3$, ppm): 145.6, 142.7, 135.5, 129.8, 128.0, 125.1, 115.1, 110.7, 104.0, 77.5, 74.4, 69.8, 62.9, 41.0, 28.1, 27.0, 22.0, 0.0. $^1$C NMR (75 MHz, CDCl$_3$, ppm): 145.6, 142.7, 135.5, 129.8, 128.0, 125.1, 115.1, 110.7, 104.0, 77.5, 74.4, 69.8, 62.9, 41.0, 28.1, 27.0, 22.0, 0.0. MS (EI) m/z (relative intensity): 456 (M$^+$ – CH$_3$, 30), 415 (10), 414 (30), 413 (23), 259 (11), 258 (30), 242 (7), 230 (10), 220 (5), 215 (5), 161 (6), 156 (8), 155 (29), 149 (11), 140 (5), 139 (13), 129 (6), 108 (5), 107 (7), 106 (12), 105 (9), 99 (6), 98 (11). HRMS (EI) calcd. for C$_{23}$H$_{26}$O$_5$NSSi-CH$_3$: 456.1301; found: 456.1289.
Fig. 2. Cyclotrimerization approach to aromatic core variants of pancratistatin.

Substitution pattern instead. These efforts were divided into three distinct areas: (i) synthesis of building blocks exhibiting the stereochemistry of the “natural” or trans series, with respect to stereochemical configuration at C-1 and C-2; (ii) synthesis of the corresponding “unnatural” or cis series; and (iii) comparison of the overall efficiency of these two approaches with one that would employ propargyl amides vs. propargyl amines. Upon attaining the nucleus of Amaryllidaceae constituents, all of these approaches would be evaluated and the best one chosen for the eventual production of analogs.

Cyclotrimerization of scaffolds in the trans or natural series

The intermediate reflecting the natural amino inositol configuration was synthesized as shown in Scheme 2 (23). Vinylaziridine 10 (26) was reacted with the aluminum complex prepared from lithium (trimethylsilyl)acetylene to provide 18 in 69% yield. After column chromatography, the product of this reaction was treated with 2,2-dimethoxypropane (DMP) and acetone to reprotect the diol liberated in the portion of the mixture by the action of AlCl₃. The reprotected compound was used without further purification. The tosylaziridine 18 was first converted to the cis-diol 24 by the action of OsO₄ and N-methylmorpholine-N-oxide (NMO) (44% yield, 76% conversion), and the cyclic sulfate 25 was then generated in 82% yield by treatment with SO₃·CH₂·Cl and NEt₃. Cyclic sulfates, whose reactivity resembles that of epoxides (27), are easily opened with weak nucleophiles such as ammonium benzoate. Such opening generates the required trans relationship at C-1/C-2 of pancratistatin, as has been previously demonstrated (27b). Treatment of 25 with ammonium benzoate generated, surprisingly, a mixture of the desired 26, as a minor product accompanied by the elimination product 27, displaying the substitution parameters of narciclasine or lycoricidine. Investigation of this reaction revealed that 27 does not originate in 26 nor is it derived from 25 by syn elimination. Careful experimentation revealed that the likely source of 27 is the intramolecular elimination of proton at C-10b by the intermediate sulfate anion 25a as shown in Fig. 4. Further study is required to optimize the production of either 26 or 27, the latter containing the structural features of narciclasine.

The TMS group was removed with tetrabutylammonium triphenylsilanolfluorosilicate (TBAT) in 84% yield from acetylene 26 to avoid previously encountered problems with steric bulk at the incipient C-10 of the aromatic nucleus. Following the protection of the C-2 alcohol as a TBS ether (89%), tosylamide 29 was alkylated with propargyl bromide to yield the required compound 30 in 79% yield. As mentioned above, the prospects for high yields in the cyclotrimerization were not promising based on the rather modest yields reported throughout the literature. Yet, after optimization, acetylene derivative 30 was converted to tetracyclic tosylamide 31 in 83% yield (slow addition over 36 h of a mixture of 30, catalyst, and BTMSA to a heated solution of BTMSA, which was recovered by distillation upon completion of the reaction). Tosylamide 31 was converted to fully deprotected tetraol 34 (as shown in Scheme 3) to provide compounds lacking the phenanthridone carbonyl group for biological evaluation. Oxidation of 31 to the state of phenanthridone proved somewhat arduous, proceeding in 15% yield to 35 with NaO₂·RuCl₂. Oxidation studies on bisbenzoate 37 led to the same results under these conditions. With the reaction buffered by solid Na₂CO₃, the oxidation occurred more slowly to give 38 in 33% yield. This material was subjected to reductive detosylation with sodium naphthalide, during which a partial loss of the benzoate groups occurred as a result of the basic conditions. The crude material was treated first under stronger basic conditions CH₃ONa in MeOH) then under acidic conditions (Dowex 50WX-100 in MeOH) to provide the 7-deoxypancratistatin nucleus having TMS bulk at the incipient C-10 of the aromatic nucleus. Following investigation of this reaction revealed that 31 as shown in Fig. 4. Further study is required to optimize the production of either 26 or 27, the latter containing the structural features of narciclasine.

The unnatural or cis series intermediate was synthesized as shown in Scheme 4. The purpose of this approach was twofold. First, it would avoid the lack of selectivity in the cyclic sulfate opening encountered with 25, leaving this reaction for the latter part of the synthesis. Second, it would provide the analogs with unnatural C-1 configuration for biological testing. The bisbenzoate 41 was subjected to cyclotrimerization under the optimized conditions applied to compound 30 in the trans series and provided tetracycle 42 in 87% yield (as shown in Scheme 5).

Deprotection of the benzoate and generation of the cyclic sulfate was accomplished in high yield and trans-benzoate alcohol 36 was generated in essentially quantitative yield. Upon exposure of 44 to ammonium benzoate in dimethylformamide (DMF) in this series, the elimination to the narciclasine/lycoricidine manifold was not observed. A possible explanation may lie in the relative acidities of propargylic vs. benzylic protons at C-10b in 25 vs. 44, respectively. Fully deprotected analogs 34 (lacking the phenanthridone carbonyl) and 39 (containing the amide) were ob-
Fig. 3. Applications of cyclotrimerization strategy in total synthesis (Vollhardt’s estrone and morphine).

Scheme 1. Cyclotrimerization approach to fully silylated aromatic core. Reagents and conditions: (i) DMP, p-TSA, acetone, rt, then PhINTs, Cu(acac)$_2$, H$_2$CCN, 0 °C to rt, then n-Bu$_3$SnH, AIBN, THF, reflux, 25% over three steps; (ii) BuLi, TMS–acetylene, AlCl$_3$, toluene, 0 °C to rt, then DMP, p-TSA, acetone, rt, 69% over two steps; (iii) BuLi, TMS – propargyl bromide, (n-Bu)$_3$NI, THF, rt, 46% (66% by conversion); (iv) CpCo(CO)$_2$, BTMSA, 140 °C; (v) BuLi, propiolic acid anhydride, THF, 0 °C to rt, 46%; (vi) Ni(COD)$_2$, PPh$_3$, toluene, BTMSA, rt, 47%.
Scheme 2. Scaffold for cyclotrimerization in the trans or natural series. Reagents and conditions: (i) BuLi, TMS–acetylene, AlCl₃, toluene, 0 °C to rt; (ii) DMP, acetone, rt, 69% over two steps; (iii) OsO₄, NMO, CH₂Cl₂, rt, 44% (76% by conversion); (iv) SO₂Cl₂, NEt₃, CH₂Cl₂, 0 °C to rt, 82%; (v) H₂C₅COONH₄, DMF, 70 °C, then H₂O, H₂SO₄, THF, rt; (vi) TBAT, H₂CCN, rt, 84%; (vii) TBSCl, imidazole, DMF, rt, 89%; (viii) NaHMDS, propargyl bromide, (nBu)₄NI, THF, -0 °C to rt, 79%.

Fig. 4. Generation of enyne 25.

Cyclotrimerization of propargyl amides

To avoid the modest yields of benzyl oxidation in the tetracycles 31 and 37, we chose to investigate the cyclotrimerization protocol on propargyl amides, which could be easily generated by acylation of tosylamide 18. Initially, the enyne 45, obtained by acylation of 18 with propionic acid anhydride, was chosen for this purpose (as shown in Scheme 6). Cyclotrimerization of this material furnished metal complex 46 in 11% yield and with apparent isomerization of the olefin to the configuration representing 2-deoxylycoricidine. When 47 was synthesized from 40 in 35% yield over two steps (cis series) and subjected to the same optimized conditions for cyclotrimerization, the tetracyclic phenanthridone 48 was obtained in 5% yield. It remains unclear whether these low yields are a function of unfavorable rotamer population of the imides such as 45 or 47 or whether the additional basic oxygen interferes with the catalytic cycle by complexation with the catalyst. Apparently these issues did not prevent the aforementioned cyclotrimerization of amide 22 to the dimeric phenanthridone 23 obtained in 47% yield (Scheme 1).

Synthesis of the bisacetyl derivative of 7-deoxypancratistatin

As a prelude to a de novo synthesis of one of the Amaryllidaceae constituents, we decided to prepare the bisacetyl derivative 51 shown in Scheme 7. Both arylsilanes and acetophenones should respond to Tamao oxidation (28) or Baeyer–Villiger oxidation (29), respectively, as means of generating the required oxygenation of the aromatic nucleus. Having noticed the experimental difficulties experienced by Vollhardt and Funk (19) in establishing the phenolic unit in estrone from a TMS group, we thought the bis(acetyl)arene would provide an alternative way to accomplish this task. To this end, the cyclotrimerization of bisacetylene 41 (cis series) was performed with hex-3-yne-2,5-diol protected as a bisTBS ether 49. Tetracycle 50 was obtained as a mixture of diastereomers in 31% yield. The mixture was treated with tetrabutyloammonium fluoride (TBAF) and oxidized to the bisacetylated tetracycle 51 in 51% yield over two steps. In future endeavors, the oxidation of this compound to acetyl catechols will be pursued as the means of establishing the C-8/C-9 oxygenation of pancratistatin-type constituents.

Biological evaluation

Several of the compounds in both the trans or natural and the C-1 epimeric series were evaluated in the cancer cell line series listed in Table 1. The activity profiles of pancratistatin, 7-deoxypancratistatin, and narciclasine (Table 1, entries 1, 2, and 3, respectively) are shown for comparison, along with two unnatural analogs previously synthesized in our laboratory (Table 1, entries 4 and 5). Some rather surprising and unexpected results were obtained. While the fully protected core of 7-deoxypancratistatin (Table 1, entry 6) is essentially inactive, the partially deprotected intermediates (Table 1, entries 7 and 8), as well as the fully deprotected tetaol (Table 1, entry 9) are quite active, having activities only 10-fold less than those of 7-deoxypancratistatin. This is surprising for several reasons: First, it has been widely held that the phenanthridone amide carbonyl is essential for activity, since Chapleur and co-workers (13) demonstrated that

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the lactone analogs 5 and 6 are inactive. Second, these compounds represent the first examples of pancratistatin analogs that retain activity despite the absence of all aromatic oxygenation, in addition to lacking the amide moiety. Third, and very surprising, these derivatives have shown greater activity than the fully deprotected bisTMS derivative 39 (Table 1, entry 16) in which the phenanthridone amide is present. This difference in activity may also be ascribed to the fact that a tosyl group is a common pharmacophore and several truncated derivatives of pancratistatin containing tosyl groups were shown to be more active than those lacking it (9c). As it has been assumed that the phenolic hydroxyl and the amide may be required as a donor–acceptor pair for hydrogen bonding, our results indicate that these requirements may be offset by other structural features. The only other active compound was the C-1 epimeric diol (Table 1, entry 10), where activity supports the observation that changes at C-1 of the pharmacophore do not drastically alter biological profiles. The fact that four of the intermediates displayed profiles only an order of magnitude lower that those of 7-deoxypancratistatin is promising and will guide us in further design of unnatural analogs with variable functionality in the aromatic core.

