THE STRUCTURE AND ANTIMALARIAL ACTIVITY OF SOME *CIS*-FUSED BICYCLIC 1,2,4-TRIOXANE DERIVATIVES

Charles W. Jefford*, Danielle Jaggi, Shigeo Kohmoto, Géza Timári, Gérald Bernardinelli, Craig J. Canfield*, and Wilbur K. Milhous[⊥]

Department of Organic Chemistry and Laboratory of Crystallography,
University of Geneva
1211 Geneva 4, Switzerland

*Pharmaceutical Systems, Inc., Talent, OR 97540, USA

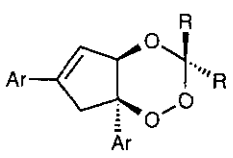
[⊥]Walter Reed Army Institute of Research, Division of Experimental Therapeutics, Washington, DC 20307, USA

Abstract- (4a*RS*,7a*RS*)-4a,7a-Dihydro-3,3-dimethyl-6,7a-diphenyl-7*H*-cyclopenta[1,2-*e*][1,2,4]trioxine (**1**) was converted into its *exo*-5,6-epoxide (**7**) and dichloromethylene (**8**) derivatives. The reaction of (4'a*RS*,7'a*RS*)-6',7'a-bis(4-fluorophenyl)-4'a,7'a-dihydrospiro[cyclopentane-1,3'-7'*H*-cyclopenta[1,2-*e*]-[1,2,4]trioxine] (**3**) with $Pb(OAc)_4$ and *N*-aminophthalimide gave the *exo*-5,6-*N*-phthalimidoimine (**9**). Acid catalysis of **9** afforded the cyclopentenylamino derivative (**10**). Treatment of **3** with Me_3SiN_3 and C_6H_5IO gave mainly the *exo*-5-azidobenzyl dimer (**12**) of C_2 symmetry. A minor isomer was assigned as the *meso*-dimer (**14**). The structure of **12** was determined by X-Ray. The *in vitro* activity of **7**, **8**, **9**, **10** and **11** against *Plasmodium falciparum* was determined and found, with the exception of **8**, to be similar to that of **1** and **3**.

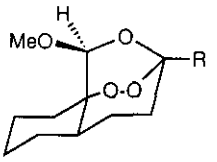
INTRODUCTION

We have shown that simple *cis*-fused bicyclic and tricyclic 1,2,4-trioxanes (**1-5**) exhibit significant antimalarial activity in various *in vitro* and *in vivo* models.[1-4] This finding confirms that much of the molecular architecture and functionality of the lead compound, the tetracyclic sesquiterpene artemisinin (**6**), is redundant and not essential for strong parasiticidal action.[5] Although the diarylcyclopentene trioxanes (**1-3**) have excellent potential as drug candidates, they are neutral molecules displaying poor solubility in aqueous media. As part of our program of study on the chemical and biological properties of polycyclic peroxides, we now describe some selected reactions of the olefinic part of **1** and **3** which are designed to produce usefully functionalized derivatives of improved antimalarial activity without destroying the trioxane entity.

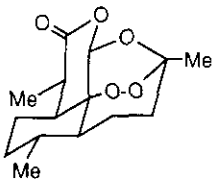
Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday



1 Ar = Ph, R = Me
2 Ar = Ph, RR = $(CH_2)_4$
3 Ar = C_6H_4F-*p*, RR = $(CH_2)_4$



4 R = Me
5 R = Ph



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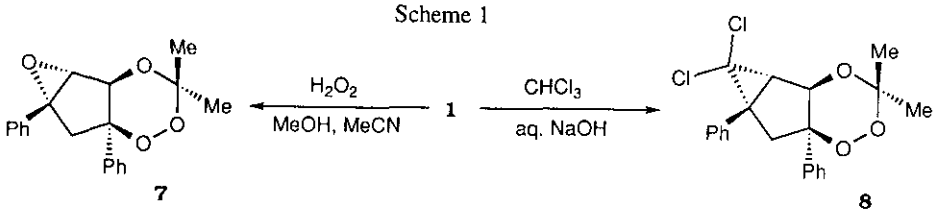
RESULTS AND DISCUSSION

First, the least active trioxane of the cyclopentene series, namely **1**, was submitted to two reactions typical of olefins, epoxidation and cyclopropanation. A solution of **1** in methanol and acetonitrile on treatment with 30% aqueous hydrogen peroxide gave a single product, the epoxide (**7**), in 84% yield (Scheme 1). An equally high yield of the dichlorocarbene adduct (**8**) was obtained when **1** was treated with chloroform and aqueous sodium hydroxide. The *exo* configurations of both adducts follow from the coupling constants of the vicinal protons attached to the C4a,C5 atoms in **7** and **8**. As these have values of almost zero, a dihedral angle of about 90^0 is indicated for the two C-H bonds.

