

Cyclotrimerization approach to unnatural structural modifications of pancratistatin and other amaryllidaceae constituents — Synthesis and biological evaluation¹

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 phenanthridone **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.

Résumé : Faisant appel à une cyclotrimérisation des dérivés acétyléniques **30** et **41** qui reflètent respectivement les configurations naturelle et C-1-épi, on a préparé la phénanthridone, le squelette fondamental de la pancratistatine ne comportant pas d'oxygène aromatique. La formation catalysée par le cobalt du noyau fondamental a conduit aux dérivés bisTMS **39** et **48** ainsi qu'au dérivé bisacétylé **51**. On a comparé l'efficacité de la cyclotrimérisation de la série nature ou trans avec celle de la série cis. De plus, on a comparé les rendements des cyclotrimérisations avec des amines et des amides propargyliques. Onze dérivés, y compris la phénanthridone totalement hydroxylé (**39**) ont été évalués contre sept souches de cancer. Trois de ces composés présentent des activités qui ne sont qu'un ordre de grandeur inférieures à celle de la 7-désoxypancratistatine. On rapporte l'ensemble des détails expérimentaux et spectraux relatifs à tous les intermédiaires clés. Les projections relatives à la préparation d'analogues non naturels des constituants de l'Amaryllidaceae sont avancées et l'on possède déjà de nombreuses pistes nouvelles concernant la nature du pharmacophore minimal de la pancratistatine.

Mots clés : cyclotrimérisation, alcaloïdes, catalyseur de cobalt.

[Traduit par la Rédaction]

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

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Dedicated to Dr. Alfred Bader in recognition of his service to the organic chemistry community.

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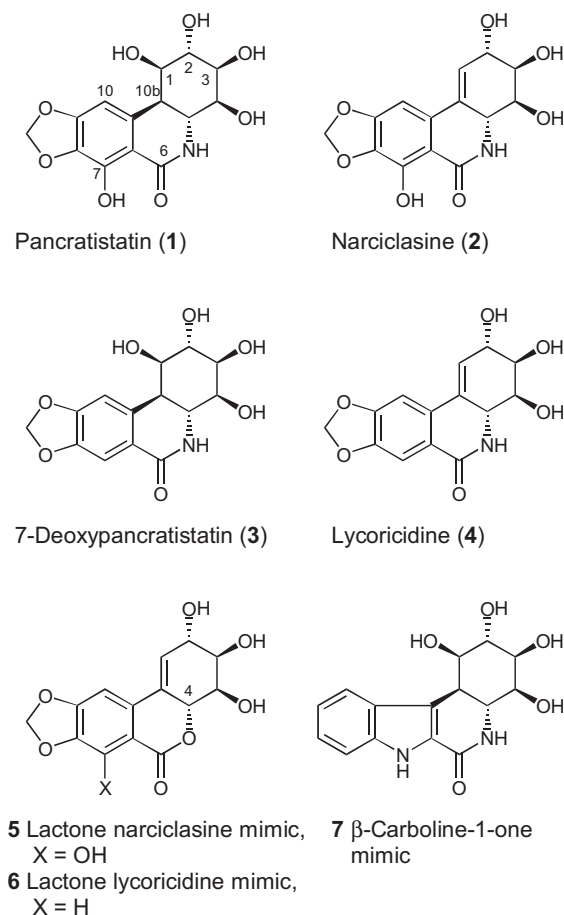
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Fig. 1. Amaryllidaceae constituents (1–4) and some recently synthesized unnatural mimics (5–7).

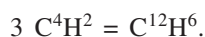


have emerged with regard to the structural elements essential to activity. First, the hydroxyphenanthridone moiety is thought to be essential to high activity of pancratistatin and narciclasine; its deletion, as in 7-deoxypancratistatin and lycoricidine, leads to a significant drop in activity (10). 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 (17*b*, 17*c*). This is not the correct citation and for historical interest we include the original description of his 1864 experiment here:

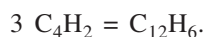
Il est un cas de condensation de l'acétylène naissant très-remarquable et qui mérite un examen particulier, bien que la démonstration en soit plutôt vraisemblable que rigoureusement établie: c'est la condensation de l'acétylène en benzine. Entre la formule de l'acétylène, C^4H^2 , et celle de la benzine $C^{12}H^6$, 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 :



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. Répétons cette expérience avec le formène tribromé (bromoforme), C^2HBr^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.

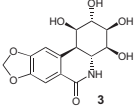
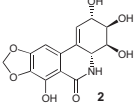
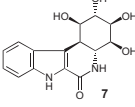
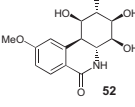
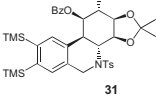
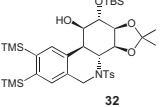
This is an example of condensation of the nascent acetylene that is very remarkable and deserves a close examination, even though the demonstration is rather plausible than rigorously established: it is the condensation of the acetylene into benzene. There is a very simple relationship between the formula 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:



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_2HBr_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-

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

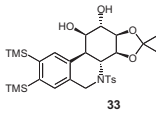
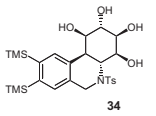
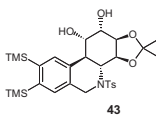
Entry	Compound	Murine P388 lymphocytic leukemia and human cancer cell results (GI ₅₀ values in µg/mL)						
		Murine P388 lymphocytic leukemia	Pancreas BXPC-3	Breast MCF-7	CNS SF-268	Lung NCI-H460	Colon KM20L2	Prostate DU-145
2		0.44				0.29	0.22	
3		0.0012	0.026	0.019	0.021	0.032	0.021	0.011
4		18.3	>10	>10			>10	
5		4.3	4.9	4.4	3.3	2.8	3.6	2.6
6		> 10	> 10	> 10	> 10	> 10	> 10	> 10
7			3.6	2.2	3.8	4.7	3.1	13.1

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 cyclotri-

Table 1 (concluded).

Entry	Compound	Murine P388 lymphocytic leukemia and human cancer cell results (GI ₅₀ values in µg/mL)						
		Murine P388 lymphocytic leukemia	Pancreas BXPC-3	Breast MCF-7	CNS SF-268	Lung NCI-H460	Colon KM20L2	Prostate DU-145
8		3.0	1.7	1.5	1.6	1.7	1.6	1.6
9		3.3	1.7	1.7	1.6	1.7	1.4	1.8
10		3.9						

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

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

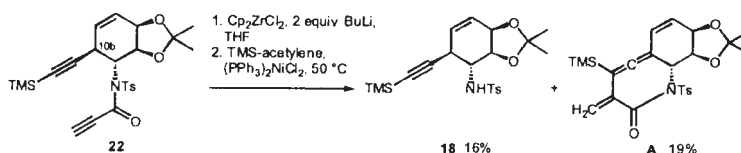
The original intent of our study was the investigation of a *de novo* approach to pancratistatin (**1**) from scaffold **9** in which the acetylene partners would provide a triply silylated arene that could be converted to the fully oxygenated core of pancratistatin. Portrayed in Scheme 1 are the results 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.³

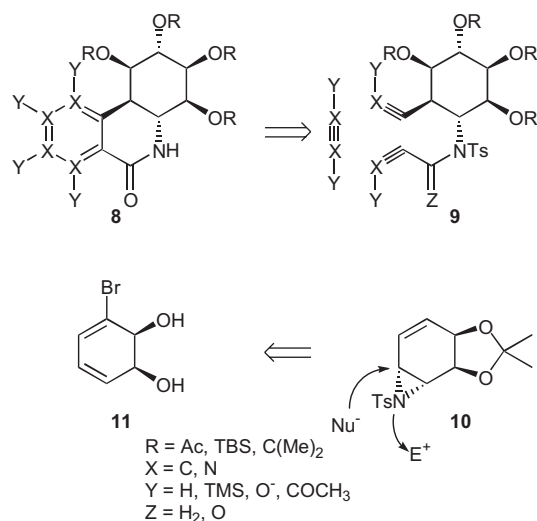
Adjustments in the strategic plan led to the construction of simpler scaffolds unencumbered by TMS groups and cyclo-trimerization attempts to attain a 7-deoxypancratistatin

³The exposure of propargylic amide **22** to a zirconium-based catalyst led to some unusual results. The propargylic 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 [(1*R*,2*S*,6*R*)-4,4-Dimethyl-12-methylene-14-(4-methylphenylsulfonyl)-11-trimethylsilyl-3,5-dioxo-14-azatricyclo-[7.5.0.0^{2,6}]tetradeca-7,9,10-trien-13-one]: [α]_D²⁸ +79.0 (c 0.95, CHCl₃). *R*_T 0.81 (hexanes – ethyl acetate, 4:1). IR (CHCl₃, cm⁻¹) ν : 3683, 3020, 2962, 2932, 2401, 2167, 1736, 1660, 1598, 1509, 1374, 1308, 1278, 1251, 1216, 1189, 1176, 1091, 1063, 950, 908, 847, 757, 669, 582. ¹H NMR (300 MHz, CDCl₃, 50 °C, ppm) δ : 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, 1 H), 2.43 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 0.14 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ : 145.6, 142.7, 135.5, 129.8, 128.9, 128.0, 125.1, 121.5, 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⁺ – CH₃, 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 C₂₃H₂₆O₅NSSi-CH₃: 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 AlCl_3 . The reprotected compound was used without further purification. The tosylaziridine **18** was first converted to the *cis*-diol **24** by the action of OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) (44% yield, 76% conversion), and the cyclic sulfate **25** was then generated in 82% yield by treatment with SO_2Cl_2 and NEt_3 . 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 (27*b*). 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-10*b* by the

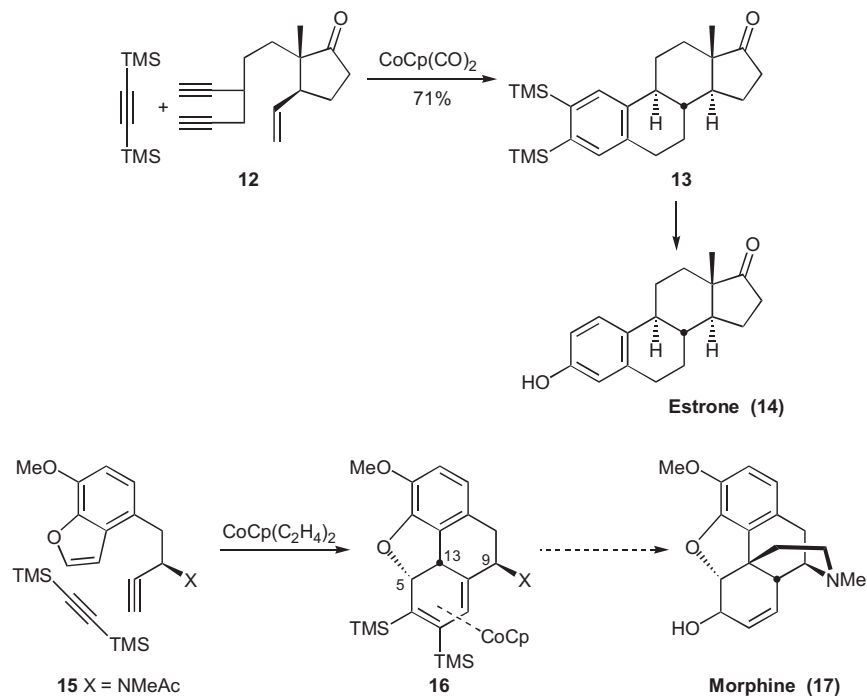
intermediate sulfate anion **25a** as shown in Fig. 4. Further study is required to optimize the production of either **26** or **27**, the latter containing the structural features of narciclasine.

The TMS group was removed with tetrabutylammonium triphenyldifluorosilicate (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 NaIO_4 - RuCl_3 . Oxidation studies on bisbenzoate **37** led to the same results under these conditions. With the reaction buffered by solid Na_2CO_3 , 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 (CH_3ONa in MeOH) then under acidic conditions (Dowex 50WX8-100 in MeOH) to provide the 7-deoxypancratistatin nucleus having TMS groups in place of the aromatic oxygenation. The preparation of this key compound in 14 steps and 0.3% overall yield starting from aziridine **10** signified the successful validation of the cyclotrimerization strategy as an approach to compounds with variations in the aromatic core.