**Summary and conclusion**

The successful synthesis of several analogs of pancratistatin was achieved by the cobalt-catalyzed cyclotrimerization of acetylenic scaffolds with BTMSA and protected 2,5-hex-3-yne. Both configurations at the C-1 hydroxylated aminoinositol unit were examined, with the unnatural, or cis series, being clearly a higher-yielding and more efficient process. The cyclotrimerizations of bisacetylenes with N-propargylic substituents were also much higher yielding than the corresponding processes that employed the propargylic amides. The attainment of bisacetyl derivative 51 bodes well for eventual installation of the methylenedioxy unit via the Baeyer–Villiger reaction in a de novo synthesis of 7-
deoxypancratistatin. Based on the surprising and promising results of biological activity, it now seems prudent to proceed further with the preparation of diversely functionalized analogs of Amaryllidaceae constituents.

**Experimental section**

All nonaqueous reactions were conducted in an argon atmosphere using standard Schlenk techniques for the exclusion of moisture and air. Methylene chloride was distilled from calcium hydride; THF and toluene were dried over potassium/benzophenone. Analytical thin-layer chromatography was performed on Silicycle 60 Å 250 µm TLC plates with F-254 indicator. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Melting points were recorded on a Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a PerkinElmer One FT-IR spectrometer. Optical rotation was measured on a PerkinElmer 341 polarimeter at a wavelength of 589 nm. 1H and 13C NMR spectra were recorded on a 300 MHz Brucker spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent (CHCl3). The data for the proton spectra are reported as follows: chemical shift (multiplicity, singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m), coupling constants (Hz), integration). Carbon spectra were recorded with complete proton decoupling and the chemical shifts are reported in ppm (δ) relative to solvent resonance as internal standard. Combustion analysis were performed by Chemisar Laboratories Inc., Guelph, Ontario. Mass spectra and high-resolution mass spectra were performed by the analytical division at Brock University, St. Catharines, Ontario.

\[ N-[(1R,2R,5R,6S)-2-(2-Trimethylsilylethynyl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-4-methylbenzenesulfonamide (18) \]

To a solution of of (trimethylsilyl)acetylene (2.75 g, 28.00 mmol) in 40 mL toluene was added BuLi (1.6 mol/L, 17.50 mL, 28.00 mmol) at 0 °C. During the addition, a heavy white precipitate formed. The reaction mixture was stirred at 0 °C for 10 min before AlCl3 (1.24 g, 9.33 mmol) was added. After stirring for a further 10 min, aziridine 10b (1.00 g, 3.11 mmol), dissolved in 5 mL toluene, was added dropwise. Additional AlCl3 (622 mg, 4.67 mmol) was added and the suspension was allowed to warm to room temperature over 18 h. The reaction was quenched by addition of 1 mol/L HCl (100 mL) and diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (40 mL), dried over...
MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 2:1 to 1:2) afforded the title compound and the corresponding free diol. The diol was dissolved in 40 mL of acetone and protected by addition of 2,2-dimethoxypropane (486 mg, 4.67 mmol) and p-TSA (0.2 g). After 15 min the solution was diluted with ethyl acetate (200 mL), washed with satd. aq. NaHCO₃ (3 × 40 mL) and brine (40 mL). The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure affording 900 mg of pure acetonide (2.14 mmol, 69%); mp 168 °C. [α]D +30.2 (c 0.20, CH₂Cl₂). Rf 0.48 (hexanes – ethyl acetate, 2:1). IR (CHCl₃, cm⁻¹) ν: 3269, 3020, 2401, 2176, 1600, 1427, 1375, 1330, 1251, 1216, 1159, 1094, 1075, 972, 928, 846, 759, 669. ¹H NMR (300 MHz, CDCl₃, ppm) δ: 7.83 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H), 5.83 (m, 2H), 4.63 (d, J = 8.0 Hz, 1H), 4.50 (m, 1H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.60 (q, J = 8.3 Hz, 1H), 3.14 (d, J = 8.4 Hz, 1H), 2.41 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 0.14 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ: 143.2, 138.9, 130.4, 129.4, 127.5, 124.6, 110.1, 103.5, 87.9, 76.5, 71.8, 56.8, 34.6, 27.9, 25.9, 21.6, 0.0. MS (EI) m/z (relative intensity): 420 (MH⁺, 0.6), 419 (M⁺, 1.6), 255 (12), 254 (76), 253 (17), 207 (20), 191 (11), 190 (20), 175 (26), 171 (10), 155 (28), 149 (16), 147 (11), 139 (43), 124 (17), 123 (10), 121 (16), 117 (7), 107 (10), 105 (10), 100 (10), 99 (82), 98 (57), 97 (11), 92 (15), 91 (100), 89 (10), 85 (10), 84 (13), 83 (15), 77 (12), 75 (24), 73 (64), 65 (16), 59 (11), 58 (14), 57 (10), 45 (14), 44 (18), 43 (56), 41 (11). HRMS (EI) calcd. for C₂₁H₂₉O₄NSSi: 419.1587; found: 419.1582. Anal. calcd. for C₂₁H₂₉O₄NSSi: C 60.11, H 6.97; found: C 60.33, H 7.07.

(3aS,4R,5R,7aR)-2,2-Dimethyl-4-[4-methylphenyl(3-trimethylsilyl-2-propynyl)sulfonamido]-5-(2-trimethylsilyl-1-ethynyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole (19)

To a solution of tosylamide (200 mg, 0.48 mmol) in 3 mL THF was added BuLi (1.6 mol/L, 0.30 mL, 0.48 mmol) at 0 °C under argon. The solution was stirred for 5 min and trimethylsilyl propargyl bromide (0.37 mL, 2.38 mmol) and a catalytic amount of N(n-Bu)₄I were added. The reaction mixture was allowed to stir for 1 h at 0 °C and then it was warmed to room temperature and stirred for 16 h. The reaction was quenched by the addition of satd. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 2:1 to 1:2) afforded the title compound and the corresponding free diol. The diol was dissolved in 40 mL of acetone and protected by addition of 2,2-dimethoxypropane (486 mg, 4.67 mmol) and p-TSA (0.2 g). After 15 min the solution was diluted with ethyl acetate (200 mL), washed with satd. aq. NaHCO₃ (3 × 40 mL) and brine (40 mL). The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure affording 900 mg of pure acetonide (2.14 mmol, 69%); mp 168 °C. [α]D +30.2 (c 0.20, CH₂Cl₂). Rf 0.48 (hexanes – ethyl acetate, 2:1). IR (CHCl₃, cm⁻¹) ν: 3269, 3020, 2401, 2176, 1600, 1427, 1375, 1330, 1251, 1216, 1159, 1094, 1075, 972, 846, 759, 669. ¹H NMR (300 MHz, CDCl₃, ppm) δ: 7.83 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 7.5 Hz, 2H), 5.83 (m, 2H), 4.63 (d, J = 8.0 Hz, 1H), 4.50 (m, 1H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.60 (q, J = 8.3 Hz, 1H), 3.14 (d, J = 8.4 Hz, 1H), 2.41 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 0.14 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ: 143.2, 138.9, 130.4, 129.4, 127.5, 124.6, 110.1, 103.5, 87.9, 76.5, 71.8, 56.8, 34.6, 27.9, 25.9, 21.6, 0.0. MS (EI) m/z (relative intensity): 420 (MH⁺, 0.6), 419 (M⁺, 1.6), 255 (12), 254 (76), 253 (17), 207 (20), 191 (11), 190 (20), 175 (26), 171 (10), 155 (28), 149 (16), 147 (11), 139 (43), 124 (17), 123 (10), 121 (16), 117 (7), 107 (10), 105 (10), 100 (10), 99 (82), 98 (57), 97 (11), 92 (15), 91 (100), 89 (10), 85 (10), 84 (13), 83 (15), 77 (12), 75 (24), 73 (64), 65 (16), 59 (11), 58 (14), 57 (10), 45 (14), 44 (18), 43 (56), 41 (11). HRMS (EI) calcd. for C₂₁H₂₉O₄NSSi: 419.1587; found: 419.1582. Anal. calcd. for C₂₁H₂₉O₄NSSi: C 60.11, H 6.97; found: C 60.33, H 7.07.
removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 7:1 to 2:1) afforded sulfonamide 19 (115 mg, 0.22 mmol, 46%) and starting material 18 (40 mg, 20%). IR (CHCl₃ cm⁻¹): ν = 2959, 2926, 2180, 1599, 1497, 1381, 1347, 1249, 1216, 1159, 1095, 1068, 1016, 1000, 972, 920, 843, 814, 760, 734, 699, 666, 642, 596, 568, 544, 482. ¹H NMR (300 MHz, CDCl₃, ppm) δ = 8.01 (d, J = 8.3 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 5.91 (m, 2H), 4.62 (m, 2H), 4.17 (m, 1H), 4.10 (d, J = 7.3 Hz, 2H), 3.77 (d, J = 10.5 Hz, 1H), 2.42 (s, 3H), 1.53 (s, 3H), 1.34 (s, 3H), 0.18 (s, 9H), 0.08 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ = 143.0, 138.0, 132.8, 129.1, 128.5, 123.3, 109.8, 104.2, 100.6, 90.5, 88.0, 77.3, 74.0, 61.3, 33.2, 28.0, 25.8, 21.6, 0.0, –0.4. MS (EI) ml/z (relative intensity): 529 (M⁺, 0.2), 514 (M⁺ – CH₃, 4.1), 366 (12), 365 (27), 364 (100), 347 (12), 215 (16), 209 (28), 207 (15), 168 (11), 155 (10), 149 (17), 139 (66), 115 (11), 97 (11), 94 (10), 84 (10), 83 (33), 75 (16), 73 (86), 71 (12), 59 (16), 53 (13), 43 (32). HRMS (EI) calcd. for C₂₇H₃₉O₄NSSi: 471.1536; found: 471.1527.

N-[(1R,2R,5R,6S)-2-(2-Trimethylisilyl)ethyl]-5,6-isopropylidenedioxy)cyclohex-3-en-1-yl]-N-propioyloxy-4-methylbenzenesulfonamide (22)

To a solution of of acetonide 18 (250 mg, 0.60 mmol) in 5 mL THF was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of satd. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 7:1 to 2:1) afforded the tosylamide 21 (21.6, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (5 mL THF was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of satd. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 7:1 to 2:1) afforded the tosylamide 21 (21.6, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (5 mL THF was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of satd. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 7:1 to 2:1) afforded the tosylamide 21 (21.6, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (5 mL THF was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of satd. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 7:1 to 2:1) afforded the tosylamide 21 (21.6, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (5 mL THF was added BuLi (1.6 mol/L, 0.41 mL, 0.66 mmol) at 0 °C under argon. Propiolic acid anhydride (87 mg, 0.72 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by the addition of satd. aq. NH₄Cl (20 mL) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure.

