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Synthesis of "Trioxaquantel"® Derivatives as Potential New Antischistosomal Drugs

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Over the past 20 years, praziquantel, a pyrazinoisoquinoline derivative, has become the mainstay for morbidity control of human and animal schistosomiasis. From early in their lives in vertebrate hosts, schistosomes ingest hemoglobin and aggregate the released heme as a dark pigment very similar to the hemozoin produced by *Plasmodium* in malaria infection. The antimalarial artemisinin derivatives have real, though low, schistosomicide activity. Because of the complementarity of the two drug classes – praziquantel and artemisinin derivatives – we designed new molecules, named trioxaquantels®, that combine the 1,2,4-trioxane unit responsible for the activity of artemisinin, and the pyrazinoisoquinoline moiety of praziquantel within a single drug. The synthesis of these new drugs and their preliminary evaluation in mice infected with *Schistosoma mansoni* is reported here.

Introduction

Schistosomiasis is a major parasitic disease. Current estimates indicate that 200 million people are currently infected, 10% of them having severe illness, in more than 74 countries all over the tropical and subtropical belt.[1,2] In spite of efforts to reduce the incidence of human schistosomiasis in the world, the disease continues to spread to new geographic areas. For example, the epidemiological survey of schistosomiasis is now a public health priority in China, where the disease has reemerged in areas in which it was previously controlled.[3]

Schistosomiasis is caused by the parasite trematode worms *Schistosoma*, which reside mainly in the abdominal veins of their vertebrate hosts.[4] All schistosome infections follow direct contact with fresh water that harbors cercariae, the free-swimming larval forms of the parasite. Cercariae penetrate the skin of humans in few minutes. At this parasite stage they are then referred to as schistosomules. Schistosomules enter capillaries and lymphatic vessels en route to the lungs and, two weeks after infection, they accumulate in the liver to undergo rapid growth by feeding with portal blood. Three to four weeks post-penetration, migration of young adults either to the mesenteric veins (*S. mansoni* and *S. japonicum*) or the vesical plexus (*S. haematobium*) takes place, and sexual maturation and mating occur. Egg production (200 to 2000 eggs/day/female) begins 6 weeks post-infection and lasts for all the life of the worm, usually 5 years, but people may remain infected for 30 to 40 years after leaving the endemic region. The symptoms result from the host's immune response to schistosome eggs, inducing chronic inflammation, fibrosis, and ulceration of the tissues at the sites of accumulation of eggs, namely the intestine and the liver (*S. mansoni* and *S. japonicum*) or the genito–urinary tract (*S. haematobium*).

Praziquantel, a pyrazinoisoquinoline derivative (**1**, Figure 1) is the current drug of choice in the treatment of all five schistosome species that infect humans. It is marketed as a racemate, although only one enantiomer is biologically active.[5] Since its discovery by E. Merck (Darmstadt) and Bayer (Leverkusen) in the mid-1970s,[6] its safety, efficacy, and low cost (7 US cents per 600 mg tablet) have ensured its widespread use. The drug is usually administered at a single oral dose of 40 mg kg^{-1} of bodyweight; it reliably cures 60–90% of patients and substantially decreases the worm burden and egg production in those who are not cured.[7] Over the past 20 years, several million people have been effectively treated with praziquantel, and the drug has become the mainstay for morbidity control of schistosomiasis.

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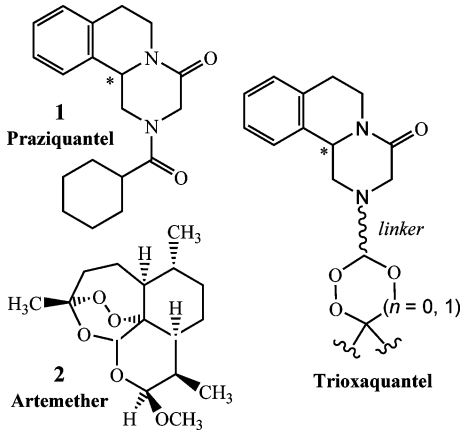


Figure 1. Structures of praziquantel (**1**), artemether (**2**), and general structure of trioxaquantels.