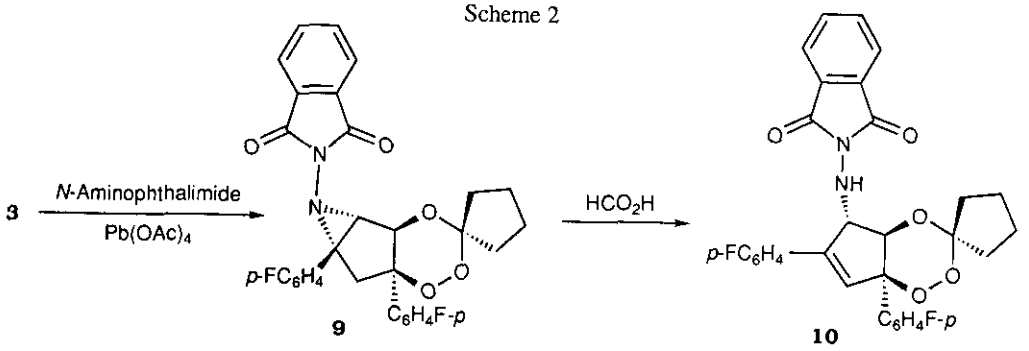
Scheme 1



7 **8**

Next, nitrogen substituents were introduced into **3**, the most active trioxane of the series.[3] The action of *N*-aminophthalimide and lead tetraacetate on **3** was highly effective.[6] The intermediate phthalimidonitrene so generated underwent addition exclusively on the *exo* face of the double bond giving the aziridine derivative (**9**) in 76% yield (Scheme 2). Subsequent rearrangement to the *exo* allylic amino derivative (**10**) was readily accomplished by exposing **9** to formic acid. It is worth noting that the foregoing reactions proceed by the same stereochemical course which had been previously observed for hydroperoxidation with singlet oxygen[7] and for osmium-catalyzed asymmetric dihydroxylation.[8] In all cases, the electrophile in question is directed to the convex rather than the concave side of the *cis*-fused cyclopentene entity presumably because it is the least congested of the two. An anomeric effect by the allylic oxygen substituent may also contribute. In all cases, the various reagents used leave the trioxane ring unaffected.

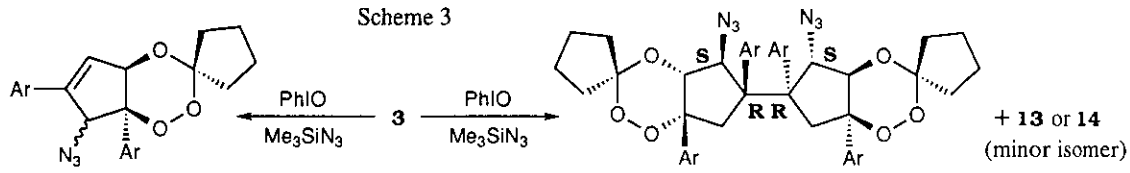
Scheme 2



9 **10**

In view of reports[9] that phenyl iodosobenzene and trimethylsilyl azide effect allylic azidation in certain cyclic tri-isopropylsilyl enol ethers, it seemed likely that **3** would behave similarly. As the spirocyclic attachment and the trioxane ring appear to mimic the bulky siloxy substituent, it was expected that the reagents would attack **3** forming the corresponding allylic azide (**11**) (Scheme 3).