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Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of satd. aq. NaHSO$_3$ (50 mL), the organic and the aqueous phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were separated, and the aqueous phase was evaporated to dryness. Flash column chromatography of the residue (hexanes – ethyl acetate, 1:1) afforded diol 24 (768 mg, 1.69 mmol). 19F NMR (300 MHz, CDCl$_3$, ppm) £ 7.79 (d, $J$ = 6.3 Hz, 1H), 7.29 (d, $J$ = 6.1 Hz, 2H), 6.98 (d, $J$ = 8.2 Hz, 3H), 6.68 (d, $J$ = 8.2 Hz, 3H), 6.66 (d, $J$ = 8.2 Hz, 3H), 6.64 (d, $J$ = 8.2 Hz, 3H), 6.62 (d, $J$ = 8.2 Hz, 3H), 6.60 (d, $J$ = 8.2 Hz, 3H), 6.58 (d, $J$ = 8.2 Hz, 3H). HRMS (EI) calcld. for C$_{14}$H$_8$S$_2$O$_{10}$N$_2$: 592.5287; found: 592.5284.

(C$_3$A$_{4}$R$_5$R$_6$S$_7$S$_7a$)-6,7-Dihydroxy-2,2-dimethyl-1-(4-methylphenylsulfonamido)-5-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (24)

To a solution of of (trimethylsilyl)acetylene 18 (1.55 g, 3.68 mmol) in 40 mL CH$_2$Cl$_2$ was added N-methylmorpholine-N-oxide (5.18 mg, 4.42 mmol) and six small crystals of OsO$_4$. The reaction mixture was stirred for 10 min at 0 °C. The solution was stirred for 10 min and SO$_2$Cl$_2$ (0.515 g, 2.65 mmol) was added dropwise. After the addition, the solution was allowed to warm to room temperature and was stirred for 3 h. Further addition of triethylamine (0.37 mL, 2.65 mmol) and SO$_2$Cl$_2$ (0.99 mL, 1.0 mol/L solution, 0.99 mmol) led to total consumption of the starting material (2 h). The reaction mixture was diluted with CH$_2$Cl$_2$ (30 mL) and extracted with water (2 × 10 mL). The organic phase was dried over Na$_2$SO$_4$, filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes – ethyl acetate, 2:1) afforded cyclic sulfate 25 (140 mg, 0.27 mmol, 82%); mp 169 °C. 

4.48 (m, 1H), 4.14 (m, 1H), 3.52 (m, 1H), 3.04 (m, 1H), 2.43 (s, 3H), 1.38 (s, 3H), 1.19 (s, 3H), 0.21 (s, 9H). 13C NMR (75 MHz, CDCl$_3$, ppm) δ: 143.5, 138.4, 129.8, 127.2, 109.5, 102.5, 89.6, 78.1, 77.4, 72.5, 69.9, 54.9, 36.9, 27.9, 25.9, 21.7, 0.0. MS (EI) m/z (relative intensity): 438 (M$^+$ – CH$_3$, 28), 380 (7), 366 (11), 351 (7), 322 (15), 282 (6), 254 (12), 242 (6), 226 (13), 225 (24), 224 (8), 222 (9), 212 (6), 211 (9), 194 (7), 193 (6), 180 (7), 178 (8), 172 (5), 171 (8), 157 (5), 156 (6), 155 (60), 154 (5), 153 (7), 152 (6), 151 (60), 149 (16), 141 (7), 140 (13), 139 (27), 129 (8), 128 (5), 125 (12), 124 (8), 123 (6), 109 (5), 108 (7), 107 (7), 101 (14), 100 (16), 99 (15), 98 (14), 97 (9), 92 (14), 91 (100), 90 (5), 89 (6), 86 (5), 85 (11), 84 (14), 83 (8), 77 (8), 75 (29), 74 (10), 73 (84), 72 (5), 71 (8), 70 (33), 69 (9), 65 (15), 64 (6), 63 (5), 61 (7), 60 (6), 59 (29), 58 (9), 55 (10), 53 (8), 45 (14), 44 (9), 43 (57), 42 (6), 41 (8). HRMS (EI) calcld. for C$_{14}$H$_8$O$_6$N$_2$S$_2$: 438.1407; found: 438.1400. Anal. calcld. for C$_{14}$H$_8$O$_6$N$_2$: C 55.60, H 6.89; found: C 55.20, H 7.02.

19F NMR (300 MHz, CDCl$_3$, ppm) δ: 7.81 (d, $J$ = 8.2 Hz, 2H), 7.28 (d, $J$ = 8.3 Hz, 2H), 7.03 (m, 3H), 4.48 (m, 1H), 4.14 (m, 1H), 3.52 (m, 1H), 2.43 (s, 3H), 1.38 (s, 3H), 1.19 (s, 3H), 0.21 (s, 9H). 13C NMR (75 MHz, CDCl$_3$, ppm) δ: 143.6, 138.3, 129.5, 127.5, 110.6, 98.1, 93.3, 82.4, 80.7, 77.3, 73.4, 54.4, 36.0, 27.4, 25.2, 21.7, –0.2. MS (EI) m/z (relative intensity): 500 (M$^+$ – CH$_3$, 15), 391 (16), 309 (7), 244 (5), 243 (5), 242 (100), 238 (6), 234 (5), 233 (5), 231 (6), 229 (9), 228 (8), 225 (8), 222 (6), 207 (5), 206 (6), 205 (8), 204 (18), 191 (6), 190 (7), 180 (6), 178 (6), 177 (8), 176 (8), 175 (6), 171 (6), 169 (5), 167 (9), 165 (12), 164 (8), 163 (13), 162 (7), 161 (9), 160 (5), 159 (5), 156 (7), 155 (34), 153 (7), 152 (6), 151 (10), 149 (9), 141 (49), 147 (6), 140 (6), 139 (16), 135 (8), 137 (11), 135 (10), 133 (7), 129 (7), 127 (6), 126 (8), 125 (8), 124 (9), 123 (11), 122 (5), 121 (7), 119 (9), 115 (5), 113 (8), 112 (9), 111 (15), 110 (7), 109 (12), 108 (7), 107 (7), 105 (7), 102 (6), 100 (7), 99 (10), 98 (10), 97 (21), 96 (9), 95 (15), 93 (5), 92 (9), 91 (42), 89 (6), 85 (21), 84 (13), 83 (23), 82 (10), 81 (16), 80 (7), 79 (7), 77 (6), 76 (8), 75 (11), 73 (26), 72 (6), 71 (48), 70 (23), 69 (45), 68 (9), 67 (12), 65

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To a solution of cyclic sulfate 25 (462 mg, 0.90 mmol) in 5 mL dry DMF was added ammonium benzoate (312 mg, 2.24 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to 40 °C and the excess DMF was removed under reduced pressure. The residue was suspended in 25 mL THF and 3 drops of H2O and H2SO4 were added. The resulting mixture was stirred for 1.5 h, then quenched with satd. aq. NaHCO3 (25 mL), and diluted with CH2Cl2. The aqueous phase was extracted with CH2Cl2 (3 × 10 mL). The combined organic phases were dried over Na2SO4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 2:1) afforded acetylene 26 (167 mg, 0.30 mmol, 33%); mp 105 °C. [α]D22 −38.4 (c 0.98, CHCl3). Rf 0.19 (hexanes – ethyl acetate, 2:1). IR (CHCl3, cm−1): ν: 3275, 2924, 2853, 1664, 1601, 1542, 1433, 1332, 1274, 1249, 1199, 1159, 1093, 1067, 875, 841, 761, 712, 664, 568, 550. 1H NMR (300 MHz, CDCl3, ppm): δ: 8.07 (d, J = 7.2 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 7.28 (d, J = 7.2 Hz, 2H), 5.75 (d, J = 7.1 Hz, 1H), 5.53 (dd, J = 4.2, 7.7 Hz, 1H), 4.30 (m, 1H), 4.23 (m, 1H), 4.08 (m, 2H), 3.26 (m, 1H), 3.16 (s, 1H), 2.41 (s, 1H), 1.50 (s, 3H), 1.24 (s, 3H), 0.10 (s, 9H). 13C NMR (75 MHz, CDCl3, ppm): δ: 166.7, 143.7, 138.1, 133.7, 130.3, 129.9, 128.7, 127.6, 110.0, 101.0, 95.0, 78.5, 77.5, 72.2, 70.5, 66.6, 54.3, 36.2, 28.2, 26.0, 21.8, 0.0. MS (EI) m/z (relative intensity): 542 (M+ – CH3, 2.1), 366 (10), 351 (75), 276 (16), 264 (6), 263 (27), 225 (8), 224 (8), 212 (5), 180 (5), 179 (6), 169 (6), 155 (22), 151 (6), 150 (8), 149 (8), 141 (8), 140 (8), 139 (14), 137 (3), 135 (6), 133 (7), 132 (7), 127 (12), 126 (8), 125 (13), 124 (8), 123 (13), 122 (37), 121 (9), 120 (7), 113 (11), 112 (12), 111 (23), 110 (6), 109 (14), 106 (30), 107 (7), 106 (9), 105 (58), 104 (12), 101 (6), 100 (8), 99 (19), 98 (18), 97 (38), 96 (10), 95 (17), 94 (7), 93 (10), 92 (13), 91 (60), 89 (5), 87 (5), 86 (7), 85 (61), 84 (21), 83 (53), 82 (13), 81 (19), 80 (11), 79 (9), 78 (9), 77 (32), 75 (8), 74 (6), 73 (15), 72 (7), 71 (65), 70 (34), 69 (53), 68 (11), 67 (15), 65 (16), 64 (7), 63 (6), 60 (7), 59 (12), 58 (11), 57 (100), 56 (22), 55 (57), 54 (7), 53 (11), 52

(3aS,4S,5R,6R,7R,7aS)-7-Hydroxy-2,2-dimethyl-4-[(4-methylphenylsulfonylamo)-5-phenylcarbonyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (28)

To a solution of TMS-protected acetylene 26 (436 mg, 0.78 mmol) in 15 mL dry acetonitrile was added TBAT (633 mg, 1.17 mmol). The reaction mixture was stirred at
room temperature for 4 h, quenched with satd. aq. \(\text{NH}_4\text{Cl}\) (25 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over \(\text{Na}_2\text{SO}_4\), filtered, and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 1:1) afforded alcohol 28 (318 mg, 0.65 mmol, 84%) as white crystals; mp 103 °C. \(\delta\) [\(\text{D}^1\)] = -23.4 (c 0.85, CHCl$_3$). \(R_f\) 0.41 (hexanes – ethyl acetate, 1:1). IR (CHCl$_3$, m –1): 3309, 3066, 2988, 2955, 2931, 2896, 2859, 2254, 1720, 1601, 1586, 1495, 1472, 1463, 1452, 1383, 1373, 1328, 1272, 1221, 1160, 1112, 1094, 1081, 1054, 1027, 1005, 987, 909, 840, 814, 781, 734, 664, 650, 579, 564, 549, 514, 466. \(^1\)H NMR (300 MHz, CDCl$_3$, ppm): 8.08 (d, \(J = 8.2\) Hz, 2H), 7.86 (d, \(J = 8.2\) Hz, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.22 (d, \(J = 8.1\) Hz, 2H), 5.29 (d, \(J = 7.5\) Hz, 1H), 5.23 (m, 1H), 4.32 (m, 1H), 4.10 (m, 1H), 4.08 (m, 2H), 3.09 (m, 1H), 2.38 (s, 3H), 1.83 (d, \(J = 2.3\) Hz, 1H), 1.52 (s, 3H), 1.26 (s, 3H), 0.86 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl$_3$, ppm): 165.8, 143.1, 139.2, 133.5, 130.1, 129.9, 129.3, 128.6, 127.7, 109.6, 80.1, 78.5, 77.7, 73.8, 72.7, 67.4, 55.0, 33.3, 28.1, 26.2, 25.8, 21.7, 18.1, -4.8, -4.9. MS (EI) \(m/z\) (relative intensity): 584 (M$^+$ – CH$_3$, 3.7), 420 (9), 378 (5), 377 (18), 363 (6), 362 (20), 288 (5), 207 (7), 206 (7), 192 (6), 191 (32), 181 (5), 180 (15), 179 (89), 155 (12), 139 (5), 129 (5), 106 (9), 105 (100), 91 (34), 85 (5), 77 (20), 75 (14), 73 (32), 59 (6), 57 (9), 43 (13), 41 (7). HRMS (EI) calcld. for C$_{31}$H$_{38}$O$_2$NSSi-CH$_3$: 584.2138; found: 584.2150. Anal. calcld. for C$_{31}$H$_{38}$O$_2$NSSi: C 60.28, H 6.89; found: C 61.86, H 6.64.