Possible resistance (or innate tolerance) of schistosomes to praziquantel has been reported for at least 10 years.[8–10] Fortunately, the degree of praziquantel resistance in *Schistosoma* isolated from treated but uncured patients is so far relatively low: none of them has an ED_{50} value greater than 5–6 times those of drug-susceptible isolates used as controls. Nevertheless, a small decrease in susceptibility can be clinically significant, and there is a real concern in having a single drug as cornerstone for the control of a disease affecting millions of people. There is currently no new antischistosomal drug in development, and the only current proposal is to produce the active enantiomer of praziquantel for less than the cost of the racemic drug.[11] This strategy will obviously not delay or circumvent the potential schistosome resistance to praziquantel.

Several other compounds have been widely used in the past, among them antimonium derivatives, metrifonate, and oxamniquine.[12] All of them have been withdrawn from the market or disused both because of toxicity and of lack of efficacy. The only remaining oxamniquine, more efficient in specific cases than praziquantel,[13] is expensive and its continued commercial availability is uncertain. A recent report suggests that thioredoxin glutathione reductase, a parasitic enzyme with several functions, might be a target for antischistosomal therapy.[14]

From early in their lives in their vertebrate hosts, schistosomules and schistosomes ingest hemoglobin. Red blood cells are lyzed in the oesophagus.[15] Proteolytic digestion of hemoglobin occurs in the schistosome intestine, supplying the parasite with amino acids.[16] This catabolic process releases free iron-heme, redox active, and thus potentially toxic. This iron-heme aggregates within the schistosome intestine as a dark pigment very similar to the hemozoin produced by *Plasmodium* in malaria infection.[17–19] This heme aggregate is then regurgitated by the parasite and accumulates in the host liver.

This likeness between *Schistosoma* and *Plasmodium* has led to the evaluation of the antischistosomal activities of antimalarial drugs that interact with heme metabolism. The schistosomicide activity of the antimalarial artemisinin [or its hemi-synthetic derivatives such as artemether (**2**, Figure 1) or artesunate] has been known for a long time.[20–24] Synthetic antimalarial peroxidic derivatives based on a trioxolane structure instead of the 1,2,4-trioxane of artemisinin have also been evaluated against *S. mansoni* and *S. japonicum*.[25–27] In all the reports, the doses required to decrease the worm number by 80–85%, as high as 200 to 400 mg kg^{-1} in mice, are prohibitive to envisage in a monotherapy. However, while praziquantel is only effective on adult worms (6–7 weeks post-infection for *S. mansoni*), artemether does kill schistosomules during the first 21 days in the body,[23] and these two drugs may have complementary effects.[28,29] Then, in regions where people are constantly reinfected, combining artemether with praziquantel may appear potentially to kill all schistosome developmental stages. The distributions of malaria and schistosomiasis exhibit a large geographical overlap, however, so the selection of artemether-resistant *P. falciparum* could be possible. In addition, the adverse clinical outcomes resulting from the co-administration of praziquantel and artemether in patients infected by both *Plasmodium* and *Schistosoma* are still largely unclear.[30]