Scheme 3



11 ? Ar = C_6H_4F-*p* **12** (major isomer)

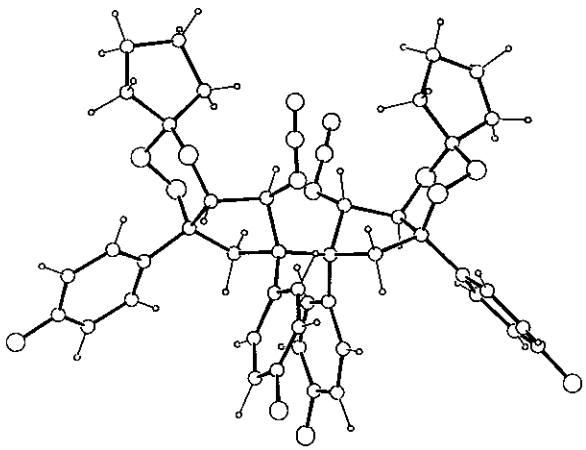


Figure 1. A perspective drawing of the crystal structure of the azido-dimer (**12**).

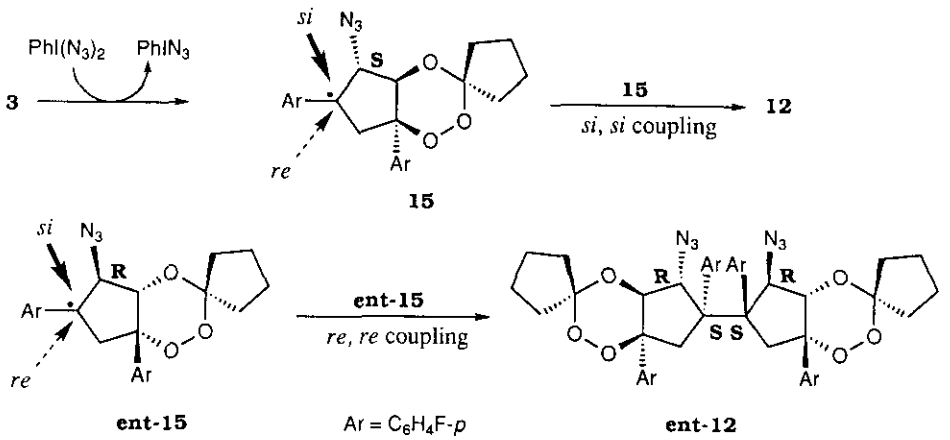
In practice, the outcome was quite different. A 3:1 mixture of just two products of molecular formula $C_{44}H_{40}O_6N_6F_4$ was obtained in 66% yield. Chromatography afforded a pure sample of the major isomer, a crystal of which was analyzed by X-Ray. The structure was identified as the azido dimer (**12**) of C_2 symmetry (Figure 1). Evidently, two radicals of the same configuration have combined. Their origin stems from azide radical arising from the homolysis of phenylazidyliodonium azide produced by the reaction of trimethylsily azide with iodosobenzene (Equation 1).[10] Just like conventional electrophilic reagents, azide radical attacks the least hindered face of the cyclopentene ring of **3** (Scheme 4). The resulting benzyl radical (**15**) then has the option of dimerizing on its enantiotopic faces in four possible ways. Clearly, coupling of two molecules of **15** on the *si* faces is the main event, giving **12**. A molecular model indicates that the steric impediment presented by the *syn* diaxially disposed aryl and azide substituents outweighs that of the flexible *cis*-fused trioxane ring. In other words, the *re* face of the radical (**15**) is barricaded against attack. The other enantiomer of the racemic mixture, **ent-3**, gives **ent-15** which dimerizes in the same way on the *re* faces of the benzylic radical centers to produce **ent-12**.

The structure of the minor isomer is difficult to assign. However, dimerization of **15** on its *re* face, and inversely of **ent-15** on its *si* face, can be ruled out because of the doubly prohibitive encumbrance which would be encountered. Therefore, **13** and **14** are left as the most likely structures. If **15** couples on its *si*

face with a second molecule of **15** on its sterically hindered *re* face then **13** would be produced (Scheme 5). By the same maneuver, two molecules of **ent-15** would give **ent-13**. However, a far more plausible alternative is the joining of **15** and **ent-15** on their uncluttered and sterically equivalent *si* and *re* faces respectively to furnish the *meso* dimer (**14**).