(\(3aS,4S,5R,6R,7R,7aS\))-2,2-Dimethyl-7-(4-methylphenylsulfonamido)-4-(tert-butyldimethylsilyloxy)-5-phenylcarbonyloxy-6-(1-ethynyl)perhydro-1,3-benzoxazole (30)

To a solution of tosylamide 29 (411 mg, 0.69 mmol) in 11 mL of dry THF was added NaHMDI (0.82 mL, 0.82 mmol) at -70 °C. The reaction mixture was stirred for 0.5 h, while warming up to 0 °C. TMS – propargyl bromide (408 mg, 3.43 mmol) and (n-Bu)$_4$NI (252 mg, 0.69 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, quenched with satd. aq. \(\text{NH}_4\text{Cl}\) (30 mL), extracted with ethyl acetate (3 × 30 mL), dried over \(\text{Na}_2\text{SO}_4\), and the solvent was evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 9:1) afforded TBS-protected alcohol 29 (319 mg, 0.53 mmol, 89%) as white crystals; mp 83 °C. \(\delta\) [\(\text{D}^1\)] = -36.9 (c 1.20, CHCl$_3$). \(R_f\) 0.33 (hexanes – ethyl acetate, 5:1). IR (CHCl$_3$, cm$^{-1}$): v: 3309, 3066, 2988, 2955, 2931, 2896, 2859, 2255, 1720, 1601, 1586, 1495, 1472, 1463, 1452, 1383, 1373, 1328, 1272, 1221, 1160, 1112, 1094, 1081, 1054, 1027, 1005, 987, 909, 840, 814, 781, 734, 664, 650, 579, 564, 549, 514, 466. \(^1\)H NMR (300 MHz, CDCl$_3$, ppm): 8.08 (d, \(J = 8.2\) Hz, 2H), 7.86 (d, \(J = 8.2\) Hz, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.22 (d, \(J = 8.1\) Hz, 2H), 5.29 (d, \(J = 7.5\) Hz, 1H), 5.23 (m, 1H), 4.32 (m, 1H), 4.10 (m, 1H), 4.08 (m, 2H), 3.09 (m, 1H), 2.38 (s, 3H), 1.83 (d, \(J = 2.3\) Hz, 1H), 1.52 (s, 3H), 1.26 (s, 3H), 0.86 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl$_3$, ppm): 165.8, 143.1, 139.2, 133.5, 130.1, 129.9, 129.3, 128.6, 127.7, 109.6, 80.1, 78.5, 77.7, 73.8, 72.7, 67.4, 55.0, 33.3, 28.1, 26.2, 25.8, 21.7, 18.1, -4.8, -4.9. MS (EI) \(m/z\) (relative intensity): 584 (M$^+$ – CH$_3$, 3.7), 420 (9), 378 (5), 377 (18), 363 (6), 362 (20), 288 (5), 207 (7), 206 (7), 192 (6), 191 (32), 181 (5), 180 (15), 179 (89), 155 (12), 139 (5), 129 (5), 106 (9), 105 (100), 91 (34), 85 (5), 77 (20), 75 (14), 73 (32), 59 (6), 57 (9), 43 (13), 41 (7). HRMS (EI) calcld. for C$_{31}$H$_{38}$O$_2$NSSi-CH$_3$: 584.2138; found: 584.2150. Anal. calcld. for C$_{31}$H$_{38}$O$_2$NSSi: C 60.28, H 6.89; found: C 61.86, H 6.64.
To a solution of benzoate 31 (110 mg, 0.13 mmol) in 1 mL THF was added 0.5 mL of a 2.25 mol/L solution of freshly prepared sodium methoxide in methanol. The reaction was stirred for 10 min, quenched with NH4Cl (3 mL), and diluted with ethyl ether (10 mL). The organic phase was separated and washed with NaHCO3 (3 mL) and satd. NaCl solution (3 mL). After drying over MgSO4 and filtration, the solvent was removed under vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 3:1). The product 32 was isolated as crystalline foam in 99% yield (88 mg, 0.12 mmol); mp 97 °C. [α]D = +17.6 (c 0.65, CHCl3). 1H NMR (300 MHz, CDCl3, ppm) δ: 7.24 (s, 1H), 7.15 (s, 1H), 6.86 (d, J = 7.6 Hz, 2H), 7.37 (m, 2H), 7.38 (m, 4H), 6.63 (d, J = 7.9 Hz, 2H), 5.96 (s, 1H), 4.85 (m, 2H), 4.49 (m, 4H), 3.12 (d, J = 11.9 Hz, 1H), 2.21 (s, 3H), 1.91 (s, 3H), 1.59 (s, 3H), 1.05 (s, 9H), 0.45 (s, 9H), 0.35 (m, 12H), 0.33 (s, 3H). 13C NMR (75 MHz, CDCl3, ppm) δ: 165.6, 145.9, 143.6, 141.9, 137.1, 134.5, 133.2, 132.7, 130.7, 130.1, 129.6, 128.5, 128.4, 127.5, 109.1, 79.4, 77.3, 76.1, 71.6, 68.5, 57.0, 48.5, 35.8, 28.2, 26.1, 25.7, 21.3, 18.0, 1.8, 1.8, –4.9, –5.2. MS (EI) m/z (relative intensity): 750 (M+ – C(CH3)2, 15), 692 (6), 653 (6), 652 (11), 596 (8), 595 (16), 594 (12), 572 (5), 571 (10), 570 (19), 562 (8), 496 (7), 495 (5), 472 (6), 471 (6), 430 (6), 415 (6), 414 (12), 179 (22), 167 (7), 155 (8), 151 (5), 150 (5), 149 (29), 139 (7), 137 (6), 135 (6), 129 (5), 127 (5), 125 (10), 123 (9), 121 (6), 115 (8), 112 (8), 111 (18), 110 (7), 109 (13), 106 (6), 105 (59), 99 (9), 98 (12), 97 (34), 96 (11), 95 (20), 91 (14), 88 (6), 87 (5), 86 (37), 85 (32), 84 (65), 83 (35), 82 (13), 81 (20), 77 (10), 75 (10), 74 (5), 73 (41), 72 (6), 71 (51), 70 (29), 69 (54), 68 (10), 67 (16), 60 (7), 59 (7), 58 (8), 57 (96), 56 (37), 55 (80), 54 (7), 53 (7), 51 (6), 49 (12), 47 (14), 45 (9), 44 (7), 43 (100), 42 (17), 41 (73). HRMS (EI) calcd. for C32H30O7NSSi3-C(CH3)2: 750.2772; found: 750.2772.

To a solution of benzoate 31 (110 mg, 0.13 mmol) in 1 mL THF was added 0.5 mL of a 2.25 mol/L solution of freshly prepared sodium methoxide in methanol. The reaction was stirred for 10 min, quenched with NH4Cl (3 mL), and diluted with ethyl ether (10 mL). The organic phase was separated and washed with NaHCO3 (3 mL) and satd. NaCl solution (3 mL). After drying over MgSO4 and filtration, the solvent was removed under vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 3:1). The product 32 was isolated as crystalline foam in 99% yield (88 mg, 0.12 mmol); mp 97 °C. [α]D = +17.6 (c 0.65, CHCl3). 1H NMR (300 MHz, CDCl3, ppm) δ: 7.24 (s, 1H), 7.15 (s, 1H), 6.86 (d, J = 7.8 Hz, 2H), 7.24 (s, 1H), 7.15 (s, 1H), 6.86 (d, J = 7.8 Hz, 2H), 5.07 (m, 1H), 4.65 (dd, Jx = 75.0 Hz, Jy = 17.1 Hz, 2H), 4.26 (m, 3H), 4.04 (m, 1H), 2.82 (d, J = 12.9 Hz, 1H), 2.34 (m, 1H), 2.24 (s, 3H), 1.57 (s, 3H), 1.41 (s, 3H), 0.92 (s, 9H), 0.33 (s, 9H), 0.28 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). 13C NMR (75 MHz, CDCl3, ppm) δ: 144.7, 143.7, 142.3, 137.8, 134.0, 133.2, 133.0, 132.2, 128.6, 127.4, 109.4, 79.1, 75.3, 75.3, 69.2, 58.5, 51.4, 36.3, 28.5, 26.1, 25.6, 21.4, 17.9, 1.8, 1.8, –5.0, –5.1. MS (EI) m/z (relative intensity): 689 (M+ – CH3, 5), 688 (7), 684 (10), 647 (18), 646 (32), 588 (7), 550 (11), 549 (22), 548 (50), 491 (9), 490 (14), 476 (5), 460 (9), 459
To a solution of TBS-protected alcohol 32 (49 mg, 0.07 mmol) in 0.1 mL THF was added 84 μL of a 1.0 mol/L solution of TBAF in THF. The reaction was stirred for 10 min at room temperature, quenched with NH₄Cl (3 mL) and diluted with ethyl ether (5 mL). The organic phase was separated and extracted three times with ethyl ether (3 mL). After drying over MgSO₄ and filtration, the solvent was re-separated and extracted three times with ethyl ether (3 mL) for 10 min at room temperature, quenched with NH₄Cl (3 mL) solution of TBAF in THF. The reaction was stirred for 0.07 mmol) in 0.1 mL THF was added 84.00, 81.1, 79.0, 73.4, 75.3, 65.0, 62.6, 57.8, 56.1, 54.2. 1H NMR (300 MHz, CDCl₃, ppm): δ 7.45 (d, J = 8.4 Hz, 2H), 7.36 (s, 1H), 7.19 (s, 1H), 6.95 (d, J = 8.4 Hz, 2H), 4.88 (dd, J₁ = 8.7 Hz, J₂ = 6.0 Hz, 1H), 4.45 (m, 3H), 4.28 (t, J = 5.4 Hz, 1H), 4.18 (m, 1H), 4.07 (dd, J₁ = 12.0 Hz, J₂ = 8.7 Hz, 1H), 2.88 (dd, J₁ = 12.0 Hz, J₂ = 2.4 Hz, 1H), 2.58 (d, J = 2.7 Hz, 1H), 2.27 (s, 3H), 2.21 (d, J = 4.8 Hz, 1H), 1.58 (s, 3H), 1.37 (s, 3H), 0.32 (s, 3H), 0.30 (s, 3H). 13C NMR (75 MHz, CDCl₃, ppm): δ 145.4, 143.8, 142.5, 137.3, 134.5, 132.9, 132.6, 131.8, 128.9, 127.6, 109.9, 78.3, 76.2, 72.5, 71.4, 57.3, 49.2, 38.4, 28.1, 25.7, 21.5, 1.9, 1.9. MS (EI) m/z (relative intensity): 574 (M⁺ – CH₃, 0.1), 458 (5), 155 (5), 149 (15), 111 (11), 109 (6), 105 (7), 99 (6), 98 (19), 97 (37), 96 (9), 95 (10), 91 (9), 87 (18), 86 (6), 85 (29), 84 (23), 83 (38), 82 (10), 81 (15), 77 (5), 75 (14), 73 (19), 72 (5), 71 (50), 70 (45), 69 (87), 68 (13), 67 (11), 60 (8), 59 (9), 58 (11), 57 (82), 56 (45), 55 (72), 54 (6), 53 (5), 44 (5), 43 (100), 42 (15), 41 (60). HRMS (EI) calcd. for C₉H₁₄O₇NSi₂: 589.2350; found: 589.2322. Anal. calcd. for C₉H₁₄O₇NSi₂: C 59.05, H 7.35; found: C 58.72, H 6.92.