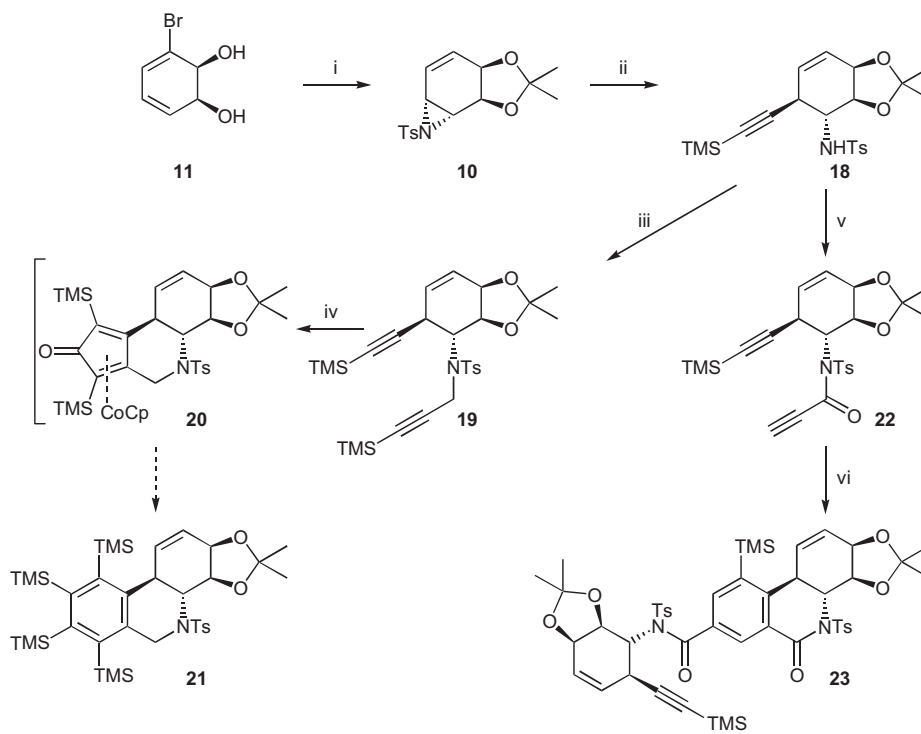
Cyclotrimerization of scaffolds in the *cis* or unnatural series

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/lycoridine manifold was not observed. A possible explanation may lie in the relative acidities of propargylic vs. benzylic protons at C-10*b* 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, $\text{Cu}(\text{acac})_2$, H_3CCN , 0 °C to rt, then *n*- Bu_3SnH , 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) $_4\text{NI}$, THF, rt, 46% (66% by conversion); (iv) $\text{CpCo}(\text{CO})_2$, BTMSA, 140 °C; (v) BuLi, propionic acid anhydride, THF, 0 °C to rt, 46%; (vi) $\text{Ni}(\text{COD})_2$, 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) H₅C₆COONH₄, DMF, 70 °C, then H₂O, H₂SO₄, THF, rt; (vi) TBAT, H₃CCN, rt, 84%; (vii) TBSCl, imidazole, DMF, rt, 89%; (viii) NaHMDS, propargyl bromide, (*n*Bu)₄NI, THF, -0 °C to rt, 79%.

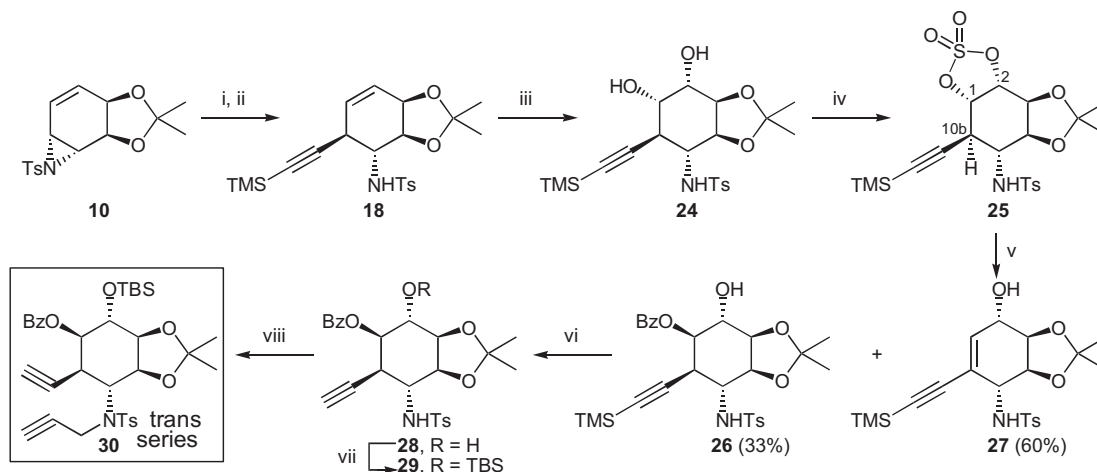
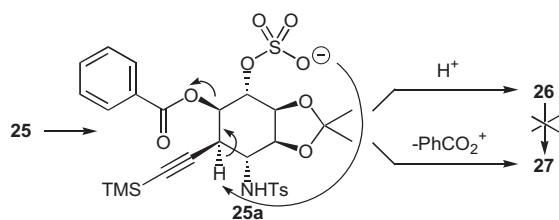


Fig. 4. Generation of enyne **25**.



tained in a manner similar to that employed in the trans series. Overall, the cis series synthesis of phenanthridone **48** proved to be three times higher yielding because of higher selectivity in the cyclic sulfate opening. The eventual synthesis of C-1 epimeric analogs would originate in the cis-diol **24**.

Cyclotrimerization of propargyl amides

To avoid the modest yields of benzylic oxidation in the tetracycles **31** and **37**, we chose to investigate the cyclotrimerization protocol on propargylic amides, which could be easily generated by acylation of tosylamide **18**. Initially, the enyne **45**, obtained by acylation of **18** with propiolic 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-deoxyglycorididine. 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).

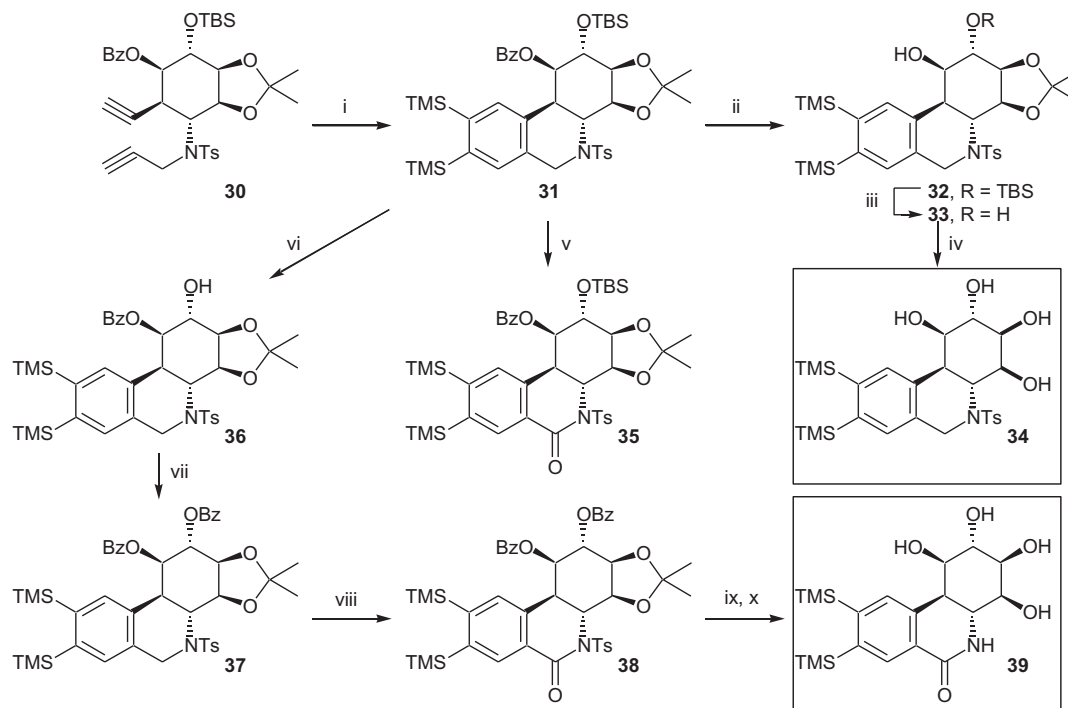
Synthesis of the bisacetyl derivative of 7-deoxypancratistatin

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 tetrabutylammonium fluoride (TBAF) and oxidized to the bisacylated 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.

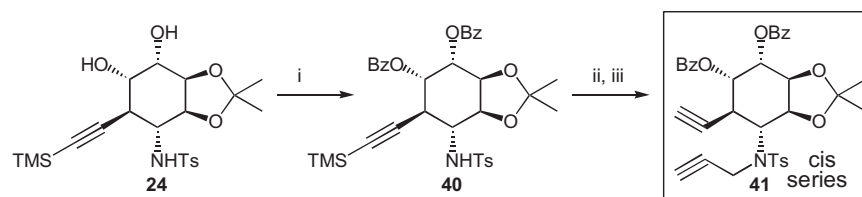
Biological evaluation

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 tetraol (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

Scheme 3. Cyclotrimerization of the trans scaffold. Reagents and conditions: (i) CpCo(CO)₂, BTMSA, xylene, 140 °C, 83%; (ii) NaOMe, MeOH, rt, 99%; (iii) TBAF, THF, rt, 85%; (iv) Dowex 50WX8-100, MeOH, 70 °C, 79%; (v) NaIO₄, RuCl₃, CH₃CN–CCl₄–H₂O, rt, 15%; (vi) TBAF, THF, rt, 84%; (vii) BzCl, pyridine, rt, 86%; (viii) NaIO₄, RuCl₃, Na₂CO₃, CH₃CN–CCl₄–H₂O, rt, 33%; (ix) Na-naphthalide, THF, –65 °C, then NaOMe, MeOH, rt, 32%; (x) Dowex 50WX8-100, MeOH, 70 °C, 94%.



Scheme 4. Scaffold for cyclotrimerization in the cis or unnatural series. Reagents and conditions: (i) BzCl, pyridine, 0 °C to rt, 80%; (ii) TBAT, H₃CCN, rt, 76%; (iii) NaHMDS, propargyl bromide, (nBu)₄NI, THF, –70 °C to rt, 94%.



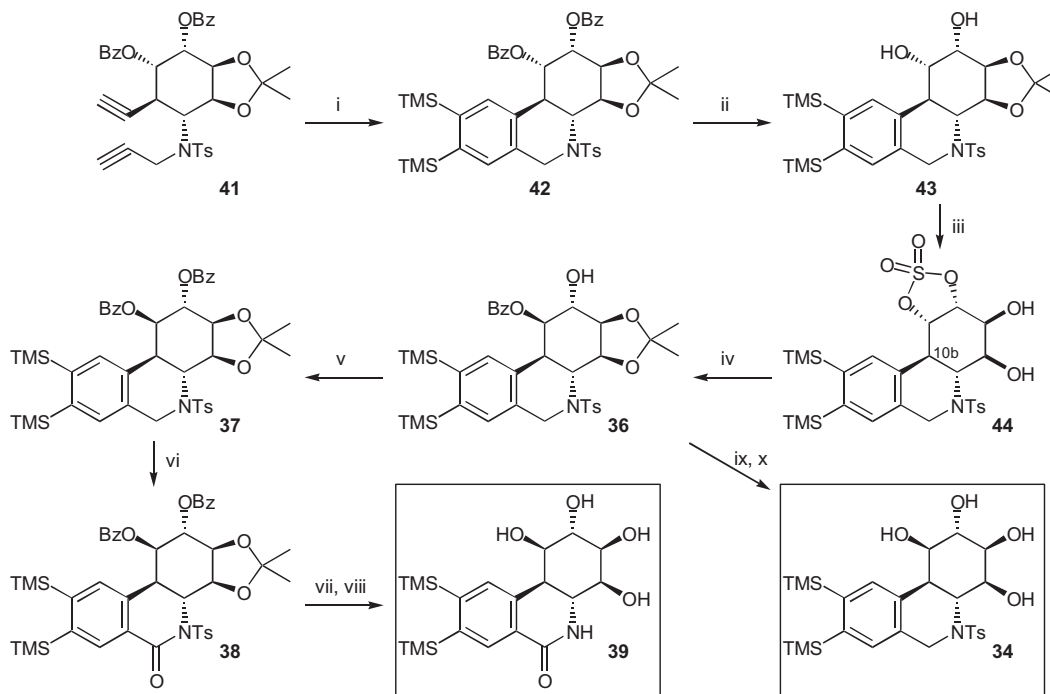
the lactone analogs **5** and **6** are inactive. Second, these compounds represent the first examples of pancratistatin analogs that retain activity despite the absence of all aromatic oxygenation, in addition to lacking the amide moiety. Third, and very surprising, these derivatives have shown greater 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 than 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-

Scheme 5. Cyclotrimerization of the cis scaffold. Reagents and conditions: (i) $\text{CpCo}(\text{CO})_2$, BTMSA, xylene, 140 °C, 87%; (ii) 1% NaOH, MeOH, rt, 99%; (iii) SO_2Cl_2 , NEt_3 , CH_2Cl_2 , 0 °C to rt, 70%; (iv) $\text{H}_5\text{C}_6\text{COONH}_4$, DMF, 70 °C, 99%; (v) BzCl, pyridine, rt, 86%; (vi) NaIO_4 , RuCl_3 , Na_2CO_3 , $\text{CH}_3\text{CN}-\text{CCl}_4-\text{H}_2\text{O}$, rt, 33%; (vii) Na-naphthalide, THF, -65 °C, then NaOMe, MeOH, rt, 32%; (viii) Dowex 50WX8-100, MeOH, 70 °C, 94%; (ix) NaOMe, MeOH, rt, 99%; (x) Dowex 50WX8-100, MeOH, 70 °C, 79%.