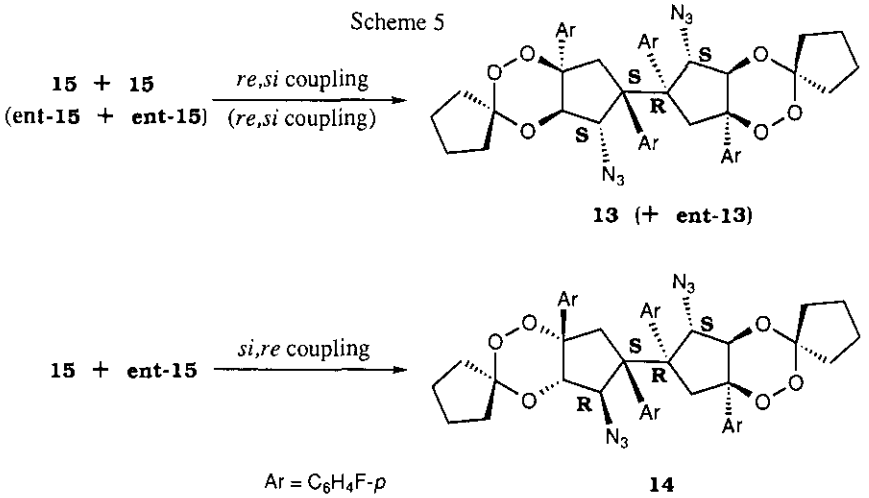
$$PhIO + 2Me_3SiN_3 \longrightarrow PhI(N_3)_2 + Me_3SiOSiMe_3 \quad \text{(Equation 1)}$$

Scheme 4



The important stereochemical finding is that dimerization is diastereoselective. The controlling factor is the ease of access to the radical centers. Radicals of like configuration prefer to couple with each other and do so exclusively on the same, least encumbered, enantiotopic faces. A pair of 5*S* radicals (**15**) joins exclusively on their *si* faces, whereas 5*R* radicals (**ent-15**) select the *re* faces for bond formation. Assuming the minor isomer to be **14**, then its formation can also be rationalized in terms of steric considerations. The combination of radicals of opposite configuration (**15** and **ent-15**), though less favored, occurs exclusively on their equally accessible, opposite enantiotopic faces.

Scheme 5



The oxidation of azide anion to its radical in the presence of olefins has been previously accomplished with a variety of reagents.[11] The radical adds to the double bond to give the most stable C-centered radical which is then usually captured by azide radical or an addend to give the corresponding 1,2-disubstituted alkane. Surprisingly, reports of the dimerization of such azido carbon radicals are rare. A pertinent example is the formation of 1,4-diazido-2,3-diphenylbutane from styrene when treated in an electrolytic cell with sodium azide in acetic acid.[12] Another is the reaction of trimethylsilyl azide and iodosobenzene diacetate with 2,3-dimethylbuta-1,3-diene to give 2,3,5-trimethyl-3,6-diazidomethylhepta-1,5-diene as a mixture of the *E* and *Z* isomers.[13]

Having shown that the cyclopentene ring can be functionalized while preserving the trioxane moiety, the antimalarial activity of the resulting monomeric derivatives (**7**), (**8**), (**9**), and (**10**), together with the parent trioxanes (**1**) and (**3**), and appropriate reference compounds, was examined. Tests were performed *in vitro* against *Plasmodium falciparum* clones by using a standard method.[14] The concentration of the sample which inhibited parasite growth by 50% (IC_{50}) in the Indochina W-2 and Sierra Leone D-6 clones was determined. The W-2 clone is markedly resistant to chloroquine (CLQ), quinine, pyrimethamine, and sulfadoxine, but susceptible to mefloquine. Conversely, the D-6 clone is relatively resistant to mefloquine, but sensitive to chloroquine, quinine, pyrimethamine, and sulfadoxine (Table 1).