(1S,2S,3S,4S,4aR,10bR)-5-(4-Methylphenylsulfonyl)-8,9-dihydrotriphenyldienetetraol (34)

To a solution of acetone 33 (27 mg, 0.05 mmol) in MeOH (0.5 mL) was added 1 drop of water and a spatula tip of strong acidic Dowex 50WX-8-100 ion exchange resin. The reaction was heated for 4 h at 70 °C, dried by addition of MgSO₄, and filtered. The solvent was removed under vacuum and the residue was diluted in CHCl₃ and filtered again. After removal of the solvent, the deprotected tetraol 34 was isolated as an oily solid in 79% yield (20 mg, 0.04 mmol). [α]D²₅ +23.9 (c 0.61, CH₂Cl₂), Kf 0.44 (hexanes – ethyl acetate, 1:2). IR (CH₂Cl₂, cm⁻¹): 3410, 2954, 2926, 2902, 2253, 1793, 1654, 1599, 1494, 1450, 1409, 1331, 1307, 1289, 1265, 1249, 1186, 1153, 1122, 1089, 1063, 1020, 970, 909, 856, 840, 811, 735, 673, 650, 629, 582, 565, 539, 481.

1H NMR (300 MHz, CDCl₃, ppm): δ 7.42 (s, 1H), 7.25 (d, J = 6.0 Hz, 2H), 7.14 (s, 1H), 6.85 (d, J = 8.1 Hz, 2H), 6.49 (d, J = 16.2 Hz, 1H), 4.49 (s, 1H), 4.36 (m, 3H), 4.27 (d, J = 10.5 Hz, 1H), 4.03 (m, 1H), 3.57 (brs, 4H) 2.91 (d, J = 11.7 Hz, 1H), 2.21 (s, 3H), 0.32 (s, 9H), 0.28 (s, 9H). 13C NMR (75 MHz, CDCl₃, ppm): δ 145.5, 143.0, 143.0, 134.7, 134.3, 133.9, 132.2, 131.3, 128.9, 127.4, 74.9, 70.8, 70.4, 69.6, 55.3, 47.9, 38.9, 21.4, 1.9, 1.9. MS (EI) m/z (relative intensity): 534 (M⁺ – CH₃, 5), 467 (5), 466 (11), 460 (8), 459 (15), 458 (35), 457 (5), 450 (6), 430 (6), 396 (6), 395 (12), 394 (35), 387 (8), 386 (36), 324 (36), 324 (33), 322 (33), 322 (33), 319 (5), 304 (7), 303 (7), 302 (8), 288 (6), 287 (5), 286 (6), 276 (6), 275 (10), 274 (21), 273 (5), 272 (7), 258 (6), 257 (5), 256 (8), 252 (6), 244 (6), 242 (6), 234 (9), 232 (6), 231 (8), 230 (8), 229 (8), 228 (11), 216 (6), 215 (17), 214 (52), 213 (21), 212 (5), 206 (9), 205 (7), 204 (12), 203 (8), 202 (15), 200 (6), 193 (10), 191 (5), 190 (7), 189 (6), 188 (9), 187 (14), 186 (15), 185 (7), 184 (5), 181 (6), 171 (5), 167 (6), 162 (6), 159 (6), 158 (7), 157 (8), 156 (11), 155 (8), 149 (19), 143 (6), 141 (6), 140 (10), 139 (15), 138 (6), 137 (37), 136 (16), 135 (8), 134 (6), 133 (8), 132 (5), 131 (12), 130 (12), 129 (13), 128 (8), 127 (7), 126 (7), 125 (14), 122 (5), 116 (6), 115 (7), 113 (7), 112 (5), 111 (10), 109 (10), 108 (8), 107 (10), 105 (7), 99 (11), 98 (31), 97 (18), 96 (8), 95 (13), 93 (10), 92 (22), 91 (52), 90 (5), 83 (8), 82 (21), 80 (8), 79 (8), 78 (5), 77 (13), 76 (5), 75 (27), 74 (13), 73 (100), 71 (31), 69 (22), 68 (8), 67 (12), 65 (4), 64 (9), 63 (6), 60 (11), 59 (5), 57 (56), 56 (15), 55 (38), 54
To a suspension of tosylamide 31 (20 mg, 0.02 mmol) in CH₃CN–CH₂Cl₂–H₂O (2:2:3, 0.5 mL) were added NaOAc (22 mg, 0.10 mmol) and a catalytic amount of RuCl₃–H₂O. After 3 h, NaOAc (15 mg) and another catalytic amount of RuCl₃–H₂O were added. The reaction mixture was stirred at room temperature overnight. After another addition of NaOAc (15 mg) and another catalytic amount of RuCl₃–H₂O the next day, the starting material was fully converted. The heterogeneous reaction was diluted with CH₂Cl₂ (25 mL) and extracted with water. The organic phase was dried with Na₂SO₄, filtered, and purified by flash chromatography (hexanes–ethyl acetate, 2:1). The oxidized product 35 was isolated as colorless oil in 15% yield (3 mg, 0.003 mmol).

HRMS (EI) calcd. for C₂₆H₃₉O₆NSSi₂: 549.2037; found: 549.2031.

(3aS,3bR,9bR,10R,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxy-10-phenylcarbonyloxy-11-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydronaphtho[1,3]dioxol[4,5-c]phenanthridine (35)

To a solution of cyclic sulfate 44 (344 mg, 0.53 mmol) in dry DMF (8 mL) was added ammonium benzoate (184 mg, 1.32 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to 40 °C, and the DMF was removed under reduced pressure. The residue was suspended in THF (8 mL) before 1 drop each of H₂O and H₂SO₄ were added. The resulting mixture was stirred for 1.5 h and then quenched with satd. aq. NaHCO₃ (30 mL) and diluted with CH₂Cl₂. The aqueous phase was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic phases were dried over Na₂SO₄, filtered, and evaporated at reduced pressure. Benzoate 36 (410 mg, 0.59 mmol, 99%) was obtained as foamy white crystals and used without further purification; mp 91 °C. [α]²²D +67.3 (c 1.00, CH₂Cl₂). Rf 0.38 (hexanes – ethyl acetate, 2:1). IR (CHCl₃, cm⁻¹): 3055, 2986, 2957, 2930, 2857, 2305, 1721, 1697, 1600, 1581, 1509, 1452, 1422, 1363, 1265, 1221, 1175, 1148, 1108, 1068, 939, 895, 880, 840, 739, 705, 656, 636, 603, 544, 516, 476. ¹H NMR (300 MHz, CDCl₃, ppm): δ: 8.38 (m, 3H), 7.64 (m, 3H), 7.44 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.24 (m, 2H), 5.93 (s, 1H), 5.74 (m, 1H), 4.57 (m, 1H), 4.44 (s, 1H), 4.34 (m, 1H), 3.94 (m, 1H), 2.45 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 0.99 (s, 9H), 0.32 (s, 3H), 0.25 (m, 2H). MS (EI) m/z (relative intensity): 764 (M⁺ – C(CH₃)₃, 4), 693 (2), 484 (8), 472 (9), 471 (23), 317 (12), 316 (37), 285 (5), 260 (20), 155 (6), 149 (8), 147 (6), 139 (5), 123 (8), 122 (44), 121 (5), 119 (14), 111 (6), 106 (7), 105 (7), 97 (9), 97 (11), 95 (7), 81 (11), 86 (83), 85 (12), 84 (100), 83 (11), 82 (89), 81 (10), 78 (6), 77 (44), 75 (9), 74 (10), 73 (56), 71 (12), 70 (7), 69 (26), 67 (7), 65 (6), 60 (5), 59 (5), 58 (3), 57 (21), 56 (7), 53 (9), 52 (5), 50 (13), 49 (12), 47 (25), 45 (12), 44 (8), 43 (13), 42 (6), 41 (18). HRMS (EI) calcd. for C₃₅H₄₇NO₇SSi₂: 693.9979; found: 693.2603. Anal. calcd. for C₃₅H₄₇NO₇SSi₂: C 62.30, H 6.83; found: C 62.18, H 6.70.

(3aS,3bR,9bR,10R,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-10,11-di(phenylcarbonyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxol[4,5-c]phenanthridine (37)

To a solution of of alcohol 36 (142 mg, 0.21 mmol) in pyridine (1 mL) was added benzoyl chloride (35 µL,
0.31 mmol) at 0 °C. The ice bath was removed and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched with 5 drops of MeOH, diluted with ethyl acetate (50 mL), and washed with 1.0 mol/L HCl (2 x 20 mL) and brine (20 mL). The organic phase was dried over Na2SO4, filtered, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 5:1) afforded dibenzoate 37 (140 mg, 0.18 mmol, 86%) as foamy white crystals; mp 107 °C. [α]25D –12.7 (c 1.39, CH2Cl2). Rf 0.62 (hexanes – ethyl acetate, 2:1). IR (CHCl3, cm–1): 3057, 2956, 2927, 2856, 2306, 1768, 1729, 1698, 1600, 1582, 1494, 1452, 1365, 1315, 1266, 1211, 1176, 1093, 1070, 1027, 983, 954, 857, 743, 710, 666, 637, 608, 587, 545. 1H NMR (300 MHz, CDCl3, ppm) δ: 8.35 (s, 1H), 8.34 (d, J = 6.9 Hz, 2H), 8.11 (d, J = 6.9 Hz, 2H), 7.62 (m, 3H), 7.48 (m, 4H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (m, 2H), 6.17 (t, J = 5.7 Hz, 1H), 5.82 (t, J = 3.3 Hz, 1H), 4.69 (d, J = 8.7 Hz, 1H), 5.70 (dd, J1 = 5.7 Hz, J2 = 8.4 Hz, 1H), 4.69 (d, J = 8.7 Hz, J2 = 12.6 Hz, 1H), 4.52 (m, 1H), 3.94 (dd, J1 = 3.3 Hz, J2 = 12.6 Hz, 1H), 2.45 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 0.25 (s, 9H), 0.19 (s, 9H). 13C NMR (75 MHz, CDCl3, ppm) δ: 166.9, 165.1, 164.6, 154.8, 146.0, 144.1, 138.5, 135.6, 133.8, 133.3, 131.6, 130.0, 129.6, 129.1, 129.0, 128.9, 128.7, 128.2, 127.3, 109.9, 74.6, 73.5, 68.8, 68.5, 63.0, 40.1, 28.3, 26.1, 21.7, 1.6, 1.3 (two signals missing). MS (EI) m/z (relative intensity): 796 (M+ – CH3, 0.4), 477 (6), 356 (5), 335 (6), 331 (6), 179 (6), 122 (5), 106 (8), 105 (100), 97 (9), 91 (13), 85 (6), 83 (8), 81 (7), 77 (19), 73 (19), 71 (8), 69 (14), 67 (5). HRMS (EI) calcd. for C43H49O9NSSi2·CH3: 796.2432; found: 796.2444.