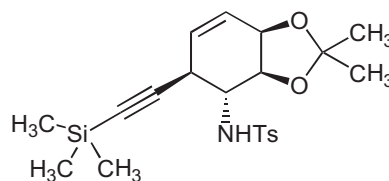
deoxypancratistatin. Based on the surprising and promising results of biological activity, it now seems prudent to proceed further with the preparation of diversely functionalized analogs of Amaryllidaceae constituents.

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 ^{13}C NMR spectra were recorded on a 300 MHz Bruker spectrometer. All chemical shifts are referenced to TMS or residual undeuterated solvent (CHCl_3). 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 per-

formed by the analytical division at Brock University, St. Catharines, Ontario.

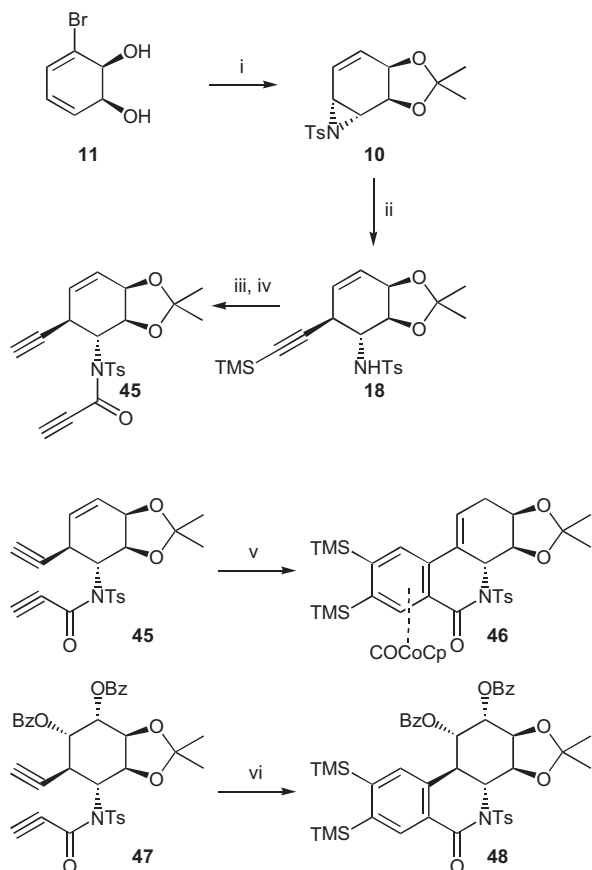
N-[(1*R*,2*R*,5*R*,6*S*)-2-(2-Trimethylsilylethynyl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-4-methylbenzenesulfonamide (**18**)



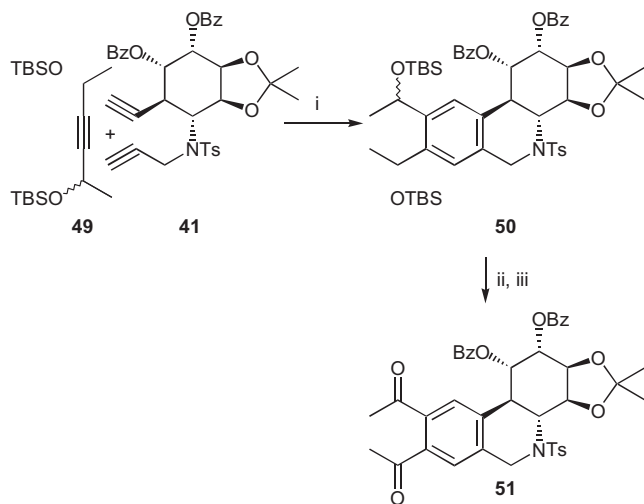
$\text{C}_{21}\text{H}_{29}\text{NO}_4\text{SSi}$
419.61 g/mol

To a solution 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 AlCl_3 (1.24 g, 9.33 mmol) was added. After stirring for a further 10 min, aziridine **10** (1.00 g, 3.11 mmol), dissolved in 5 mL toluene, was added dropwise. Additional AlCl_3 (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

Scheme 6. Propargyl amide series. Reagents and conditions: (i) DMP, *p*-TSA, acetone, rt, then PhINTs, Cu(acac)₂, H₃CCN, 0 °C to rt, then *n*-Bu₃SnH, AIBN, THF, reflux, 25% over three steps; (ii) BuLi, TMS-acetylene, AlCl₃, toluene, 0 °C to rt, then DMP, *p*-TSA, acetone, rt, 69% over two steps; (iii) BuLi, propionic acid anhydride, THF, 0 °C to rt, 46%; (iv) TBAT, H₃CCN, rt, 61%; (v) CpCo(CO)₂, BTMSA, xylene, 140 °C, 11%; (vi) CpCo(CO)₂, BTMSA, xylene, 140 °C, 5%.

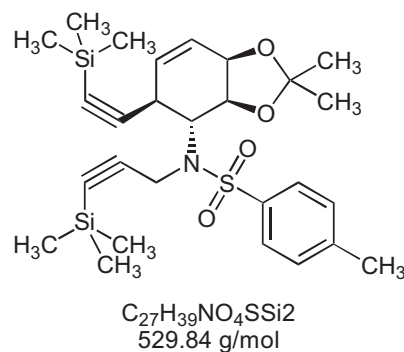


Scheme 7. Bisketone approach. Reagents and conditions: (i) CpCo(CO)₂, xylene, 140 °C, 31%; (ii) TBAF, THF, rt, 72%; (iii) IBX, DMSO, rt, 71%.



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 acetone **18** (2.14 mmol, 69%); mp 168 °C. [α]_D²¹ +30.2 (*c* 0.20, CH₂Cl₂). *R*_f 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.

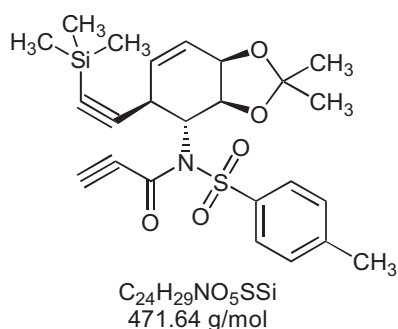
(3a*S*,4*R*,5*R*,7a*R*)-2,2-Dimethyl-4-[4-methylphenyl(3-trimethylsilyl-2-propynyl)sulfonamido]-5-(2-trimethylsilyl-1-ethynyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole (19**)**



To a solution of tosylamide **18** (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, 7:1 to 2:1) afforded sulfonamide **19** (115 mg, 0.22 mmol, 46%) and starting material **18** (40 mg, 20%). R_f 0.63 (hexanes – ethyl acetate, 5:1). 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, 72.7, 61.3, 33.2, 28.0, 25.8, 21.6, 0.0, -0.4. MS (EI) m/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), 111 (15), 97 (11), 91 (47), 84 (10), 83 (33), 75 (16), 73 (86), 71 (12), 59 (16), 53 (13), 43 (32). HRMS (EI) calcd. for C₂₇H₃₉O₄NSSi: 529.2138; found: 529.2144.

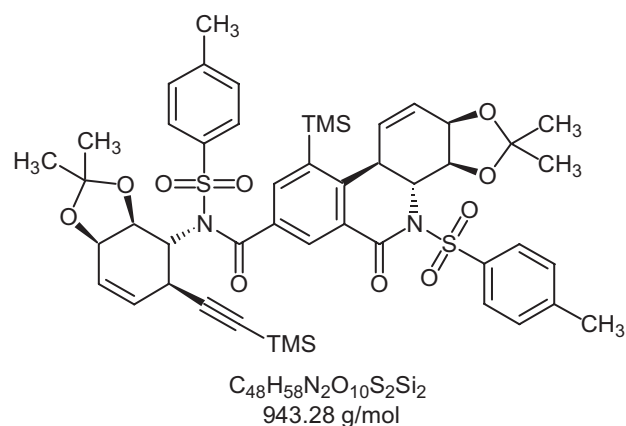
***N*-[(1*R*,2*R*,5*R*,6*S*)-2-(2-Trimethylsilylethynyl)-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-*N*-propioloyl-4-methylbenzenesulfonamide (**22**)**



To a solution of of acetone **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, 3:1) afforded the tosylamide **22** (128 mg, 0.27 mmol, 46%) as a slightly yellow foam. $[\alpha]_D^{25} +29.2$ (c 0.25, CH₂Cl₂). R_f 0.71 (hexanes – ethyl acetate, 3:1). IR (CHCl₃, cm⁻¹) ν : 3297, 3021, 2988, 2961, 2177, 2110, 1932, 1795, 1739, 1675, 1597, 1494, 1457, 1366, 1307, 1250, 1216, 845, 756. ¹H NMR (300 MHz, CDCl₃, ppm) δ : 8.03 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.98 (m, 2H), 5.11 (m, 1H), 4.74 (m, 2H), 4.25 (d, J = 10.8 Hz, 1H), 3.23 (s, 1H), 2.43 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 0.02 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ : 153.7, 145.2, 136.0, 132.6, 130.1, 129.2, 123.3, 110.6, 103.4, 89.6, 82.7, 75.5, 73.7, 72.8, 65.8, 34.0, 27.9, 25.8, 21.9, -0.2. MS (EI) m/z

(relative intensity): 471 (MH⁺, 0.1), 456 (9), 306 (19), 258 (7), 248 (16), 242 (7), 224 (7), 207 (7), 191 (24), 190 (72), 176 (8), 175 (35), 161 (7), 159 (7), 157 (7), 156 (10), 155 (90), 151 (6), 149 (9), 147 (9), 139 (15), 131 (7), 124 (11), 123 (8), 121 (7), 119 (5), 117 (6), 115 (6), 112 (8), 109 (5), 108 (6), 107 (5), 105 (7), 100 (7), 99 (7), 98 (9), 97 (10), 92 (13), 91 (100), 90 (5), 89 (9), 85 (7), 84 (7), 83 (12), 79 (5), 77 (8), 75 (19), 74 (10), 73 (77), 71 (6), 70 (7), 69 (9), 65 (13), 64 (10), 63 (5), 60 (6), 59 (12), 58 (8), 57 (9), 56 (5), 55 (8), 53 (30), 51 (5), 45 (14), 44 (17), 43 (49), 42 (6), 41 (10). HRMS (EI) calcd. for C₂₁H₂₉O₄NSSi: 471.1536; found: 471.1527.

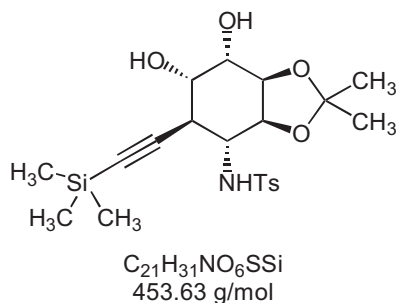
***N*-[(1*R*,2*R*,5*R*,6*S*)-2-Trimethylsilylethynyl-5,6-(isopropylidenedioxy)cyclohex-3-en-1-yl]-*N*-(4-methylphenylsulfonyl)-(3*aS*,3*bR*,9*bR*,10*R*,11*aS*)-2,2-dimethyl-5-oxo-9-trimethylsilyl-3*a*,3*b*,4,5,9*b*,11*a*-hexahydro[1,3]dioxolo[4,5-*c*]phenanthridine-10-en-7-carboxamide (**23**)**



To a solution of of bis(cyclooctadiene)nickel(0) (15 mg, 0.06 mmol) and triphenylphosphine (57 mg, 0.22 mmol) in 5 mL toluene was added bisacetylene **22** (86 mg, 0.18 mmol), immediately followed by of (trimethylsilyl)acetylene (27 mg, 0.27 mmol, 39 μ L) at room temperature under argon. The solution was stirred overnight, 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, 5:1) afforded the cyclotrimerized dimer **23** (40 mg, 0.04 mmol, 47%) as a slightly yellow oil. $[\alpha]_D^{28} +53.6$ (c 0.74, CHCl₃). R_f 0.64 (hexanes – ethyl acetate, 4:1). IR (CHCl₃, cm⁻¹) ν : 3430, 3020, 2172, 1686, 1677, 1598, 1374, 1253, 1216, 1171, 1076, 845, 756. ¹H NMR (300 MHz, CDCl₃, 50 °C, ppm) δ : 8.30 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 7.9 Hz, 1H), 7.49 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.16 (m, 2H), 7.08 (d, J = 7.9 Hz, 1H), 5.16 (m, 4H), 5.55 (m, 1H), 4.76 (m, 3H), 4.58 (m, 1H), 4.42 (m, 1H), 4.20 (d, J = 10.8 Hz, 1H), 3.63 (t, J = 10.5 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H), 1.38 (m, 12H), 0.49 (s, 9H), 0.16 (s, 9H). MS (EI) m/z (relative intensity): 943 (M⁺, 0.1), 927 (0.1), 456 (9), 256 (7), 255 (8), 254 (47), 253 (12), 231 (5), 229 (15), 207 (19), 206 (6), 191 (12), 190 (27), 189 (6), 176 (7),

175 (18), 161 (6), 156 (6), 155 (32), 151 (5), 149 (20), 147 (8), 145 (5), 140 (6), 139 (39), 135 (6), 133 (5), 131 (10), 129 (6), 123 (6), 121 (10), 119 (9), 117 (8), 116 (6), 115 (5), 109 (5), 108 (6), 107 (7), 105 (7), 100 (8), 99 (45), 98 (36), 97 (12), 95 (7), 93 (7), 92 (13), 91 (86), 90 (6), 89 (9), 86 (5), 85 (10), 84 (16), 83 (12), 82 (5), 81 (8), 79 (6), 77 (10), 75 (24), 74 (12), 73 (100), 71 (15), 70 (13), 69 (19), 67 (7), 65 (17), 64 (6). HRMS (EI) calcd. for $C_{48}H_{58}O_{10}N_2S_2Si_2-CH_3$: 927.2837; found: 927.2824.