Table 1. *In vitro* antimalarial activity of some *cis*-cyclopenteno-1,2,4-trioxane derivatives against *P. falciparum* clones (IC_{50} values in ng/mL)

entry	Trioxane[a)]	Sierra Leone D-6	Indochina W-2
1	**1**	5.9	5.3
2	**7**	8.2	6.6
3	**8**	43.6	49.2
4	**3**	6.6	3.8
5	**9**	10.5	8.9
6	**10**	13.1	10.8
7	CLQ	3.3	54.55
8	Artesunic acid	0.54-0.97	0.45-0.57

[a)] All trioxanes are racemic mixtures

It is immediately noticed that the presence of the epoxide in **7** scarcely alters the activity of the parent dimethyltrioxane (**1**), the IC_{50} values being nearly the same for both clones (Table 1, entries 1 and 2). In contrast, on comparing **1** with **8**, it is seen that cyclopropanation lowers activity (entries 1 and 3). Both the epimino and amino functions in **9** and **10** diminish, but not adversely so, the inherent activity of the parent diaryl-trioxane (**3**) (entries 4, 5 and 6). As has been noted previously, the conventional antimalarial chloroquine is surpassed in effectiveness by the synthetic trioxanes, especially against the critical chloroquine-resistant W-2 clone. Nevertheless the semi-synthetic artesunic acid remains unrivaled in activity.

CONCLUSIONS

The present results demonstrate that epoxidation, epimination, and cyclopropanation of the double bond of the *cis*-fused cyclopenteno-1,2,4-trioxane entity, exemplified by **1** and **3**, occur completely on the *exo* face. Azidation by azide radicals also proceeds *exo*, but leads to dimeric products *via* diastereoselective dimerization of the intermediate benzyl radicals. It is further shown that epoxidation, epimination and amination do not drastically impair the high antimalarial activity of the parent cyclopenteno-trioxanes.

ACKNOWLEDGMENTS

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EXPERIMENTAL PART

1. General. All solvents were either puriss grade (Fluka or Aldrich) or distilled prior to use. Column chromatography: Merck silica gel 60 (230-400 mesh). Mps were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H- and ^{13}C-NMR: Bruker-AMX-400, Bruker-WH-360, Varian-XL-200 spectrometers; chemical shifts (δ) in ppm relative to internal TMS (= 0 ppm), coupling constants (*J*) in Hz; commercial $CDCl_3$ was used without further purification. Elemental analyses were carried out by Dr. H.J. Eder, Microchemistry Service, Institute of Pharmaceutical Chemistry, University of Geneva.

2. Starting materials. (4a*RS*,7a*RS*)-4a,7a-Dihydro-3,3-dimethyl-6,7a-diphenyl-7*H*-cyclopenta[1,2-*e*]-[1,2,4]trioxine (**1**) and (4'a*RS*,7'a*RS*)-6',7'a-bis(4-fluorophenyl)-4'a,7'a-dihydrospiro[cyclopentane-1,3'-7'*H*-cyclopenta[1,2-*e*][1,2,4]trioxine] (**3**) were prepared according to standard procedures.[3,7]

3. (4a*RS*,5*RS*,6*RS*,7a*RS*)-4a,5,6,7a-Tetrahydro-3,3-dimethyl-5,6-epoxy-6,7a-diphenylcyclopenta[1,2-*e*][1,2,4]trioxine (**7**). To a solution of **1** (308 mg, 1.0 mmol) in MeOH (40 mL) was added successively MeCN (15 mL) and 30% aqueous H_2O_2 (12 mL, 0.1 mol). After stirring the resulting mixture for 5 h at rt CH_2Cl_2 (40 mL) was added. The solution was washed successively with water, an aq. solution of Na_2SO_3 (3%), a saturated aq. solution of NaCl, dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue over silica gel (CH_2Cl_2/hexane, 4:1) gave **7** (271 mg, 84%) as colorless crystals. mp: 88-92 °C (recrystallized from hexane). ^{1}H-NMR (360 MHz): at -27 °C, δ 1.27 (br s, 3H, major), 1.62 (br s, 3H, major), 1.75 (br s, 3H, minor), 1.77 (br s, 3H, minor), 2.50 (br d, *J* = 15.0 Hz, 1H, major), 2.85 (br d, *J* = 15.0 Hz, 1H, major), 3.01 (br d, *J* = 15 Hz, 1H, minor), 3.67 (br d, *J* = 15 Hz, 1H, minor), 3.67 (br s, 1H, minor, overlapped), 3.90 (br s, 1H, major), 4.60 (br s, 1H, major), 4.76 (br s, 1H, minor), 7.7-7.2 (m, 10 H). Comparison of the integrals indicates a ratio of 2:1 for the conformers. ^{13}C-NMR (90.6 MHz): at rt, δ (methyl groups only) 22.5 (major), 23.4 (minor), 24.9 (minor), 25.1 (major). Ratio of integrals 5:1. Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06, H 6.22. Found: C 73.84, H 6.24.