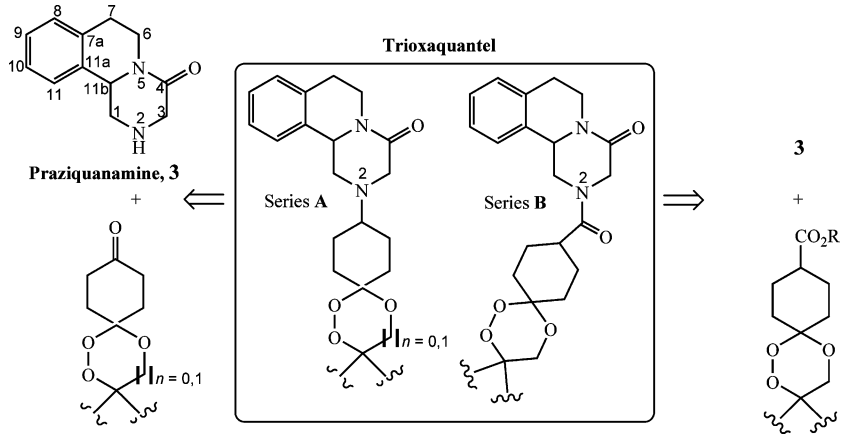
Small hybrid molecules with dual modes of action deserve consideration as a possible approach to create drugs by rational design.[31] As an efficient illustration of this concept, trioxaquines®, dual molecules containing both a quinoline and a 1,2,4-trioxane unit, are currently under development for malaria treatment.[32–34] In a similar approach, because of the complementarity of the two drugs – praziquantel (PZQ) and artemether (Artm) – we designed new molecules, named trioxaquantels® (Figure 1), that combine the 1,2,4-trioxane responsible for the activity of artemether (or a trioxolane) and the pyrazinoisoquinoline moiety of praziquantel within a single drug. The synthesis of these new drugs and their evaluation in mice infected with *Schistosoma mansoni* is reported here.

Results and Discussion

Two categories of molecules were prepared, according to the absence (**A**, Scheme 1) or the presence (**B**, Scheme 1) of an acyl function at the 2-position in the pyrazinoisoquinoline residue. Both series of molecules have a common intermediate praziquanamine **3** and were synthesized with convergent routes. In the first approach, the reductive amination of **3** with the ketone function of trioxanes gave trioxaquantels **A**. In the second approach, a peptidic coupling between the secondary amine unit in **3** and the ester function of trioxanes provided trioxaquantels **B**.

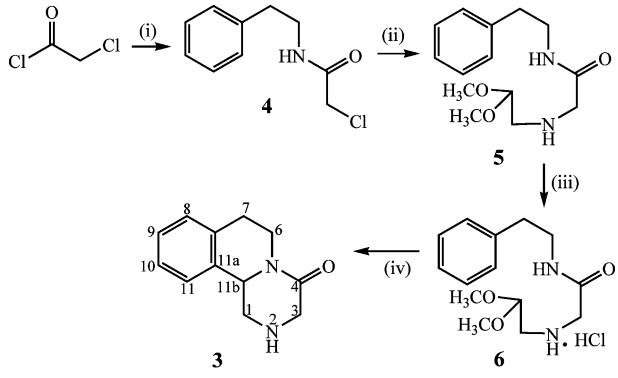
Trioxaquantels A

Praziquanamine **3** was synthesized by the method described by Kim et al.[35] with minor modifications (Scheme 2). The reaction between chloroacetyl chloride and phenethylamine gave chloroacetamide **4** in 92% yield. Compound **4** reacted with aminoacetaldehyde dimethyl acetal to



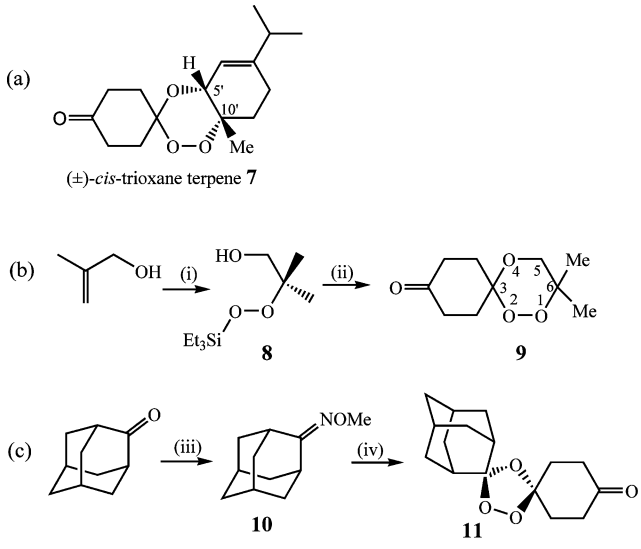
Scheme 1. Structure and retrosynthesis of the trioxaquantel series (**A**) and (**B**).

give acetal **5**, which was transformed into the hydrochloride derivative **6** by addition of hydrochloric acid solution in diethyl ether. The synthesis of **3** was based on a Pictet–Spengler cyclization of hydrochloride **6** in concentrated sulfuric acid. Praziquanamine **3** was thus prepared in four steps from phenethylamine with an overall yield of 49%.