(3aS,3bR,9bR,10R,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10,11-di(phenylcarboxyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-c]phenanthridine (38)

To a suspension of tosylamide 37 (141 mg, 0.18 mmol) in CH3CN–CCL4–H2O (4:4:3, 11 mL) was added a solution of Na2CO3 (60 mg) and NaIO4 (340 mg, 1.59 mmol) in H2O (3 mL). A catalytic amount of RuCl3·H2O (1 mg) was added and the reaction was stirred at room temperature. After 3 h, the same amount of NaIO4 buffered with Na2CO3 and another catalytic amount of RuCl3·H2O were added. The reaction mixture was stirred at room temperature overnight. After another addition of the same amount of oxidant the next day and one additional hour, the starting material was fully converted. The heterogeneous reaction was diluted with CH2Cl2 (25 mL) and washed with water and brine. The organic phase was dried with Na2SO4, filtered, and purified by flash chromatography (hexanes – ethyl acetate, 3:1). The oxidized product 38 was isolated as colorless oil in 33% yield (48 mg, 0.059 mmol); mp 105 °C. [α]23D –72.5 (c 0.65, CH2Cl2). Rf 0.74 (hexanes – ethyl acetate, 2:1). IR (CH2Cl2, cm–1) v: 3057, 2956, 2927, 2856, 2306, 1768, 1729, 1698, 1600, 1582, 1494, 1452, 1365, 1315, 1266, 1211, 1176, 1093, 1070, 1027, 983, 954, 857, 743, 710, 666, 637, 608, 587, 545. 1H NMR (300 MHz, CDCl3, ppm) δ: 8.35 (s, 1H), 8.34 (d, J = 6.9 Hz, 2H), 8.11 (d, J = 6.9 Hz, 2H), 7.62 (m, 3H), 7.48 (m, 4H), 7.34 (d, J = 8.4 Hz, 2H), 7.25 (m, 2H), 6.17 (t, J = 5.7 Hz, 1H), 5.82 (t, J = 3.3 Hz, 1H), 4.69 (d, J = 8.7 Hz, 1H), 5.70 (dd, J1 = 5.7 Hz, J2 = 8.4 Hz, 1H), 4.69 (d, J = 8.7 Hz, J2 = 12.6 Hz, 1H), 4.52 (m, 1H), 3.94 (dd, J1 = 3.3 Hz, J2 = 12.6 Hz, 1H), 2.45 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 0.25 (s, 9H), 0.19 (s, 9H). 13C NMR (75 MHz, CDCl3, ppm) δ: 166.9, 165.1, 164.6, 154.8, 146.0, 144.1, 138.5, 135.6, 133.8, 133.3, 131.6, 130.0, 129.6, 129.1, 129.0, 128.9, 128.7, 128.2, 127.3, 109.9, 74.6, 73.5, 68.8, 68.5, 63.0, 40.1, 28.3, 26.1, 21.7, 1.6, 1.3 (two signals missing). MS (EI) m/z (relative intensity): 796 (M+ – CH3, 0.4), 477 (6), 356 (5), 335 (6), 331 (6), 179 (6), 122 (5), 106 (8), 105 (100), 97 (9), 91 (13), 85 (6), 83 (8), 81 (7), 77 (19), 73 (19), 71 (8), 69 (14), 67 (5). HRMS (EI) calcd. for C43H49O9NSSi2·CH3: 796.2432; found: 796.2444.

To a solution of of tosylate 38 (39 mg, 0.05 mmol) in THF (0.5 mL) under argon was added a 0.4 mol/L solution of sodium naphthalide (at –65 °C) until the green colour persisted. The reaction was quenched with satd. aq. NH4Cl and extracted with CH2Cl2 (6 × 10 mL). The combined organic phases were dried over MgSO4, filtered, and the organic solvent was removed under reduced pressure. The residue was dissolved in MeOH. After addition of a 2.25 mol/L solution...
of sodium methoxide (64 µL), the reaction mixture was stirred for 20 min. The solution was quenched with satd. aq. NH₄Cl and extracted with CH₂Cl₂ (6 × 10 mL). The combined organic phases were dried over MgSO₄, filtered, and the solvent was removed under vacuum. Flash column chromatography of the residue (pentane – diethyl ether, 1:2) afforded a diol (7 mg, 0.02 mmol, 32%). The diol (6 mg, 0.01 mmol) was dissolved in MeOH and heated to reflux for 4 h after addition of a spatula tip of Dowex 50WX8-100. The ion exchange resin was removed by filtration and the solvent was removed under reduced pressure. Flash column chromatography of the residue (CHCl₃–MeOH, 6:1) afforded tetraol 39 (5 mg, 0.01 mmol, 25% over three steps); mp 213 °C. [α]D +60.5 (c 0.15, MeOH). Rf 0.38 (CHCl₃–MeOH, 6:1). IR (CHCl₃, cm⁻¹) v: 3385, 2953, 2926, 1705, 1652, 1600, 1586, 1447, 1410, 1318, 1250, 1217, 1155, 1128, 1093, 1055, 955, 837, 757, 667, 630, 572, 549. 1H NMR (300 MHz, CD₂OD, ppm): 8.31 (s, 1H), 7.79 (s, 1H), 4.87 (s, 5H), 4.61 (m, 1H), 4.22 (t, J = 3.3 Hz, 1H), 4.05 (m, 1H), 3.95 (m, 2H), 3.33 (m, 1H), 0.41 (s, 9H), 0.40 (s, 9H). 13C NMR (75 MHz, CDCl₃, ppm): 168.3, 153.0, 145.3, 139.0, 134.9, 132.7, 129.1, 75.1, 72.1, 72.0, 70.2, 51.6, 41.1, 2.0, 1.9. MS (ESI) m/z (relative intensity): 454 ([M + formate]⁻, 72), 444 ([M + Cl⁻], 100), 408 ([M – H⁻]⁻, 2), 394 (7), 311 (5), 265 (8), 171 (17), 111 (7), 89 (12). HRMS (ESI) calcd. for C₃₅H₃₉O₈NSSi: 661.2166; found: 661.2158. Anal. calcd. for C₃₅H₃₉O₈NSSi: C 63.52, H 5.94; found: C 63.97, H 5.95.

(3aS,4S,5S,6R,7R,7aS)-2,2-Dimethyl-7-(4-methylphenylsulfonamido)-4,5-di(phenylcarbonyloxy)-6-(2-trimethylsilyl-1-ethylthio)perhydro-1,3-benzodioxole (40)

To a solution of TMS-protected acetylene 40 (976 mg, 1.48 mmol) in dry acetonitrile (35 mL) was added TBAT (1.19 g, 2.21 mmol). The reaction mixture was stirred at room temperature for 1.5 h, quenched with satd. aq. NH₄Cl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate) afforded unprotected acetylene (664 mg, 1.13 mmol, 76%) as white crystals. To these crystals (418 mg, 0.71 mmol) dissolved in THF (2 mL) was added NaHMDS (1.0 mol/L, 0.85 mL, 0.85 mmol) at −70 °C under argon. The reaction mixture was allowed to warm up to 0 °C over a period of 20 min and was further stirred for 10 min at this temperature. Propargyl bromide (422 mg, 3.54 mmol) and (nBu)₄NI (262 mg, 0.71 mmol) were added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by addition of satd. aq. NH₄Cl (40 mL) and extracted with ethyl acetate (4 × 40 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 4:1) afforded tosylamide 41 (419 mg, 0.67 mmol, 94%; 71% over two steps) as crystalline foam; mp 86 °C. [α]D +99.9 (c 4.50, CH₂Cl₂). Rf 0.29 (hexanes – ethyl acetate, 3:1). IR (CH₂Cl₂, cm⁻¹) v: 3300, 3064, 2988, 2939, 2593, 2126, 1918, 1732, 1602, 1586, 1494, 1452, 1386, 1374, 1352, 1303, 1286, 1274, 1162, 1094, 1070, 1026, 1003, 910, 848, 814, 792, 734, 711, 686, 662, 650, 575, 548, 512, 466. 1H NMR (300 MHz, CDC₁₃, ppm): δ: 7.95 (m, 4H), 7.79 (d, J = 8.1 Hz, 2H), 7.56 (m, 2H), 7.42 (m, 4H), 7.28 (d, J = 8.4 Hz, 2H), 5.86 (dd, J₁ = 2.7 Hz, J₂ = 4.2 Hz, 1H), 5.68 (dd, J₁ = 2.7 Hz, J₂ = 8.1 Hz, 1H), 5.04 (d, J = 7.5, 1.2 Hz, 1H), 4.38 (m, 2H), 3.87 (m, 1H), 3.23 (t, J = 7.8 Hz, 1H), 2.42 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H), 0.06 (s, 9H). 13C NMR (75 MHz, CDC₁₃, ppm): 165.3, 165.3, 143.6, 138.8, 133.9, 133.7, 130.1, 131.0, 129.8, 129.7, 129.6, 128.9, 128.8, 127.6, 110.6, 101.6, 90.5, 78.1, 75.1, 71.8, 69.7, 57.4, 36.4, 28.1, 26.3, 21.9, 0.0. MS (EI) m/z (relative intensity): 646 (M⁺ – CH₃, 3), 282 (6), 214 (11), 155 (7), 122 (9), 106 (10), 105 (100), 91 (15), 77 (21), 73 (8), 69 (9), 57 (6), 55 (43), 43 (11), 41 (6). HRMS (EI) calcd. for C₃₅H₃₉O₇S: 627.70 g/mol.
To a solution of CpCo(CO)₂ (5 µL) in BTMSA (12 mL) was added dropwise with a syringe pump at 140 °C over 30 h. During this slow addition, extra additive was added directly into the reaction mixture in aliquots: 3 µL after 5 h, 5 µL after 20 h, and 3 µL after 29 h. The reaction mixture was heated under argon for further 12 h. BTMSA and xylene were removed under high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 3:1). The cyclooligomer product 42 was isolated as crystalline foam in 87% yield (407 mg, 0.51 mmol); mp 131 °C. [α]D25 +43.1 (c 0.75, CH2Cl2). Rf 0.37 (hexanes – ethyl acetate, 3:1). IR (CDCl₃, cm⁻¹) v: 3065, 3059, 2986, 2954, 2901, 2255, 1911, 1729, 1602, 1586, 1493, 1452, 1384, 1374, 1348, 1316, 1272, 1251, 1218, 1178, 1162, 1120, 1093, 1069, 1027, 1002, 971, 910, 874, 856, 839, 812, 784, 734, 670, 649, 628, 564, 519. ¹H NMR (300 MHz, CDCl₃, ppm) δ: 7.89 (d, J = 7.5 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 7.52 (m, 4H), 7.34 (m, 4H), 7.26 (m, 2H), 7.04 (d, J = 8.1 Hz, 2H), 6.19 (dd, J₁ = 5.4 Hz, J₂ = 8.4 Hz, 1H), 5.70 (dd, J₁ = 5.1 Hz, J₂ = 9.3 Hz, 1H), 4.98 (t, J = 7.5 Hz, 1H), 4.76 (dd, J₁ = 7.2 Hz, J₂ = 9.0 Hz, 1H), 4.59 (dd, J₁ = 16.5 Hz, J₂ = 60.0 Hz, 2H), 4.03 (dd, J₁ = 8.4 Hz, J₂ = 12.6 Hz, 1H), 3.28 (dd, J₁ = 8.7 Hz, J₂ = 12.6 Hz, 1H), 2.31 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 0.39 (s, 9H), 0.12 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ: 165.4, 165.3, 146.2, 144.3, 142.7, 137.4, 133.6, 133.3, 133.1, 132.6, 132.5, 131.4, 129.7, 129.7, 129.3, 129.1, 129.0, 128.3, 128.1, 127.5, 110.7, 76.9, 73.7, 69.5, 58.1, 48.0, 39.4, 27.5, 25.1, 21.4, 1.8. MS (EI) m/z (relative intensity): 430 (2), 256 (5), 230 (11), 167 (5), 149 (19), 137 (11), 136 (6), 129 (15), 123 (9), 122 (5), 121 (7), 113 (6), 112 (10), 117 (1), 109 (8), 197 (6), 105 (19), 98 (7), 97 (12), 96 (6), 95 (15), 93 (9), 91 (8), 87 (5), 85 (12), 84 (13), 83 (19), 82 (10), 81 (41), 79 (7), 77 (10), 73 (23), 71 (26), 70 (21), 69 (100), 68 (16), 67 (15), 61 (6), 60 (19), 58 (6), 57 (49), 56 (31), 55 (46), 54 (6), 53 (8), 45 (12), 44 (12), 43 (59), 42 (15), 41 (67). HRMS (EI) calced. for C₄₃H₅₁O₈NSSi₂: 797.2874; found: 797.2885.