4. (4a*RS*,5*RS*,6*RS*,7a*RS*)-4a,5,6,7a-Tetrahydro-3,3-dimethyl-5,6-epi(dichloromethylene)-6,7a-diphenyl-cyclopenta[1,2-*e*][1,2,4]trioxine (**8**). To a solution of **1** (50 mg, 0.16 mmol) and hexadecyltrimethyl-

ammonium bromide (5 mg) in $CHCl_3$ (1 mL) was added a 50% aq. solution of NaOH (0.3 mL). The resulting solution was stirred for 24 h at rt. Next water (10 mL) was added and the mixture was extracted with $CHCl_3$ (10 mL). The organic layer was washed (aq. saturated NaCl) and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed over silica gel (CH_2Cl_2/hexane, 3:2) to give **8** (56.5 mg, 90%). mp: 133-135 °C (recrystallized from ether/pentane). ^{1}H-NMR (360 MHz): δ 1.32 (s, 3H), 1.89 (s, 3H), 2.69 (br d, J = 16.0 Hz, 1H), 2.83 (br d, J = 16.0 Hz, 1H), 2.91 (d, J = 1.0 Hz, 1H), 5.03 (d, J = 1.0 Hz, 1H), 7.3-7.45 (m, 8H), 7.53 (m, 2H). Anal. Calcd for $C_{21}H_{20}O_3Cl_2$: C 64.46, H 5.15, Cl 18.12. Found: C 64.64, H 5.38, Cl 18.05.

5. (4'a*RS*,5*SR*,6*SR*,7'a*RS*)-4'a,5,6,7'a-Tetrahydro-6',7'a-bis(4-fluorophenyl)-5,6-epi-(*N*-phthalimido-imino)spiro[cyclopentane-1,3'-cyclopenta[1,2-*e*][1,2,4]trioxine] (**9**). To a solution of **3** (185 mg, 0.5 mmol) and *N*-aminophthalimide (117 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was added a solution of $Pb(OAc)_4$ (222 mg, 0.5 mmol) in CH_2Cl_2 (1.5 mL) with vigorous stirring during 3 min at rt. Stirring was continued for a further 45 min after which time water (5 mL) was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 3 mL) and the combined organic layers dried ($MgSO_4$) and evaporated. The semi-solid residue was chromatographed on a silica gel column (CH_2Cl_2/hexane 1:1) to give **9** as yellow crystals (228 mg, 76%). mp: 107-109 °C (recrystallized from hexane). ^{1}H-NMR (200 MHz): δ 2.22-1.53 (m, 8H), 2.95 (d, J = 16.0 Hz, lH), 3.20 (d, J = 16.0 Hz, 1H), 4.82 (s, lH), 5.03 (s, 1H), 6.9-7.65 (m, 12H). ^{13}C-NMR (50 MHz): δ 23.3, 24.06, 35.l, 36.5, 52.2, 59.8, 77.2, 113.0, 114.8, 115.2, 115.0, 122.8, 128.1, 129.1, 129.2, 129.9, 131.1, 131.2, 134.0, 136.1, 161.2, 161.6, 163.6, 164.0, 165.4. Anal. Calcd for $C_{30}H_{24}N_2O_5F_2$: C 67.92, H 4.56, N 5.28. Found: C 68.05, H 4.61, N 5.20.