(3a*S*,4*R*,5*R*,6*S*,7*S*,7a*S*)-6,7-Dihydroxy-2,2-dimethyl-4-(4-methylphenylsulfonamido)-5-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (24)

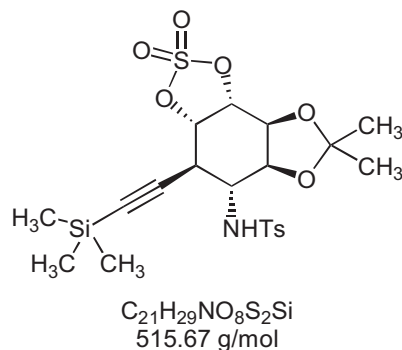


To a solution of (trimethylsilyl)acetylene **18** (1.55 g, 3.68 mmol) in 40 mL CH_2Cl_2 was added *N*-methylmorpholine-*N*-oxide (5.18 mg, 4.42 mmol) and six small crystals of OsO_4 . The reaction mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of satd. aq. $NaHSO_3$ (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 washed with brine (20 mL), dried over Na_2SO_4 , and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 1:1) afforded diol **24** (768 mg, 1.69 mmol, 46%) as white crystals (mp 87 °C) and the starting material (488 mg, 1.16 mmol, 32%). $[\alpha]_D^{25} +32.5$ (*c* 0.45, $CHCl_3$). R_f 0.37 (hexanes – ethyl acetate, 1:1). IR ($CHCl_3$, cm^{-1}) ν : 3684, 3577, 3359, 3020, 2991, 2962, 2903, 2401, 2178, 1731, 1599, 1519, 1423, 1383, 1375, 1334, 1306, 1250, 1216, 1160, 1093, 1066, 929, 848, 814, 771, 669, 627, 598, 557, 512, 460. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.79 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.80 (d, *J* = 9.4 Hz, 1H), 4.11 (m, 3H), 4.01 (d, *J* = 5.8, 1H), 3.89 (m, 1H), 3.26 (s, 2H), 2.80 (t, *J* = 5.5 Hz, 1H), 2.42 (s, 3H), 1.41 (s, 3H), 1.25 (s, 3H), 0.13 (s, 9H). ^{13}C 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 (6), 156 (6), 155 (60), 154 (5), 153 (7), 152 (6), 151 (6), 150 (6), 149 (16), 141 (7), 140 (11), 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 (7), 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) calcd. for $C_{21}H_{31}O_6NSSi-CH_3$: 438.1407; found: 438.1400. Anal. calcd. for $C_{21}H_{31}O_6NSSi$: C 55.60, H 6.89; found: C 55.20, H 7.02.

(3a*S*,4*R*,5*R*,5a*S*,8a*S*,8b*S*)-*N*-(7,7-Dimethyl-2,2-dioxo-4-trimethylsilanylethynyl hexahydro-1,3,6,8-tetraoxa-2λ⁶-thia-*as*-indacen-5-yl)-4-methylbenzenesulfonamide (25)

To a solution of diol **24** (150 mg, 0.33 mmol) in 5 mL dry

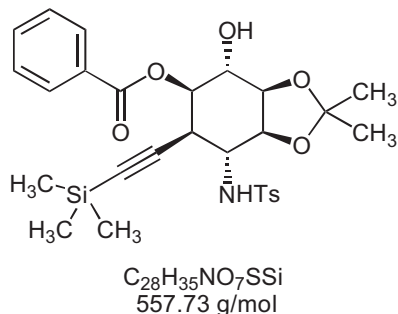


CH_2Cl_2 was added triethylamine (0.37 mL, 2.65 mmol) at 0 °C. The solution was stirred for 10 min and SO_2Cl_2 (0.99 mL, 1.0 mol/L solution, 0.99 mmol) was added dropwise. After the addition, the solution was allowed to warm to room temperature and was stirred for 3 h. Further addition of triethylamine (0.37 mL, 2.65 mmol) and SO_2Cl_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_2Cl_2 (30 mL) and extracted with water (2 × 10 mL). The organic phase was dried over Na_2SO_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. $[\alpha]_D^{26} -51.5$ (*c* 1.40, $CHCl_3$). R_f 0.89 (hexanes – ethyl acetate, 3:7). IR ($CHCl_3$, cm^{-1}) ν : 3684, 3617, 3374, 3020, 2964, 2928, 2401, 2182, 1721, 1599, 1520, 1496, 1404, 1334, 1307, 1291, 1252, 1216, 1160, 1093, 1013, 985, 924, 848, 813, 759, 669, 548, 505, 475, 462, 454. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.81 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.03 (m, 3 H), 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). ^{13}C 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 (35), 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), 150 (9), 149 (41), 147 (6), 140 (6), 139 (16), 138 (5), 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

(9), 64 (6), 59 (8), 58 (13), 57 (48), 56 (18), 55 (40), 54 (6), 53 (9), 51 (5), 45 (5), 43 (65), 42 (8), 41 (29). HRMS (EI) calcd. for $C_{21}H_{29}O_8NS_2Si-CH_3$: 500.0869; found: 500.0846. Anal. calcd. for $C_{21}H_{29}O_8NS_2Si$: C 48.91, H 5.67; found: C 49.32, H 5.86.

(3a*S*,4*S*,5*R*,6*R*,7*R*,7*aS*)-4-Hydroxy-2,2-dimethyl-7-(4-methylphenylsulfonamido)-5-phenylcarbonyloxy-6-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (26)

To a solution of cyclic sulfate **25** (462 mg, 0.90 mmol) in 5 mL dry DMF was added ammonium benzoate (312 mg,

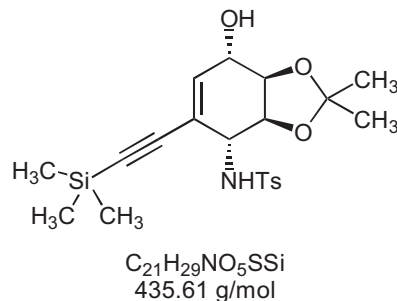


2.24 mmol). The reaction mixture was heated to 70 °C for 2 h, then cooled to 40 °C and the DMF was removed under reduced pressure. The residue was suspended in 25 mL THF before 3 drops of H_2O and H_2SO_4 were added. The resulting mixture was stirred for 1.5 h and then quenched with satd. aq. $NaHCO_3$ (25 mL) and diluted with CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 2:1) afforded benzoate **26** (167 mg, 0.30 mmol, 33%); mp 105 °C. $[\alpha]_D^{22} -38.4$ (c 0.98, $CHCl_3$). R_f 0.19 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) v: 3275, 2924, 2853, 2323, 2177, 1702, 1601, 1452, 1383, 1332, 1275, 1249, 1219, 1159, 1119, 1093, 1069, 1027, 845, 814, 761, 712, 664, 568, 550. 1H NMR (300 MHz, $CDCl_3$, 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), 5.31 (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, 3H), 1.50 (s, 3H), 1.24 (s, 3H), 0.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 166.7, 143.7, 138.1, 133.7, 130.3, 129.9, 128.7, 127.6, 110.0, 101.1, 90.5, 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 ($M^+ - CH_3$, 2.1), 366 (10), 351 (8), 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 (7), 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 (7), 109 (14), 108 (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

(9), 51 (19), 50 (12), 47(6), 45 (11), 44 (27), 43 (94), 42 (15), 41 (38). HRMS (EI) calcd. for $C_{28}H_{35}O_7NSSi-CH_3$: 542.1669; found: 542.1660.

(3a*S*,4*R*,7*S*,7*aR*)-7-Hydroxy-2,2-dimethyl-4-(4-methylphenylsulfonamido)-5-(2-trimethylsilyl-1-ethynyl)-3a,4,7,7a-tetrahydro-1,3-benzodioxole (27)

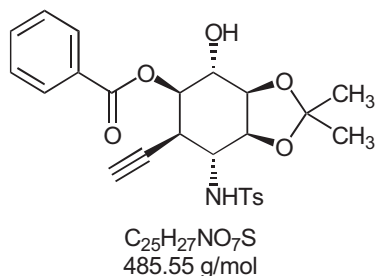
To a solution of cyclic sulfate **25** (462 mg, 0.90 mmol) in 5 mL dry DMF was added ammonium benzoate (312 mg,



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 H_2O and H_2SO_4 were added. The resulting mixture was stirred for 1.5 h, quenched with satd. aq. $NaHCO_3$ (25 mL), and diluted with CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 2:1) afforded allyl alcohol **27** (234 mg, 0.54 mmol, 60%); mp 131 °C. $[\alpha]_D^{22} -42.7$ (c 0.30, $CHCl_3$). R_f 0.33 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}) v: 3318, 3020, 2928, 2401, 2149, 1726, 1600, 1424, 1384, 1332, 1251, 1216, 1158, 1094, 1060, 926, 865, 846, 814, 771, 669, 603, 550, 515. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.80 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.37 (d, $J = 5.2$ Hz, 1H), 5.76 (d, $J = 9.5$ Hz, 1H), 4.51 (m, 1H), 4.38 (m, 1H), 4.32 (m, 1H), 3.96 (dd, $J = 3.2, 9.4$ Hz, 1H), 3.16 (s, 1H), 2.42 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 143.3, 137.8, 137.3, 129.6, 127.4, 125.0, 109.0, 102.3, 98.0, 77.6, 77.6, 66.2, 53.9, 26.4, 24.5, 21.7, -0.2. MS (EI) m/z (relative intensity): 420 ($M^+ - CH_3$, 6), 349 (9), 337 (7), 336 (15), 335 (61), 212 (16), 206 (6), 205 (7), 204 (8), 192 (6), 190 (6), 181 (8), 180 (43), 178 (12), 177 (9), 176 (11), 175 (6), 165 (5), 155 (14), 150 (6), 149 (18), 139 (15), 120 (13), 107 (8), 105 (6), 104 (6), 101 (6), 100 (7), 97 (13), 96 (6), 95 (5), 92 (12), 91 (75), 90 (5), 85 (16), 84 (7), 83 (9), 81 (5), 77 (8), 75 (25), 74 (12), 73 (100), 71 (13), 70 (6), 69 (12), 65 (13), 60 (6), 59 (13), 58 (7), 57 (12), 55 (11), 45 (11), 44 (6), 43 (44), 42 (8), 41 (13). HRMS (EI) calcd. for $C_{21}H_{29}O_5NSSi$: 435.1536; found: 435.1534. Anal. calcd. for $C_{21}H_{29}O_5NSSi$: C 57.90, H 6.71; found: C 57.45, H 7.00.

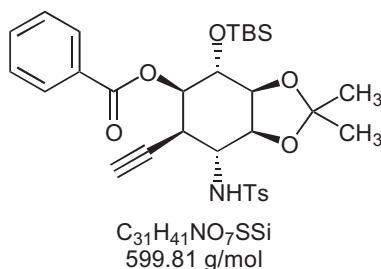
(3a*S*,4*S*,5*R*,6*R*,7*R*,7*aS*)-4-Hydroxy-2,2-dimethyl-7-(4-methylphenylsulfonamido)-5-phenylcarbonyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (28)

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. NH_4Cl (25 mL), and extracted with ethyl acetate (3×20 mL). The combined organic phases were dried over Na_2SO_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. $[\alpha]_D^{19} -23.4$ (c 0.85, $CHCl_3$). R_f 0.41 (hexanes – ethyl acetate, 1:1). IR ($CHCl_3$, cm^{-1}) v: 440, 3288, 3155, 2988, 2254, 1726, 1697, 1600, 1453, 1375, 1331, 1279, 1247, 1222, 1163, 1119, 1095, 1069, 908, 815, 734, 651, 545. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 8.06 (d, $J = 7.5$ Hz, 2H), 7.84 (d, $J = 8.2$ Hz, 2H), 7.58 (m, 1H), 7.44 (m, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 5.59 (d, $J = 8.0$ Hz, 1H), 5.31 (dd, $J = 3.6, 6.8$ Hz, 1H), 4.33 (m, 1H), 4.23 (m, 1H), 4.08 (m, 2H), 3.19 (m, 1H), 3.03 (s, 1H), 2.38 (s, 3H), 2.02 (d, $J = 2.7$ Hz, 1H), 1.51 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 166.7, 143.6, 138.2, 133.7, 130.2, 129.7, 129.5, 128.7, 127.6, 109.9, 79.6, 78.5, 77.4, 73.2, 72.4, 69.4, 54.3, 34.6, 28.0, 26.1, 21.7. MS (EI) m/z (relative intensity): 470 ($M^+ - CH_3$, 3.2), 377 (6), 362 (5), 263 (7), 225 (8), 179 (16), 155 (17), 150 (7), 139 (9), 134 (8), 132 (5), 123 (5), 122 (24), 108 (8), 106 (13), 105 (100), 92 (8), 91 (48), 85 (6), 80 (6), 78 (7), 77 (34), 75 (8), 73 (11), 71 (5), 70 (11), 69 (7), 65 (11), 59 (7), 58 (5), 57 (8), 55 (8), 53 (5), 51 (13), 50 (7), 45 (7), 44 (13), 43 (25), 41 (11). HRMS (EI) calcd. for $C_{25}H_{27}O_7NS-CH_3$: 470.1273; found: 470.1283. Anal. calcd. for $C_{25}H_{27}O_7NS$: C 61.84, H 5.60; found: C 61.45, H 5.36.