(3aS,3bR,9bR,10S,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolino[4,5-c]phenanthridine (43)

Protected diol 42 (100 mg, 0.13 mmol) was dissolved in a 1% sodium hydroxide solution in methanol (2 mL) and stirred for 1 h at room temperature. The reaction was quenched with NH₄Cl and extracted with CH₂Cl₂. The organic solvents were dried over Na₂SO₄ and removed under high vacuum. The residue was purified by column chromatography (hexanes – ethyl acetate, 1:1). The diol 43 was isolated as foam crystals in 99% yield (73 mg, 0.12 mmol); mp 121 °C. [α]D25 +35.5 (c 1.50, CH₂Cl₂), Rf 0.18 (hexanes – ethyl acetate, 2:1). IR (CH₂Cl₂, cm⁻¹) v: 3406, 3055, 2954, 2927, 2871, 1727, 1599, 1495, 1455, 1376, 1347, 1266, 1250, 1213, 1160, 1124, 1091, 1072, 1042, 1002, 972, 931, 877, 858, 840, 740, 704, 672, 656, 602, 563, 546, 519, 486, 479, 467, 463, 455. ¹H NMR (300 MHz, CDCl₃, ppm) δ: 7.65 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.21 (s, 1H), 6.98 (d, J = 8.1 Hz, 2H), 4.74 (t, J = 7.8 Hz, 1H), 4.56 (d, J = 16.2 Hz, 1H), 4.35 (m, 3H), 3.91 (m, 1H), 3.75 (m, 1H), 3.11 (s, 1H), 2.87 (s, 1H), 2.67 (dd, J₁ = 8.1 Hz, J₂ = 12.3 Hz, 1H), 2.29 (s, 1H), 1.54 (s, 3H), 1.33 (s, 3H), 0.33 (s, 9H), 0.32 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) ppm δ: 145.6, 143.9, 142.5, 137.4, 133.9, 133.8, 132.3, 132.1, 128.9, 127.4, 110.3, 77.1, 75.8, 70.3, 68.8, 57.0, 47.6, 41.0, 27.7, 25.0, 21.5, 1.9, 1.9. MS (EI) m/z (relative intensity): 574 (M⁺ – CH₃, 13), 471 (12), 459 (10), 458 (22), 435 (23), 434 (65), 432 (11), 429 (13), 428 (29), 342 (11), 335 (17), 322 (20), 285 (21), 274 (12), 185 (10), 169

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The solution was stirred for 10 min and SO$_2$Cl$_2$ (1.0 mol/L) was added dropwise via syringe pump over a period of 2 h. Additional NEt$_3$ (5 mL) and SO$_2$Cl$_2$ (15 mL) were added over a period of 2 h for full conversion (TLC). The reaction mixture was diluted with CH$_2$Cl$_2$ (15 mL) and with brine (10 mL). The organic phase was dried over MgSO$_4$ and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:1) afforded cyclic sulfate 44 (383 mg, 0.59 mmol, 70%); mp 110 °C. $^1$H NMR (300 MHz, CDCl$_3$, ppm) δ: 7.44 (s, 1H), 7.35 (dd, $J_1 = 7.2$ Hz, 1H), 7.29 (m, 1H), 4.80 (m, 2H), 4.22 (d, $J = 9.5$ Hz, 2H), 5.07 (m, 1H), 4.71 (m, 2H), 4.21 (d, $J = 9.4$ Hz, 1H), 3.29 (s, 3H), 2.19 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H), 1.88 (s, 3H), 1.84 (s, 3H), 1.76 (s, 3H), 1.56 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H). $^1$C NMR (75 MHz, CDCl$_3$, ppm) δ: 154.0, 144.0, 141.3, 135.1, 131.7, 130.8, 129.6, 128.8, 127.3, 125.6, 109.8, 80.9, 78.0, 75.1, 73.0, 54.3, 45.2, 36.5, 25.5, 22.9, 19.7, 0.0, 0.0. MS (EI) m/z (relative intensity): 636 (M$^+$ – CH$_3$, 1), 88 (11), 86 (65), 84 (100), 73 (6), 69 (6), 49 (21), 47 (27), 43 (6). HRMS (EI) calcd. for C$_{29}$H$_{43}$O$_6$NSSi$_2$: 636.1556; found: 636.1557.

To a solution of diol 43 (494 mg, 0.84 mmol) in dry CH$_2$Cl$_2$ (20 mL) was added triethylamine (5 mL) at 0 °C. The solution was stirred for 10 min and SO$_2$Cl$_2$ (1.0 mol/L solution, 15 mL) were added dropwise via syringe pump over a period of 2 h. Additional NEt$_3$ (5 mL) and SO$_2$Cl$_2$ (15 mL) were added over a period of 2 h for full conversion (TLC). The reaction mixture was diluted with CH$_2$Cl$_2$ (30 mL), quenched with satd. aq. NH$_4$Cl (50 mL), and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic phase was dried over Na$_2$SO$_4$, filtered, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (hexanes – ethyl acetate, 5:1) afforded cyclic sulfate 44 (250 mg, 0.32 mmol) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$, ppm) δ: 7.43 (s, 1H), 7.36 (d, $J = 15.8$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 2H), 4.78 (m, 2H), 4.61 (d, $J = 9.5$ Hz, 2H), 4.17 (dd, $J = 7.2$ Hz, 1H), 4.09 (d, $J = 7.2$ Hz, 1H), 3.69 (dd, $J_1 = 10.8$ Hz, 1H), 2.99 (t, $J = 7.2$ Hz, 1H), 2.43 (m, 2H), 1.98 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H), 1.57 (s, 3H), 1.55 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H). $^1$C NMR (75 MHz, CDCl$_3$, ppm) δ: 154.7, 144.0, 141.3, 135.1, 131.6, 130.7, 129.6, 128.7, 128.5, 125.6, 109.8, 80.9, 78.0, 75.1, 73.0, 54.3, 45.2, 36.5, 25.5, 22.9, 19.7, 0.0, 0.0. MS (EI) m/z (relative intensity): 830 (M$^+$ – CH$_3$, 1), 108 (11), 96 (65), 84 (100), 73 (6), 69 (6), 49 (21), 47 (27), 43 (6). HRMS (EI) calcd. for C$_{29}$H$_{43}$O$_6$NSSi$_2$: 636.1552; found: 636.1553. Anal. calcd. for C$_{29}$H$_{43}$O$_6$NSSi$_2$: C 59.05, H 7.35; found: C 59.03, H 7.38. HRMS (EI) calcd. for C$_{29}$H$_{43}$O$_6$NSSi$_2$: 636.1556; found: 636.1558. Anal. calcd. for C$_{29}$H$_{43}$O$_6$NSSi$_2$: C 55.43, H 6.34; found: C 55.36, H 6.47.

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tion of CpCo(CO)₂ (10 μL) in BTMSA (25 mL) over a period of 35 h. After the addition was completed, the reaction mixture was refluxed for an additional 6 h. The solvent was removed under reduced pressure (0.1 mbar, 1 bar = 100 kPa). The reddish brown residue was purified by flash column chromatography (pentane to ether – pentane, 1:1) and afforded the cobalt complex 46 (33 mg, 0.05 mmol, 11%) as a yellow oil. [α]D²⁶ +27.6 (c 0.23, CHCl₃), R₂ 0.53 (hexanes – ethyl acetate, 3:1). IR (CHCl₃, cm⁻¹): 3261, 3019, 2958, 2934, 2873, 2401, 1693, 1599, 1521, 1496, 1456, 1383, 1375, 1328, 1287, 1272, 1251, 1216, 1158, 1096, 1071, 969, 928, 857, 841, 812, 757, 669. ¹H NMR (300 MHz, CDCl₃, ppm) δ: 8.00 (s, 1H), 7.51 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.1 Hz, 2H), 6.01 (d, J = 7.7 Hz, 1H), 5.91 (m, 1H), 5.71 (d, J = 9.8 Hz, 1H), 4.57 (m, 1H), 4.18 (m, 3H), 4.00 (m, 1H), 3.61 (m, 1H), 2.18 (s, 3H), 1.58 (m, 2H), 1.33 (s, 3H), 1.18 (s, 3H), 0.23 (s, 9H), 0.21 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ: 169.5, 152.6, 144.8, 141.7, 141.0, 140.0, 136.3, 136.1, 135.7, 129.5, 129.1, 128.9, 126.9, 124.3, 109.9, 79.5, 79.3, 72.7, 65.9, 60.4, 41.8, 30.5, 28.7, 28.2, 26.2, 25.9, 21.6, 1.9, 1.8. MS (FAB) m/z (relative intensity): 744 (M⁺ + Na, 0.1). MS (EI) m/z (relative intensity): 656 (M⁺ – Cp, 4.8), 614 (5), 613 (11), 505 (7), 501 (8), 500 (20), 469 (40), 459 (21), 458 (8), 420 (6), 419 (14), 418 (38), 358 (6), 357 (13), 356 (7), 343 (6), 341 (7), 340 (7), 329 (5), 328 (5), 297 (4), 288 (6), 279 (5), 255 (8), 254 (37), 253 (23), 228 (6), 205 (6), 171 (6), 155 (18), 149 (17), 145 (5), 140 (7), 139 (33), 124 (8), 100 (11), 99 (65), 98 (52), 97 (6), 95 (8), 92 (11), 91 (58), 85 (7), 83 (9), 81 (5), 77 (6), 75 (18), 74 (11), 73 (100), 71 (13), 69 (13), 67 (5), 65 (10). HRMS (EI) calcld. for C₃₃H₄₄O₆NSSІ₂Co-CO: 693.1811; found: 693.1807.