6. (4'a*RS*,5*SR*,7'a*RS*)-4'a,7'a-Dihydro-6',7'a-bis(4-fluorophenyl)-5-(*N*-phthalimidoamino)spiro[cyclo-pentane-1,3'-5'*H*-cyclopenta[1,2-*e*][1,2,4]trioxine (**10**). A solution of **9** (72 mg, 0.24 mmol) and formic acid (10 µL, 0.24 mmol) in chloroform (2 mL) was allowed to stand at rt for 5 d. The resulting mixture was washed successively with saturated $NaHCO_3$ solution, water, and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by chromatography on a silica gel column ($CHCl_3$) to give **10** (69 mg, 96%) as yellow crystals. mp: 80-81 °C (recrystallized from $CHCl_3$). ^{1}H-NMR (200 MHz): δ 1.5-2.2 (m, 8H), 4.51 (d, J = 5.0 Hz, 1H), 4.68 (d, J = 1.5, 1H), 4.82 (dd, J = 5.0, 1.5 Hz, lH), 6.37 (s, 1H), 7.13-7.92 (m, 12H). ^{13}C-NMR (50 MHz): δ 23.8, 23.9, 34.5, 37.4, 70.2, 79.3, 91.1, 113.6, 115.3, 115.5, 115.8, 116.0, 122.8, 123.5, 128.9, 129.0, 129.1, 129.2, 130.1, 134.0, 134.4, 135.8, 143.6, 161.6, 162.0, 164.1, 164.5, 166.6. Anal. Calcd for $C_{30}H_{24}N_2O_5F_2$: C 67.92, H 4.56. N 5.28. Found: C 67.68, H 4.51, N 5.27.

7. Bi[(4'a*RS*,5'*SR*,6'*RS*,7'a*RS*)-5'-azido-4'a,7'a-dihydro-6',7'a-bis(4-fluorophenyl)spiro[cyclopentane-1,3'-cyclopenta[1,2-*e*][1,2,4]trioxine]-6'-yl] (**12**). To a stirred suspension of **3** (370 mg, 1 mmol) and iodosobenzene (250 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) under argon trimethylsilyl azide (243 mg, 2.1 mmol) was added at -35 °C. After stirring for 2.5 h at -20 °C the reaction mixture was allowed to warm to

0 °C. Water (5 mL) was added. After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were combined, dried ($MgSO_4$) and evaporated. The oily residue was purified by chromatography over silica gel (CH_2Cl_2/hexane, 1:1) to give a 3:1 mixture of **12** and **13** or **14** as white crystals (244 mg, 66%). Crystals of the major isomer (**12**) were obtained by flash chromatography.[15] A pure sample of **12** suitable for X-Ray was recrystallized from $CHCl_3$/EtOH. mp: 183-185 °C. ^{1}H-NMR (200 MHz): δ 1.5- 2.2 (m, 16H), 2.27 (d, *J* = 15.0 Hz, 2H), 2.64 (d, *J* = 15.0 Hz, 2H), 4.27 (d, *J* = 10.5 Hz, 2H), 4.61 (d, *J* = 10.5 Hz, 2H), 6.85-7.0 (m, 16H). ^{13}C-NMR (50 MHz): δ 21.8, 24.3, 35.9, 37.1, 43.2, 50.5, 66.2, 75.8, 79.8, 112.5, 114.3, 114.5, 115.1, 115.3, 127.7, 127.8, 131.9, 132.0, 161.0, 163.5. Anal. Calcd for $C_{44}H_{40}O_6N_6F_4$: C 64.01, H 4.85, N 10.18. Found: C 63.57, H 4.93, N 10.36.

Crystallographic data for **12**. Crystals were grown at rt from a solution in $CHCl_3$/EtOH and formed twinned crystals. A colorless crystal (0.17 x 0.20 x 0.30 mm), cut along the twin plane, was measured on a Stoe STADI4 diffractometer with graphite monochromated MoKα radiation (λ = 0.71069 Å). $C_{44}H_{40}O_6N_6F_4$, Mw 824.8, monoclinic, *P* $2_1/c$, a = 10.143(2), b = 16.098(3), c = 24.679(3) Å, β = 99.96(1)°, V = 3969(1) Å^3, Z = 4, D_x = 1.38 g.cm^{-3}, Fooo = 1720, μ = 0.099 mm^{-1}, R = ωR = 0.094 (ω = 1) for 1974 observed reflections (|F| > 4 σ(Fo)). The structure was solved by direct methods (MULTAN87)[16] and refined by full-matrix least squares (XTAL).[17] All co-ordinates of H atoms were calculated.

Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC.101939. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

The minor isomer (**13**) or (**14**): ^{1}H-NMR (200 MHz): δ 1.5-2.2 (m, 16H), 2.35 (d, *J* = 15.6 Hz, 2H), 3.05 (d, *J* = 15.0 Hz, 2H), 3.97 (d, *J* = 10.6 Hz, 2H), 4.36 (d, *J* = 10.3 Hz, 2H), 6.85-7.0 (m, 16H).

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