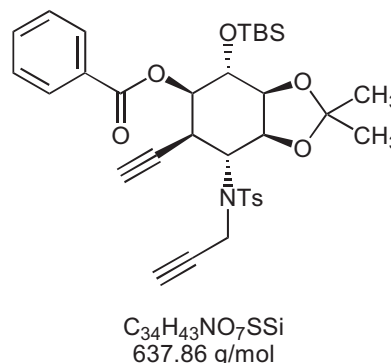
(3a*S*,4*S*,5*R*,6*R*,7*R*,7a*S*)-2,2-Dimethyl-7-(4-methylphenylsulfonamido)-4-(*tert*-butyldimethylsilyloxy)-5-phenylcarboxyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (29**)**



To a solution of alcohol **28** (290 mg, 0.60 mmol) in 4 mL dry DMF were added imidazole (204 mg, 2.99 mmol) and TBSCl (451 mg, 2.99 mmol). The reaction mixture was stirred at room temperature for 18 h, quenched with water (20 mL) and, after stirring for an additional 10 min, extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over Na_2SO_4 and 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. $[\alpha]_D^{19} -36.9$ (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, 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. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 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) δ : 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) calcd. for $C_{31}H_{41}O_7NSSi-CH_3$: 584.2138; found: 584.2150. Anal. calcd. for $C_{31}H_{41}O_7NSSi$: C 62.08, H 6.89; found: C 61.86, H 6.64.

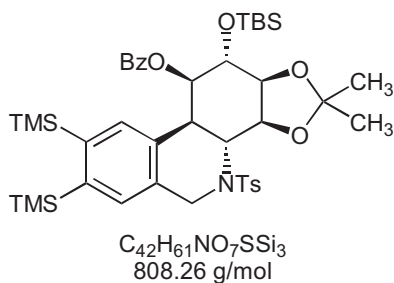
(3a*S*,4*S*,5*R*,6*R*,7*R*,7a*S*)-2,2-Dimethyl-7-(4-methylphenyl(2-propynyl)sulfonamido)-4-(*tert*-butyldimethylsilyloxy)-5-phenylcarboxyloxy-6-(1-ethynyl)perhydro-1,3-benzodioxole (30**)**



To a solution of tosylamide **29** (411 mg, 0.69 mmol) in 11 mL of dry THF was added NaHMDS (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) $_4Ni$ (252 mg, 0.69 mmol) were added. The reaction mixture was stirred at room temperature for 6 h, quenched with satd. aq. NH_4Cl (30 mL), extracted with ethyl acetate (3×30 mL), dried over Na_2SO_4 , and the solvent was evaporated at reduced pressure. Column chromatography (hexanes – ethyl acetate, 9:1) afforded imide **30** (345 mg, 0.54 mmol, 79%) as colourless foam. $[\alpha]_D^{19} -37.5$ (c 0.24, $CHCl_3$). R_f 0.54 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) v: 3309, 3068, 2987, 2956, 2931, 2896, 2859, 2255, 2125, 1722, 1601, 1586, 1495, 1472, 1463, 1453, 1384, 1373, 1351, 1331, 1308, 1269, 1221, 1159, 1095, 1027, 1006, 990, 961, 910, 865, 840, 815, 781, 734, 712, 666, 650, 599, 583, 546, 467. 1H NMR (300 MHz,

CDCl₃, ppm) δ : 8.18 (d, J = 8.1 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H), 7.59 (m, 1H), 7.47 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.35 (m, 1H), 4.84 (m, 2H), 4.42 (m, 1H), 4.15 (m, 3H), 3.64 (m, 1H), 2.42 (s, 3H), 2.22 (m, 1H), 2.00 (d, J = 2.2 Hz, 1H), 1.64 (s, 3H), 1.36 (s, 3H), 0.94 (s, 9H), 0.25 (s, 3H), 0.18 (s, 3H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ : 165.9, 143.5, 137.8, 133.4, 130.2, 129.9, 129.4, 128.6, 128.5, 109.7, 80.5, 78.7, 78.5, 74.9, 74.7, 73.9, 73.0, 66.6, 58.7, 30.9, 28.2, 26.3, 25.8, 25.8, 21.7, 18.1, -4.8, -5.0. MS (EI) m/z (relative intensity): 622 (M^+ - CH₃, 2.6), 522 (7), 401 (6), 400 (19), 245 (7), 222 (9), 192 (7), 191 (35), 181 (6), 180 (15), 179 (94), 167 (7), 155 (18), 150 (7), 149 (23), 139 (15), 137 (8), 135 (6), 129 (8), 122 (5), 113 (6), 111 (6), 109 (5), 106 (9), 105 (100), 97 (10), 95 (8), 92 (9), 91 (48), 85 (14), 84 (6), 83 (14), 81 (10), 77 (19), 75 (13), 73 (41), 71 (18), 70 (12), 69 (23), 67 (6), 66 (6), 65 (7), 59 (6), 57 (34), 56 (12), 55 (22), 53 (5), 43 (27), 41 (21). HRMS (EI) calcd. for C₃₄H₄₃O₇NSSi-CH₃: 622.2295; found: 622.2284. Anal. calcd. for C₃₄H₄₃O₇NSSi: C 64.02, H 6.79; found: C 63.82, H 6.94.

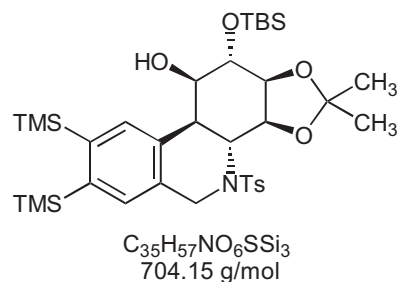
(3aS,3bR,9bR,10R,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-10-phenylcarboxyloxy-11-(*tert*-butyldimethylsilyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (31)



To a solution of CpCo(CO)₂ (5 μ L) in BTMSA (12 mL) were added dropwise with a syringe pump bisacetylene **30** (324 mg, 0.51 mmol) and CpCo(CO)₂ (5 μ L) dissolved in xylene (2 mL) and BTMSA (8 mL) at 140 °C over 30 h. During this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 5 μ L after 5 h and 3 μ L after 20 and 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, 9:1). The cyclotrimerized product **31** was isolated as crystalline foam in 83% yield (341 mg, 0.42 mmol); mp 97 °C. $[\alpha]_D^{22} +17.6$ (c 0.65, CHCl₃). R_f 0.60 (hexanes - ethyl acetate, 3:1). IR (CHCl₃, cm⁻¹): 2956, 2930, 2857, 1724, 1601, 1511, 1452, 1348, 1267, 1251, 1219, 1160, 1109, 957, 839, 757, 712, 670, 627, 560, 536, 515. ¹H NMR (300 MHz, CDCl₃, ppm) δ : 8.15 (d, J = 7.6 Hz, 2H), 7.73 (m, 1H), 7.58 (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)₃, 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), 113 (8), 112 (8), 111 (18), 110 (7), 109 (13), 106 (6), 105 (55), 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 C₄₂H₆₁O₇NSSi₃-C(CH₃)₃: 750.2772; found: 750.2772.

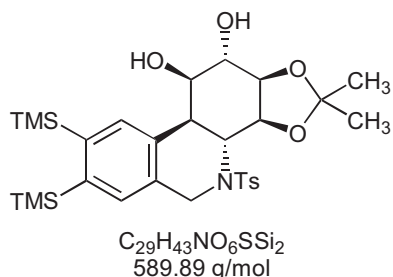
(3aS,3bR,9bR,10R,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-11-(*tert*-butyldimethylsilyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridin-10-ol (32)



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. $[\alpha]_D^{22} +14.2$ (c 0.60, CH₂Cl₂). R_f 0.40 (hexanes - ethyl acetate, 3:1). IR (CH₂Cl₂, cm⁻¹): 3516, 2986, 2954, 2931, 2898, 2859, 2253, 1912, 1738, 1599, 1553, 1495, 1471, 1463, 1455, 1407, 1383, 1371, 1361, 1346, 1308, 1250, 1220, 1161, 1122, 1091, 1007, 977, 948, 910, 858, 839, 811, 780, 756, 734, 700, 675, 656, 628, 605, 577, 559, 540, 513, 472. ¹H NMR (300 MHz, CDCl₃, ppm) δ : 7.36 (d, J = 8.1 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, J_1 = 75.0 Hz, J_2 = 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, 73.5, 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), 648 (10), 647 (18), 646 (32), 588 (7), 550 (11), 549 (22), 548 (50), 491 (9), 490 (14), 476 (5), 460 (9), 459

(14), 458 (33), 457 (34), 433 (8), 432 (9), 430 (10), 428 (6), 414 (7), 385 (5), 316 (6), 315 (7), 304 (6), 303 (7), 302 (5), 276 (8), 275 (15), 274 (24), 258 (5), 243 (5), 202 (8), 159 (14), 149 (10), 139 (9), 131 (10), 129 (11), 124 (9), 123 (6), 121 (6), 119 (7), 117 (8), 115 (6), 105 (10), 101 (7), 100 (7), 98 (5), 97 (6), 92 (8), 91 (21), 88 (9), 86 (45), 85 (10), 84 (69), 82 (6), 81 (11), 77 (9), 75 (35), 74 (13), 73 (100), 71 (6), 70 (5), 69 (10), 59 (11), 58 (6), 57 (11), 56 (8), 55 (10), 51 (6), 49 (9), 47 (18), 45 (9), 43 (24), 41 (15). HRMS (EI) calcd. for $C_{35}H_{57}O_6N_3Si_3-CH_3$: 688.2980; found: 688.3006. Anal. calcd. for $C_{35}H_{57}O_6N_3Si_3$: C 59.70, H 8.16; found: C 59.36, H 7.83.

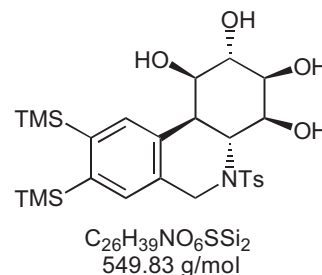
(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridin-10,11-diol (33)



To a solution of TBS-protected alcohol **32** (49 mg, 0.07 mmol) in 0.1 mL THF was added 84 μ L of a 1.0 mol/L solution of TBAF in THF. The reaction was stirred for 10 min at room temperature, quenched with NH_4Cl (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 $MgSO_4$ and filtration, the solvent was removed under vacuum and the residue was purified by column chromatography (pentane – ethyl ether, 3:1). The deprotected diol **33** was isolated as crystalline foam in 85% yield (35 mg, 0.06 mmol); mp 91 °C. $[\alpha]_D^{22} +33.7$ (c 0.39, CH_2Cl_2). R_f 0.57 (hexanes – ethyl acetate, 1:2). IR (CH_2Cl_2 , cm^{-1}): 3469, 2987, 2956, 2931, 2253, 1771, 1725, 1634, 1599, 1495, 1453, 1384, 1376, 1342, 1307, 1250, 1221, 1159, 1121, 1091, 1058, 974, 911, 872, 856, 840, 811, 790, 734, 675, 650, 626, 578, 561, 542. 1H NMR (300 MHz, $CDCl_3$, 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, $J_1 = 8.7$ Hz, $J_2 = 6.0$ Hz, 1H), 4.45 (m, 3H), 4.28 (t, $J = 5.4$ Hz, 1H), 4.18 (m, 1H), 4.07 (dd, $J_1 = 12.0$ Hz, $J_2 = 8.7$ Hz, 1H), 2.88 (dd, $J_1 = 12.0$ Hz, $J_2 = 2.4$ 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, 9H), 0.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, 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 ($M^+ - CH_3$, 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 $C_{29}H_{43}O_6N_3Si_2$: 589.2350; found: 589.2322. Anal. calcd. for $C_{29}H_{43}O_6N_3Si_2$: C 59.05, H 7.35; found: C 58.72, H 6.92.