(3aS,4S,5S,6R,7R,7aS)-6-(1-Ethynyl)-2,2-dimethyl-7-[4-methyl phenyl(1-propiolyloxy)sulfonamido]-4,5-di(phenyl carboxyloxy)perhydro-1,3-benzodioxole (47)

To a solution of TMS-protected acetylene 40 (976 mg, 1.48 mmol) in dry acetonitrile (35 mL) was added TBAT (1.19 g, 2.21 mmol). The reaction mixture was stirred at room temperature for 1.5 h, quenched with satd. aq. NH₄Cl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over Na₂SO₄ and evaporated under reduced pressure. Column chromatography (hexanes – ethyl acetate, 4:1 to 2:1) afforded unprotected acetylene (664 mg, 1.13 mmol, 76%) as white crystals. To a solution of this material (210 mg, 0.36 mmol) in THF (6 mL) was added NaHMDS (1.0 mol/L, 0.43 mL, 0.43 mmol) at −70 °C under argon. The reaction mixture was allowed to warm to 0 °C under argon for a period of 20 min and was further stirred for 10 min at this temperature. Propiolic acid anhydride (130 mg, 1.07 mmol) was added and the solution was allowed to warm to room temperature overnight. The reaction was quenched by addition of satd. aq. NH₄Cl (20 mL) and the aqueous phase extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:2) afforded an unseparable 3:2 rotamer mixture of tosylamide 47 (128 mg, 0.27 mmol, 46%) as oily white crystals; mp 121 °C. [α]D²⁶ +124.6 (c 1.05, CH₂Cl₂), R₂ 0.62 (hexanes – ethyl acetate, 2:1). IR (CH₂Cl₂, cm⁻¹): 3292, 3055, 2987, 2831, 2686, 2522, 2411, 2306, 2113, 1731, 1677, 1602, 1551, 1423, 1363, 1266, 1189, 1173, 1116, 1095, 1071, 1055, 1027, 896, 853, 740, 618, 574, 546. ¹H NMR (300 MHz, CDCl₃, ppm) δ: 8.15 (m, 3H), 8.02 (m, 1H), 7.97 (m, 2H), 7.58 (m, 1H), 7.49 (m, 3H), 7.40 (m, 4H), 6.06 (m, 1H), 5.72 (dd, J₁ = 2.1 Hz, J₂ = 10.2 Hz, 1H), 5.35/4.96 (m, 1H), 4.96 (m, 1H), 4.46 (m, 2H), 3.30/3.18 (m, 1H), 2.45/2.43 (s, 3H), 2.19/2.14 (m, 1H), 1.74/1.64 (s, 3H), 1.42 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ: 165.3, 165.1/164.9, 153.2, 145.4/145.2, 136.7, 133.7, 133.3/133.2, 130.9/130.0, 129.9, 129.9, 129.6, 124.9/123.9, 129.2/129.0, 128.7, 128.4/128.3, 111.2/111.0, 83.6/83.2, 79.4/79.0, 75.9/75.4, 75.2/75.1, 74.4/74.1, 74.0/73.2, 71.2/71.1, 68.3/68.1, 62.8, 33.8/31.5, 27.9/27.8, 26.2/26.0, 21.7. MS (EI) m/z (relative intensity): 626 (M⁺ – CH₃, 1), 122 (9), 119 (5), 105 (47), 91 (8), 88 (19), 86 (100), 84 (100), 77 (14), 64 (16), 53 (15), 51 (11), 39 (31), 30 (8), 47 (31), 47 (3), 47 (17). HRMS (EI) calcld. for C₃₅H₃₁O₉NS-CH₃: 626.1485; found: 626.1495.

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xylene were removed at high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 9:1). The cyclotrimerized product 48 was isolated as a colourless oil in 5% yield (7 mg, 0.01 mmol). [α]D 22 -20.9 (c 0.25, CH2Cl2). Rf 0.32 (hexanes – ethyl acetate, 4:1). IR (CH2Cl2, cm –1): 3061, 2987, 2957, 2928, 2856, 1728, 1704, 1601, 1584, 1494, 1452, 1405, 1366, 1316, 1266, 1219, 1189, 1175, 1094, 1027, 1003, 963, 841, 816, 739, 712, 672, 660, 638, 602, 572, 545, 512. 1H NMR (300 MHz, CDCl3, ppm) δ: 8.44 (s, 1H), 8.30 (d, J = 8.4 Hz, 2H), 8.13 (s, 1H), 8.07 (m, 2H), 7.99 (m, 2H), 7.64 (m, 1H), 7.52 (m, 3H), 7.39 (m, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.44 (s, 1H), 5.85 (dd, J1 = 7.2 Hz, J2 = 10.8 Hz, 1H), 5.25 (dd, J1 = 2.4 Hz, J2 = 7.2 Hz, 1H), 4.98 (t, J = 7.2 Hz, 1H), 3.90 (t, J = 11.1 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 2.45 (s, 3H), 1.49 (s, 3H), 1.32 (s, 3H), 0.44 (s, 9H), 0.39 (s, 9H). 13C NMR (75 MHz, CDCl3, ppm) δ: 166.4, 164.5, 165.5, 155.6, 146.7, 144.2, 138.4, 137.9, 136.7, 133.8, 133.4, 131.1, 129.9, 129.8, 129.3, 129.2, 129.0, 128.8, 128.8, 124.6, 110.4, 75.4, 73.5, 72.0, 70.5, 66.1, 46.1, 27.6, 25.5, 21.7, 1.7, 1.6. MS (EI) m/z (relative intensity): 796 (M+ – CH3, 1), 525 (6), 477 (5), 179 (5), 149 (7), 129 (8), 106 (9), 105 (100), 98 (7), 97 (13), 96 (6), 95 (8), 91 (13), 85 (10), 84 (9), 83 (17), 82 (8), 81 (13), 77 (16), 73 (25), 71 (17), 70 (10), 69 (30), 68 (30), 67 (8). HRMS (EI) calcd. for C54H39O14N6S3: C 63.60, H 6.08; found: C 63.46, H 6.00.

To a solution of 2,5-di(tert-butyl(dimethyl)silyloxy)-3-hexyne (1.00 g) in CpCo(CO)5 (5 µL), bisacetylene 41 (108 mg, 0.17 mmol) and CpCo(CO)5 (5 µL) dissolved in xylene (5 mL) were added dropwise with a syringe pump at 140 °C over 30 h. During and after this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 5 µL after 5, 17, 29, and 41 h. The reaction mixture was heated under argon for a further 12 h. Xylene was removed at high vacuum and the residue was purified by column chromatography (hexanes – ethyl acetate, 9:1 to 6:1). All four diastereoisomers of the cyclotrimerized product 50 were isolated as crystalline foam in 31% overall yield (52 mg, 0.05 mmol). MS (EI) m/z (relative intensity): 954 (M+ – CH3, 0.1), 912 (10), 526 (12), 253 (12), 179 (12), 147 (11), 106 (12), 105 (100), 91 (16), 77 (17), 75 (27), 73 (33).

The mixture of diastereoisomers was dissolved in THF (0.5 mL), treated with TBAF (1.0 mol/L solution in THF, 0.55 mL) and stirred for 2 h. The reaction mixture was quenched with satd. NH4Cl solution and extracted three times with diethyl ether. The combined organic phases were dried over MgSO4, filtered, and evaporated to dryness. Column chromatography (hexanes – ethyl acetate, 1:2) gave a mixture of four diastereomeric diols (29 mg, 0.04 mmol, 72%), used immediately in the next step. IR (CDCl3, cm –1): 3417, 3019, 2978, 2929, 2857, 1727, 1601, 1452, 1384, 1375, 1347, 1316, 1276, 1216, 1160, 1092, 1070, 1027, 758, 713, 668.

To the diastereomeric diols (17 mg, 0.02 mmol) dissolved in DMSO (1 mL) was added o-iodoxybenzoic acid (IBX, 75 mg, 0.28 mmol). The reaction mixture was stirred for 1 day, diluted with diethyl ether, and washed four times with water. The ether phase was dried over MgSO4, filtered, and evaporated to dryness. The pure product 51 was obtained by column chromatography (ethyl ether – pentane, 2:1) as a white crystalline single diastereomer in 71% yield (12 mg, 0.02 mmol); mp 119 °C. [α]D 22 +38.6 (c 0.06, CH2Cl2). Rf 0.48 (hexanes – ethyl acetate, 1:1). IR (CDCl3, cm –1): 3020, 2926, 2855, 1759, 1727, 1602, 1510, 1452, 1316, 1273, 1216, 1162, 1092, 1068, 1027, 933, 814, 758, 710, 667, 548. 1H NMR (600 MHz, CDCl3, ppm) δ: 7.89 (2m, 4H), 7.62 (d, J = 8.3 Hz, 2H), 7.58 (m, 1H), 7.52 (m, 1H), 7.52 (s, 1H), 7.40 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.08 (s, 1H), 6.12 (dd, J1 = 4.8 Hz, J2 = 8.6 Hz, 1H), 5.74 (dd, J1 = 4.7 Hz, J2 = 7.9 Hz, 1H), 5.03 (dd, J1 = 6.8 Hz, J2 = 8.8 Hz, 1H), 4.73 (t, J = 7.4 Hz, 1H), 4.62 (d, J = 16.8 Hz, 1H), 4.53 (d, J = 16.7 Hz, 1H), 4.00 (d, J1 = 8.9 Hz, J2 = 12.6 Hz, 1H), 3.43 (dd, J1 = 8.9 Hz, J2 = 12.6 Hz, 1H), 2.41 (s, 3 H), 2.35 (s, 3H), 2.20 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H). 13C NMR (150 MHz, CDCl3, ppm) δ: 201.7, 200.0, 165.4, 165.3, 143.8, 139.3, 138.6, 137.7, 137.4, 136.4, 133.8, 133.5, 129.8, 129.8, 129.4, 128.6, 128.4, 127.5, 126.2, 125.1, 110.8, 96.1, 76.2, 74.1, 70.1, 69.8, 59.4, 48.5, 39.6, 30.3, 29.2, 27.8, 27.7, 25.4, 21.5. MS (EI) m/z (relative intensity): 737 (M+*, 0.1), 133 (14), 105 (6), 89 (41), 87 (18), 73 (11), 59 (12), 45 (100). HRMS (EI) calcd. for C41H38O10NS: 737.2295; found: 737.2306.

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