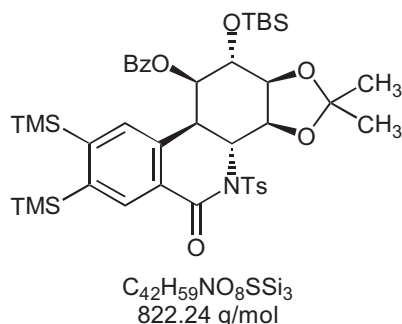
(1*S*,2*S*,3*S*,4*S*,4a*R*,10b*R*)-5-(4-Methylphenylsulfonyl)-8,9-di(trimethylsilyl)-1,2,3,4,4a,5,6,10b-octahydro-1,2,3,4-phenanthridinetetraol (34)



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 50WX8-100 ion exchange resin. The reaction was heated for 4 h at 70 °C, dried by addition of $MgSO_4$, and filtered. The solvent was removed under vacuum and the residue was diluted in $CHCl_3$ 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). $[\alpha]_D^{22} +23.9$ (c 0.61, CH_2Cl_2). R_f 0.44 (hexanes – ethyl acetate, 1:2). IR (CH_2Cl_2 , cm^{-1}): 3410, 2954, 2926, 2902, 2253, 1793, 1646, 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, $CDCl_3$, 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), 4.69 (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). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 145.5, 143.0, 143.0, 134.7, 134.3, 133.9, 132.2, 131.3, 128.9, 127.6, 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 ($M^+ - CH_3$, 5), 467 (5), 466 (11), 460 (8), 459 (15), 458 (36), 457 (5), 450 (6), 430 (6), 396 (6), 395 (12), 394 (35), 387 (8), 386 (26), 342 (6), 324 (6), 323 (5), 322 (13), 316 (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 (10), 129 (13), 128 (8), 127 (7), 126 (7), 124 (15), 122 (5), 116 (6), 115 (7), 113 (7), 112 (5), 111 (10), 110 (9), 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), 81 (22), 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 (14), 64 (9), 63 (6), 60 (11), 59 (5), 57 (56), 56 (15), 55 (38), 54

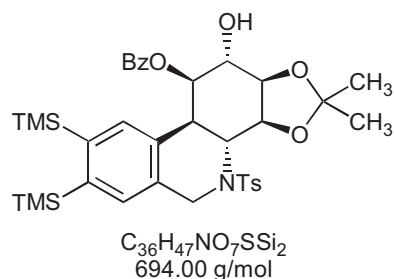
(6), 53 (7), 45 (23), 43 (43), 41 (28). HRMS (EI) calcd. for $C_{26}H_{39}O_6N_2Si_2$: 549.2037; found: 549.2031.

(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10-phenylcarbonyloxy-11-(*tert*-butyldimethylsilyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (35)



To a suspension of tosylamide **31** (20 mg, 0.02 mmol) in $CH_3CN-CCl_4-H_2O$ (2:2:3, 0.5 mL) were added $NaIO_4$ (22 mg, 0.10 mmol) and a catalytic amount of $RuCl_3 \cdot H_2O$. After 3 h, $NaIO_4$ (15 mg) and another catalytic amount of $RuCl_3 \cdot H_2O$ were added. The reaction mixture was stirred at room temperature overnight. After another addition of $NaIO_4$ (15 mg) and another catalytic amount of $RuCl_3 \cdot H_2O$ the next day, the starting material was fully converted. The heterogeneous reaction was diluted with CH_2Cl_2 (25 mL) and extracted with water. The organic phase was dried with Na_2SO_4 , 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). $[\alpha]_D^{22} -97.8$ (*c* 0.09, CH_2Cl_2). R_f 0.63 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, 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, $CDCl_3$, 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, 21H). MS (EI) m/z (relative intensity): 764 ($M^+ - C(CH_3)_3$, 4), 610 (7), 445 (5), 432 (6), 431 (11), 430 (25), 422 (5), 421 (12), 358 (6), 356 (9), 332 (10), 331 (28), 307 (9), 302 (7), 217 (5), 215 (7), 189 (8), 181 (6), 180 (11), 179 (43), 169 (6), 167 (10), 165 (5), 155 (8), 151 (7), 150 (8), 141 (9), 140 (7), 139 (11), 137 (8), 135 (10), 129 (8), 127 (8), 126 (6), 125 (11), 124 (11), 123 (16), 122 (9), 121 (20), 119 (24), 117 (9), 113 (9), 112 (10), 111 (21), 110 (8), 109 (16), 107 (7), 106 (10), 105 (100), 100 (7), 99 (13), 98 (16), 97 (38), 96 (13), 95 (25), 93 (8), 92 (11), 91 (35), 89 (6), 88 (98), 87 (12), 86 (37), 85 (55), 84 (44), 83 (46), 82 (36), 81 (32), 80 (6), 79 (9), 78 (5), 77 (27), 76 (6), 75 (14), 74 (10), 73 (73), 72 (11), 71 (65), 70 (44), 69 (71), 68 (14), 67 (20), 65 (10). HRMS (EI) calcd. for $C_{42}H_{59}O_8N_2Si_3-C(CH_3)_3$: 764.2565; found: 764.2597. HRMS (EI) calcd. for $C_{42}H_{59}O_8N_2Si_3-CH_3$: 806.3034; found: 806.3073.

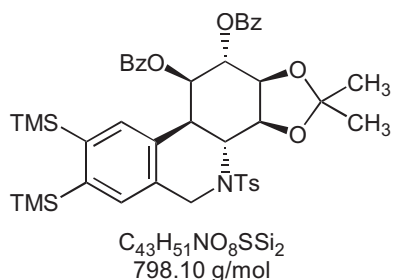
(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-11-Hydroxy-2,2-dimethyl-4-(4-methylphenylsulfonyl)-10-phenylcarbonyloxy-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (36)



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 H_2O and H_2SO_4 were added. The resulting mixture was stirred for 1.5 h and then quenched with satd. aq. $NaHCO_3$ (30 mL) and diluted with CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 , 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. $[\alpha]_D^{27} +63.7$ (*c* 1.00, CH_2Cl_2). R_f 0.38 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2 , cm^{-1}): 3019, 2954, 2401, 1719, 1602, 1494, 1452, 1384, 1346, 1318, 1269, 1250, 1216, 1159, 1115, 1091, 1070, 955, 876, 841, 810, 757, 714, 669, 627, 564, 456. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.92 (d, $J = 8.1$ Hz, 2H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.32 (d, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 7.8$ Hz, 2H), 6.59 (d, $J = 8.1$ Hz, 2H), 5.87 (m, 1H), 4.66 (m, 2H), 4.35 (m, 4H), 3.04 (m, 2H), 2.10 (s, 3H), 1.71 (s, 3H), 1.40 (s, 3H), 0.28 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 166.8, 146.0, 143.9, 142.2, 137.2, 134.8, 133.7, 132.8, 132.4, 130.8, 129.9, 128.8, 128.7, 127.7, 109.8, 78.3, 76.9, 73.0, 71.0, 56.7, 47.6, 37.0, 29.9, 28.1, 25.9, 21.6, 1.9, 1.8. MS (EI) m/z (relative intensity): 693 (2), 484 (8), 472 (9), 471 (23), 317 (12), 316 (37), 285 (5), 169 (20), 155 (6), 149 (8), 147 (6), 139 (5), 123 (8), 122 (44), 121 (5), 119 (14), 111 (6), 106 (7), 105 (74), 97 (10), 95 (7), 91 (22), 88 (11), 86 (63), 85 (12), 84 (100), 83 (11), 82 (9), 81 (10), 78 (6), 77 (44), 75 (9), 74 (10), 73 (56), 71 (12), 70 (7), 69 (26), 67 (7), 65 (6), 60 (6), 59 (8), 57 (21), 56 (7), 55 (19), 52 (5), 51 (25), 50 (13), 49 (21), 47 (25), 45 (12), 44 (8), 43 (34), 42 (6), 41 (18). HRMS (EI) calcd. for $C_{36}H_{47}O_7N_2Si_2$: 693.9979; found: 693.2603. Anal. calcd. for $C_{36}H_{47}O_7N_2Si_2$: C 62.30, H 6.83; found: C 62.18, H 6.70.

(3a*S*,3b*R*,9b*R*,10*R*,11*S*,11a*S*)-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]dioxolo[4,5-*c*]phenanthridine (37)

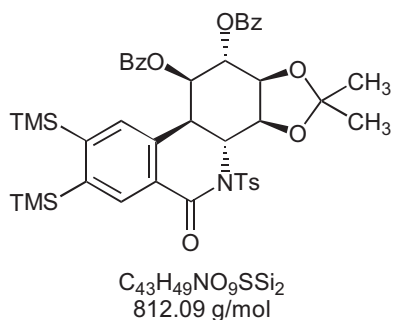
To a solution of of alcohol **36** (142 mg, 0.21 mmol) in pyridine (1 mL) was added benzoyl chloride (35 μ L,



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 × 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]_D²⁵ -12.7 (*c* 1.39, CH₂Cl₂). *R*_f 0.62 (hexanes – ethyl acetate, 2:1). IR (CHCl₃, cm⁻¹) *v*: 3020, 2954, 1726, 1602, 1585, 1493, 1452, 1407, 1384, 1373, 1349, 1316, 1249, 1218, 1170, 1159, 1093, 1070, 1027, 983, 954, 858, 841, 811, 711, 670, 627, 578, 562, 550, 532, 514, 462. ¹H NMR (300 MHz, CDCl₃, ppm) δ : 8.10 (m, 4H), 7.59 (m, 2H), 7.48 (m, 4H), 7.25 (m, 4H), 6.45 (d, *J* = 8.1 Hz, 2H), 6.21 (s, 1H), 5.74 (t, *J* = 2.4 Hz, 1H), 4.77 (d, *J* = 16.5 Hz, 1H), 4.71 (dd, *J*₁ = 5.4 Hz, *J*₂ = 10.2 Hz, 1H), 4.50 (m, 2H), 4.34 (d, *J* = 16.2 Hz, 1H), 3.04 (d, *J* = 11.7 Hz, 1H), 2.05 (s, 3H), 1.84 (s, 3H), 1.47 (s, 3H), 0.31 (s, 9H), 0.20 (s, 9H). ¹³C NMR (75 MHz, CDCl₃, ppm) δ : 165.1, 164.3, 146.3, 144.0, 141.9, 136.6, 134.6, 133.6, 133.4, 132.6, 131.9, 130.3, 130.1, 129.8, 129.7, 128.8, 128.5, 128.4, 128.4, 128.3, 127.4, 109.8, 76.3, 70.0, 68.3, 56.1, 47.4, 38.0, 27.9, 25.9, 21.3, 1.7, 1.6. MS (EI) *m/z* (relative intensity): 798 (M⁺, 4), 797 (6), 642 (6), 476 (7), 340 (7), 179 (5), 149 (5), 123 (6), 122 (31), 106 (8), 105 (100), 97 (8), 95 (5), 91 (10), 84 (6), 83 (9), 77 (37), 74 (6), 73 (23), 71 (10), 70 (5), 69 (10), 67 (6). HRMS (EI) calcd. for C₄₃H₅₁O₈NSSi₂: 797.2874; found: 797.2863. Anal. calcd. for C₄₃H₅₁O₈NSSi₂: C 64.71, H 6.44; found: C 64.71, H 6.50.

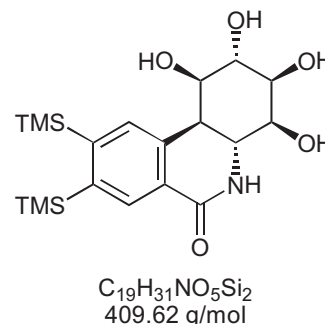
(3aS,3bR,9bR,10R,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10,11-di(phenylcarbonyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-c]phenanthridine (38)

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]_D²³ -72.5 (*c* 0.65, CH₂Cl₂). *R*_f 0.74 (hexanes – ethyl acetate, 2:1). IR (CH₂Cl₂, cm⁻¹) *v*: 3057, 2956, 2927, 2856, 2306, 1968, 1729, 1698, 1600, 1582, 1494, 1452, 1365, 1315, 1266, 1221, 1176, 1093, 1070, 1027, 955, 857, 843, 740, 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* = 3.3 Hz, 1H), 5.82 (t, *J* = 3.6 Hz, 1H), 5.70 (dd, *J*₁ = 5.7 Hz, *J*₂ = 8.4 Hz, 1H), 4.69 (dd, *J*₁ = 8.7 Hz, *J*₂ = 12.6 Hz, 1H), 4.52 (m, 1H), 3.94 (dd, *J*₁ = 3.3 Hz, *J*₂ = 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), 355 (6), 331 (6), 179 (6), 122 (5), 106 (8), 105 (100), 97 (7), 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.

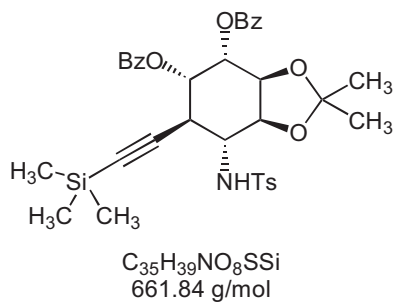
(1R,2S,3S,4S,4aR,10bR)-1,2,3,4-Tetrahydroxy-8,9-di(trimethylsilyl)-1,2,3,4,4a,5,6,10b-octahydro-6-phenanthridinone (39)



To a solution 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 μ L), the reaction mixture was stirred for 20 min. The solution was quenched with satd. aq. NH_4Cl and extracted with CH_2Cl_2 (6 \times 10 mL). The combined organic phases were dried over MgSO_4 , filtered, and the organic 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 (CHCl_3 –MeOH, 6:1) afforded tetraol **39** (5 mg, 0.01 mmol, 25% over three steps); mp 213 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{23} +60.5$ (*c* 0.15, MeOH). R_f 0.38 (CHCl_3 –MeOH, 6:1). IR (CHCl_3 , cm^{-1}) ν : 3385, 2953, 2926, 1705, 1652, 1600, 1586, 1447, 1410, 1375, 1318, 1250, 1217, 1155, 1128, 1093, 1055, 955, 857, 838, 757, 667, 630, 572, 549. ^1H NMR (300 MHz, CD_3OD , ppm) δ : 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). ^{13}C NMR (75 MHz, CDCl_3 , ppm) δ : 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 ($[\text{M} + \text{formate}]^-$, 72), 444 ($[\text{M} + \text{Cl}]^-$, 100), 408 ($[\text{M} - \text{H}]^-$, 2), 394 (7), 311 (5), 265 (8), 171 (17), 111 (7), 89 (12). HRMS (ESI) calcd. for $\text{C}_{42}\text{H}_{61}\text{O}_7\text{NSSi}_3 + \text{Cl}^-$: 444.1429; found: 444.1429.

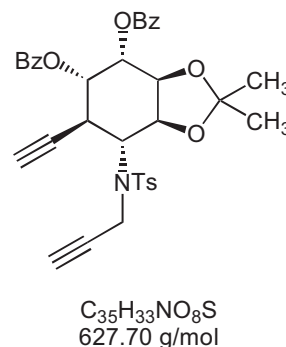
(3aS,4S,5S,6R,7R,7aS)-2,2-Dimethyl-7-(4-methylphenylsulfonamido)-4,5-di(phenylcarbonyloxy)-6-(2-trimethylsilyl-1-ethynyl)perhydro-1,3-benzodioxole (40)



To a solution of diol **24** (721 mg, 1.59 mmol) in pyridine (5 mL) was added benzoyl chloride (0.44 mL, 3.82 mmol) at 0 $^\circ\text{C}$. The ice bath was removed and the reaction mixture was stirred for 1.5 h at room temperature. The reaction was quenched with 10 drops of MeOH, diluted with ethyl acetate (150 mL), and washed with 1.0 mol/L HCl (3 \times 20 mL), water (20 mL), and brine (20 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 6:1 to 3:1) afforded dibenzoate **40** (840 mg, 1.27 mmol, 80%) as white crystals; mp 149 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{23} -99.9$ (*c* 4.50, CH_2Cl_2). R_f 0.71 (hexanes – ethyl acetate, 2:1). IR (CDCl_3 , cm^{-1}) ν : 3673, 3264, 3066, 3034, 2988, 2961, 2938, 2901, 2255, 2183, 1966, 1911, 1728, 1601, 1585, 1493, 1452, 1384, 1374, 1329, 1316, 1274, 1248, 1222, 1162, 1094, 1070, 1026, 1003, 910, 848,

814, 792, 734, 711, 686, 662, 650, 575, 548, 512, 466. ^1H NMR (300 MHz, CDCl_3 , 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, $J_1 = 2.7$ Hz, $J_2 = 4.2$ Hz, 1H), 5.68 (dd, $J_1 = 2.7$ Hz, $J_2 = 8.1$ Hz, 1H), 5.04 (d, $J = 7.5$, 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). ^{13}C NMR (75 MHz, CDCl_3 , ppm) δ : 165.3, 165.3, 143.6, 138.8, 133.9, 133.7, 130.1, 130.1, 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 ($\text{M}^+ - \text{CH}_3$, 3), 282 (6), 214 (11), 155 (7), 122 (9), 106 (10), 105 (100), 91 (15), 77 (21), 73 (8), 69 (9), 57 (6), 55 (6), 43 (11), 41 (6). HRMS (EI) calcd. for $\text{C}_{35}\text{H}_{39}\text{O}_8\text{NSSi}$: 661.2166; found: 661.2158. Anal. calcd. for $\text{C}_{35}\text{H}_{39}\text{O}_8\text{NSSi}$: C 63.52, H 5.94; found: C 63.97, H 5.95.

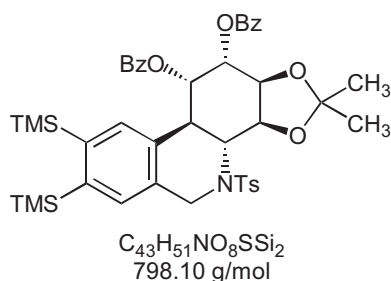
(3aS,4S,5S,6R,7R,7aS)-6-(1-Ethynyl)-2,2-dimethyl-7-[4-methylphenyl(propynyl)sulfonamido]-4,5-di(phenylcarbonyloxy)perhydro-1,3-benzodioxole (41)



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. NH_4Cl (50 mL), and extracted with ethyl acetate (3 \times 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated at 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 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 $^\circ\text{C}$ under argon. The reaction mixture was allowed to warm up to 0 $^\circ\text{C}$ over a period of 20 min and was further stirred for 10 min at this temperature. Propargyl bromide (422 mg, 3.54 mmol) and $(n\text{Bu})_4\text{NI}$ (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. NH_4Cl (40 mL) and extracted with ethyl acetate (4 \times 40 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO_4 , and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:2) afforded tosylamide **41** (419 mg, 0.67 mmol, 94%; 71% over two steps) as crystalline foam; mp 86 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{23} -99.0$ (*c* 1.40, CH_2Cl_2). R_f 0.29 (hexanes – ethyl acetate, 3:1). IR (CH_2Cl_2 , cm^{-1}) ν : 3300, 3064, 2988, 2939, 2593, 2126, 1918, 1732, 1602, 1586, 1494, 1452, 1386, 1374, 1352,

1328, 1274, 1247, 1222, 1157, 1097, 1071, 1037, 1003, 921, 894, 854, 817, 736, 710, 667, 578, 564, 545, 526, 460. ^1H NMR (300 MHz, CDCl_3 , ppm) δ : 8.04 (d, $J = 7.5$ Hz, 2H), 7.92 (m, 4H), 7.52 (m, 1H), 7.43 (m, 3H), 7.30 (m, 4H), 5.95 (m, 1H), 5.70 (dd, $J_1 = 2.1$ Hz, $J_2 = 9.6$ Hz, 1H), 4.99 (dd, $J_1 = 5.7$ Hz, $J_2 = 8.7$ Hz, 1H), 4.40 (m, 1H), 4.22 (m, 3H), 4.00 (m, 1H), 2.38 (s, 3H), 2.22 (s, 1H), 2.05 (d, $J = 1.5$ Hz, 1H), 1.65 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3 , ppm) δ : 165.0, 164.8, 143.6, 137.2, 133.5, 133.1, 129.8, 129.7, 129.3, 129.0, 128.5, 128.3, 128.0, 110.6, 79.9, 78.1, 75.0, 75.0, 74.2, 73.3, 71.3, 68.5, 62.6, 36.5, 36.4, 33.2, 28.0, 26.0, 21.5. MS (EI) m/z (relative intensity): 612 ($\text{M}^+ - \text{CH}_3$, 1), 472 (11), 414 (5), 355 (7), 246 (5), 232 (5), 214 (8), 190 (16), 189 (97), 173 (7), 171 (6), 170 (7), 155 (7), 149 (14), 139 (8), 137 (11), 136 (5), 129 (5), 123 (7), 122 (9), 121 (9), 119 (5), 106 (11), 105 (100), 97 (7), 95 (8), 92 (9), 91 (24), 85 (7), 83 (9), 82 (6), 81 (26), 78 (6), 77 (21), 73 (11), 71 (12), 70 (6), 69 (61), 68 (8), 67 (7), 65 (7), 60 (10), 59 (5), 57 (23), 56 (9), 55 (19), 45 (8), 43 (32), 41 (24), 40 (9), 39 (10). HRMS (EI) calcd. for $\text{C}_{35}\text{H}_{33}\text{O}_8\text{NS-CH}_3$: 612.1692; found: 612.1682.

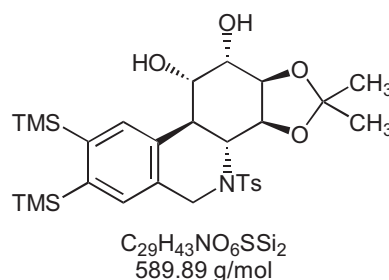
(3aS,3bR,9bR,10S,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-10,11-di(phenylcarboxyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-c]phenanthridine (42)



To a solution of $\text{CpCo}(\text{CO})_2$ (5 μL) in BTMSA (12 mL) bisacetylene **41** (370 mg, 0.59 mmol), $\text{CpCo}(\text{CO})_2$ (5 μL) dissolved in xylene (2 mL), and BTMSA (8 mL) were added dropwise with a syringe pump at 140 $^\circ\text{C}$ over 30 h. During this slow addition, extra catalyst 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, 9:1). The cyclotrimerized product **42** was isolated as crystalline foam in 87% yield (407 mg, 0.51 mmol); mp 131 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{23} +43.1$ (c 0.75, CH_2Cl_2). R_f 0.37 (hexanes – ethyl acetate, 3:1). IR (CDCl_3 , cm^{-1}) ν : 3065, 3034, 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, CDCl_3 , 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, $J_1 = 5.4$ Hz, $J_2 = 8.4$ Hz, 1H), 5.70 (dd, $J_1 = 5.1$ Hz, $J_2 = 9.3$ Hz, 1H), 4.98 (t, $J = 7.5$ Hz, 1H), 4.76 (dd, $J_1 = 7.2$ Hz,

$J_2 = 9.0$ Hz, 1H), 4.59 (dd, $J_1 = 16.5$ Hz, $J_2 = 60.0$ Hz, 2H), 4.03 (dd, $J_1 = 8.4$ Hz, $J_2 = 12.6$ Hz, 1H), 3.28 (dd, $J_1 = 8.7$ Hz, $J_2 = 12.6$ Hz, 1H), 2.31 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H), 0.39 (s, 9H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3 , 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, 69.7, 69.5, 58.1, 48.0, 39.4, 27.5, 25.1, 21.4, 1.8, 1.6. 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), 111 (7), 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) calcd. for $\text{C}_{43}\text{H}_{51}\text{O}_8\text{NSSi}_2$: 797.2874; found: 797.2885.

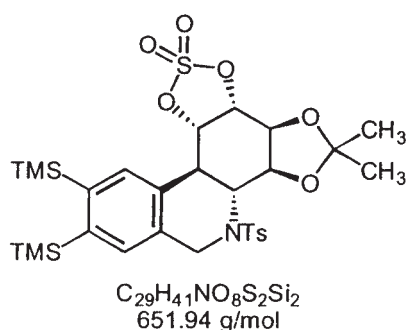
(3aS,3bR,9bR,10S,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-c]phenanthridine-10,11-diol (43)



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 NH_4Cl and extracted with CH_2Cl_2 . The organic solvents were dried over Na_2SO_4 and removed under high vacuum. The residue was purified by column chromatography (hexanes – ethyl acetate, 3:1 to 1:1). The diol **43** was isolated as foamy crystals in 99% yield (73 mg, 0.12 mmol); mp 121 $^\circ\text{C}$. $[\alpha]_{\text{D}}^{25} +35.5$ (c 1.50, CH_2Cl_2). R_f 0.18 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2 , cm^{-1}) ν : 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, CDCl_3 , 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, $J_1 = 8.1$ Hz, $J_2 = 12.3$ Hz, 1H), 2.29 (s, 3H), 1.54 (s, 3H), 1.33 (s, 3H), 0.33 (s, 9H), 0.32 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3 , 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 ($\text{M}^+ - \text{CH}_3$, 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

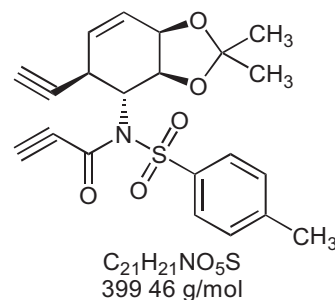
(79), 155 (30), 150 (15), 149 (19), 147 (27), 139 (15), 133 (10), 131 (13), 129 (17), 125 (14), 124 (14), 123 (14), 119 (45), 111 (21), 109 (21), 105 (15), 97 (38), 96 (17), 95 (28), 92 (12), 91 (65), 85 (23), 84 (14), 83 (32), 82 (17), 81 (31), 79 (14), 77 (14), 73 (51), 71 (33), 70 (21), 69 (75), 68 (14), 67 (22), 65 (15), 59 (12), 57 (55), 56 (19), 55 (61), 53 (11), 45 (15), 44 (15), 43 (100), 42 (15), 41 (54). HRMS (EI) calcd. for $C_{29}H_{43}O_6N_2Si_2-CH_3$: 574.2115; found: 574.2099. Anal. calcd. for $C_{29}H_{43}O_6N_2Si_2$: C 59.05, H 7.35; found: C 58.77, H 7.37.

(3aS,3bR,6aS,6bR,12bR,12cS)-5,5-Dimethyl-7-(4-methylphenylsulfonyl)-10,11-di(trimethylsilyl)-3a,3b,6a,6b,7,8,12b,12c-octahydro-1,3,4,6-tetraoxa-2-thia-7-azadicyclopenta[*a,c*]phenanthrene-2,2-dioxide (44)



To a solution of diol **43** (494 mg, 0.84 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (5 mL) at 0 °C. The solution was stirred for 10 min and SO_2Cl_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_2Cl_2 (15 mL) were added over a period of 2 h for full conversion (TLC). The reaction mixture was diluted with CH_2Cl_2 (30 mL), quenched with satd. aq. NH_4Cl (50 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic phase was dried over Na_2SO_4 , filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes – ethyl acetate, 5:1) afforded cyclic sulfate **44** (383 mg, 0.59 mmol, 70%); mp 110 °C. $[\alpha]_D^{26} +24.6$ (c 0.40, CH_2Cl_2). R_f 0.66 (hexanes – ethyl acetate, 2:1). IR ($CHCl_3$, cm^{-1}): 3462, 3021, 2963, 2870, 1732, 1597, 1456, 1385, 1355, 1308, 1249, 1213, 1182, 1162, 1127, 1090, 1056, 995, 919, 883, 840, 795, 756, 669, 627, 562. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.42 (m, 3H), 7.28 (s, 1H), 7.00 (d, $J = 8.1$ Hz, 2H), 5.35 (dd, $J_1 = 7.2$ Hz, $J_2 = 9.6$ Hz, 1H), 5.04 (t, $J = 7.2$ Hz, 1H), 4.75 (m, 2H), 4.63 (d, $J = 16.2$ Hz, 1H), 4.27 (d, $J = 16.2$ Hz, 1H), 3.69 (dd, $J_1 = 8.1$ Hz, $J_2 = 12.3$ Hz, 1H), 2.99 (t, $J = 10.8$ Hz, 1H), 2.30 (s, 3H), 1.57 (s, 3H), 1.34 (s, 3H), 0.34 (s, 9H), 0.33 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 145.0, 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 $C_{29}H_{41}O_8NS_2Si_2-CH_3$: 636.1577; found: 636.1556. Anal. calcd. for $C_{29}H_{41}O_8NS_2Si_2$: C 53.43, H 6.34; found: C 53.52, H 6.47.

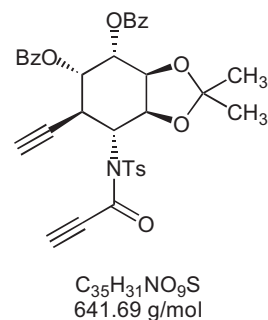
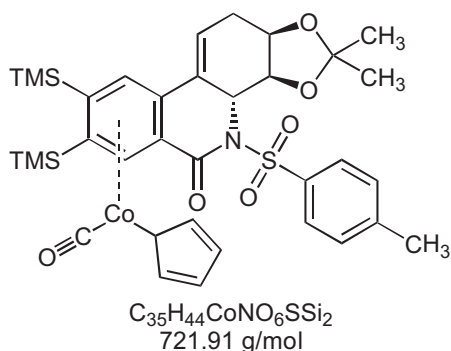
(3aS,4R,5R,7aR)-5-(1-Ethynyl)-2,2-dimethyl-4-[4-methylphenyl(propioloyl)sulfonamido]-3a,4,5,7a-tetrahydro-1,3-benzodioxolone (45)



To a solution of acetonide **18** (250 mg, 0.60 mmol) in THF (5 mL) 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 addition of satd. aq. NH_4Cl (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 $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography of the residue (hexanes – ethyl acetate, 3:1) afforded a bisacetylene (128 mg, 0.27 mmol, 46%) as a slightly yellow foam. To a solution of this bisacetylene (150 mg, 0.32 mmol) in acetonitrile (5 mL) was added TBAT (340 mg, 0.63 mmol). The reaction mixture was stirred at room temperature for 30 h, then diluted with 30 mL ethyl acetate, and washed with satd. aq. NH_4Cl (3 × 10 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 the bisacetylene **45** (77 mg, 0.19 mmol, 61%) as a colorless oil. $[\alpha]_D^{21} +30.3$ (c 0.25, CH_2Cl_2). R_f 0.40 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}): 3298, 3021, 2989, 2937, 2876, 2591, 2403, 2109, 1917, 1732, 1674, 1597, 1511, 1495, 1485, 1456, 1429, 1399, 1366, 1309, 1270, 1246, 1216, 1189, 1172, 1141, 1120, 1085, 1067, 1027, 1019, 998, 971, 946, 923, 897, 865, 830, 813, 757. 1H NMR (300 MHz, $CDCl_3$, ppm) δ : 7.97 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 9.5$ Hz, 2H), 5.98 (m, 2H), 5.07 (m, 1H), 4.70 (m, 2H), 4.21 (d, $J = 10.4$ Hz, 1H), 3.24 (s, 1H), 2.39 (s, 3H), 2.16 (s, 1H), 1.48 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 153.6, 145.4, 136.0, 132.6, 129.7, 129.2, 123.6, 110.6, 83.0, 81.5, 75.2, 73.4, 72.9, 72.7, 65.4, 32.9, 27.8, 25.8, 21.9. MS (EI) m/z (relative intensity): 384 ($MH^+ - CH_3$, 8), 306 (18), 248 (11), 228 (7), 224 (10), 204 (12), 170 (9), 156 (8), 155 (77), 152 (9), 139 (11), 135 (20), 119 (22), 118 (46), 107 (5). HRMS (EI) calcd. for $C_{21}H_{21}O_5NS-CH_3$: 384.0906; found: 384.0898.

Carbonyl- η^1 -cyclopentadienyl- η^6 -(3aS,3bR,11aR)-2,2-dimethyl-4-(4-methylphenylsulfonyl)-7,8-di(trimethylsilyl)-3a,3b,4,5,11,11a-hexahydro[1,3]dioxolo[4,5-*c*]-phenanthridin-5-onylcobalt (46)

A solution of bisacetylene **45** (165 mg, 0.43 mmol) and $CpCo(CO)_2$ (10 μ L) in BTMSA (10 mL) and xylene (10 mL) was added with a syringe pump to a refluxing solu-



tion of $CpCo(CO)_2$ (10 μ L) 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. $[\alpha]_D^{26} +27.6$ (*c* 0.23, $CHCl_3$). R_f 0.53 (hexanes – ethyl acetate, 3:1). IR ($CHCl_3$, cm^{-1}) ν : 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, $CDCl_3$, 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). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 169.5, 152.6, 144.8, 141.7, 141.0, 140.0, 136.3, 136.1, 135.7, 129.5, 129.1, 128.8, 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), 460 (9), 459 (21), 458 (8), 420 (6), 419 (14), 418 (38), 358 (6), 357 (13), 356 (7), 343 (6), 341 (7), 340 (7), 329 (5), 325 (8), 294 (7), 288 (6), 279 (5), 255 (8), 254 (37), 253 (23), 228 (6), 205 (6), 171 (6), 155 (18), 149 (17), 141 (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) calcd. for $C_{35}H_{44}O_6N_2SSi_2Co-CO$: 693.1811; found: 693.1807.

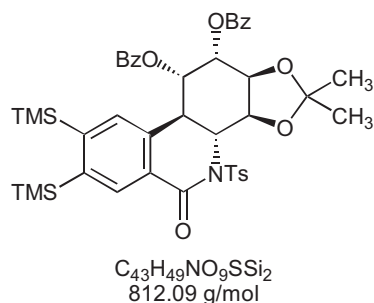
(3aS,4S,5S,6R,7R,7aS)-6-(1-Ethynyl)-2,2-dimethyl-7-[4-methylphenyl(propioloyl)sulfonamido]-4,5-di(phenylcarboxyloxy)perhydro-1,3-benzodioxole (47)

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. NH_4Cl (50 mL), and extracted with ethyl acetate (3 \times 50 mL). The combined organic phases were dried over Na_2SO_4 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 $^{\circ}C$ under argon. The reaction mixture was allowed to warm to 0 $^{\circ}C$ over 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. NH_4Cl (20 mL) and the aqueous phase extracted with ethyl acetate (4 \times 20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, 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 $^{\circ}C$. $[\alpha]_D^{23} -124.6$ (*c* 1.05, CH_2Cl_2). R_f 0.62 (hexanes – ethyl acetate, 2:1). IR (CH_2Cl_2 , cm^{-1}) ν : 3292, 3055, 2987, 2831, 2686, 2522, 2411, 2306, 2113, 1731, 1677, 1602, 1551, 1422, 1363, 1266, 1189, 1173, 1116, 1095, 1071, 1055, 1027, 896, 853, 740, 705, 618, 574, 546. 1H NMR (300 MHz, $CDCl_3$, 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, $J_1 = 2.1$ Hz, $J_2 = 10.2$ 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). ^{13}C NMR (75 MHz, $CDCl_3$, 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, 129.4/129.3, 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 ($M^+ - CH_3$, 1), 122 (9), 119 (5), 105 (47), 91 (8), 88 (19), 86 (100), 84 (100), 77 (14), 64 (16), 53 (15), 51 (11), 49 (31), 48 (6), 47 (37), 44 (7), 43 (17). HRMS (EI) calcd. for $C_{35}H_{31}O_9NS-CH_3$: 626.1485; found: 626.1495.

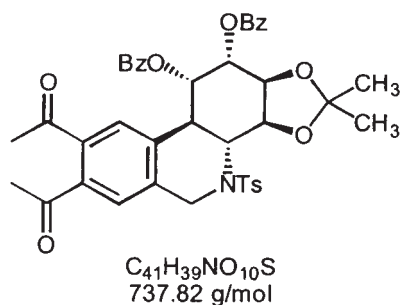
(3aS,3bR,9bR,10S,11S,11aS)-2,2-Dimethyl-4-(4-methylphenylsulfonyl)-5-oxo-10,11-di(phenylcarboxyloxy)-7,8-di(trimethylsilyl)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-c]phenanthridine (48)

To a solution of $CpCo(CO)_2$ (2 μ L) in BTMSA (6 mL), bisacetylene **47** (105 mg, 0.16 mmol) and $CpCo(CO)_2$ (2 μ L) dissolved in xylene (1 mL) and BTMSA (4 mL) were added dropwise with a syringe pump at 140 $^{\circ}C$ over 30 h. During this slow addition, extra catalyst was added directly into the reaction mixture in aliquots: 2 μ L after 5 h and after 20 h, and 1 μ L after 29 h. After 5 h and after 20 h, additional $CpCo(CO)_2$ (2 μ L) was added, and after 29 h, additional $CpCo(CO)_2$ (1 μ L) was added. The reaction mixture was heated under argon for a further 12 h. BTMSA and



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). $[\alpha]_D^{22}$ –20.9 (*c* 0.25, CH_2Cl_2). R_f 0.32 (hexanes – ethyl acetate, 4:1). IR (CH_2Cl_2 , 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, $CDCl_3$, 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, $J_1 = 7.2$ Hz, $J_2 = 10.8$ Hz, 1H), 5.25 (dd, $J_1 = 2.4$ Hz, $J_2 = 7.2$ 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). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ : 166.4, 165.5, 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, 128.4, 126.8, 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 ($M^+ - CH_3$, 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 (6), 67 (8). HRMS (EI) calcd. for $C_{43}H_{49}O_9N_1SSi_2 \cdot CH_3$: 796.2432; found: 796.2399. Anal. calcd. for $C_{43}H_{49}O_9N_1SSi_2$: C 63.60, H 6.08; found: C 63.46, H 6.00.

(3a*S*,3b*R*,9b*R*,10*S*,11*S*,11a*S*)-7,8-Diacetyl-2,2-dimethyl-4-(4-methylphenylsulfonyl)-10,11-di(phenylcarbonyloxy)-3a,3b,4,5,9b,10,11,11a-octahydro[1,3]dioxolo[4,5-*c*]phenanthridine (51**)**



To a solution of 2,5-di(*tert*-butyldimethylsilyloxy)-3-hexyne (1.00 g) in $CpCo(CO)_2$ (5 μ L), bisacetylene **41** (108 mg, 0.17 mmol) and $CpCo(CO)_2$ (5 μ L) dissolved in xylene (5 mL) were added dropwise with a syringe pump at 140 $^{\circ}C$ over 30 h. During and after this slow addition, extra

catalyst was added directly into the reaction mixture in aliquots: 5 μ L 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 ($M^+ - CH_3$, 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. NH_4Cl solution and extracted three times with diethyl ether. The combined organic phases were dried over $MgSO_4$, 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 ($CDCl_3$, cm^{-1}) ν : 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 $MgSO_4$, 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 $^{\circ}C$. $[\alpha]_D^{23}$ +38.6 (*c* 0.06, CH_2Cl_2). R_f 0.48 (hexanes – ethyl acetate, 1:1). IR ($CDCl_3$, cm^{-1}) ν : 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, $CDCl_3$, 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, $J_1 = 4.8$ Hz, $J_2 = 8.6$ Hz, 1H), 5.74 (dd, $J_1 = 4.7$ Hz, $J_2 = 7.9$ Hz, 1H), 5.03 (dd, $J_1 = 6.8$ Hz, $J_2 = 8.8$ 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 (dd, $J_1 = 8.9$ Hz, $J_2 = 12.6$ Hz, 1H), 3.43 (dd, $J_1 = 8.9$ Hz, $J_2 = 12.6$ Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 2.20 (s, 3H), 1.54 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$, 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 $C_{41}H_{39}O_{10}NS$: 737.2295; found: 737.2306.

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