Reagents: (i) phenylethylamine, $NaHCO_3$; (ii) aminoacetaldehyde dimethyl acetal, reflux; (iii) HCl in Et_2O; (iv) H_2SO_4

Scheme 2. Synthesis of (±)-praziquanamine **3**.



Reagents: (i) $Co(acac)_2$, Et_3SiH, O_2; (ii) cyclohexa-1,4-dione, *p*-toluenesulfonic acid; (iii) $H_2NOMe{\cdot}HCl$, pyridine; (iv) O_3

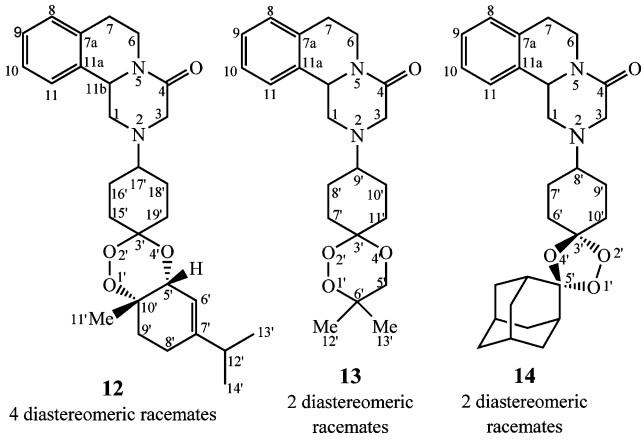
Scheme 3. Structures of trioxanes **7** **9**, and **11** used for the trioxaquantel series **A** (**12**, **13**, and **14**).

Three different trioxanes were used for the preparation of trioxaquantels **A** (Scheme 3). The *cis*-terpene trioxane **7** derived from α-terpinene (Scheme 3, a) had been developed in our laboratory for the synthesis of trioxaquines®.[33] This trioxane has two stereogenic centers at the 5′- and 10′-positions. The trioxane and cyclohexene rings are *cis*-fused, which means that H5′ and the 10′-methyl group are contiguous. Compound **7** is thus a racemic mixture of two enantiomers, with 5′*R*,10′*S* and 5′*S*,10′*R* configurations.

Usually, 3,3,6,6-tetraalkyl-1,2,4-trioxanes are prepared under drastic and hazardous conditions.[36] In our case, the strategy for the preparation of the trioxane **9** (Scheme 3, b) was based on the highly regioselective Markovnikov reaction of 2-methylprop-2-en-1-ol under Mukaiyama's and Isayama's conditions to prepare the silyl peroxide **8**.[37,38] This reaction was sensitive to the nature of the catalyst[39] and to the solvent: in dichloroethane, silylperoxidation is 6 to 8 times slower than in alcohol.[36] Agitation was also very important: the more vigorous the agitation, the more oxygen is dissolved and the better is the yield. Compound **9** was obtained after cyclization of silyl peroxide **8** and cyclohexa-1,4-dione in the presence of *p*-toluenesulfonic acid (Palumed, patent pending). Trioxane **9** has a symmetry plane and is not chiral.

Compound **11**, namely a trioxolane, was prepared by the method described by Vennerstrom et al.[25] with minor modifications (Scheme 3, c). The reaction between adamantan-2-one and methoxylamine hydrochloride in pyridine yielded the oxime **10** (79% yield). Ozonolysis of **10** in a mixture of pentane and dichloromethane (1.5:1, v/v) provided the nonchiral trioxolane **11**. The quantity of dichloromethane used as co-solvent for ozonolysis should be kept at the minimum necessary for the solubility of reactants: in fact, in less polar solvents such as alkanes, the formation of the ozonide intermediate is favored.[40]

Reductive aminations of **7**, **9**, and **11** with praziquanamine **3** were performed with sodium triacetoxyborohydride in dichloroethane at room temperature, to afford trioxaquantels **12**, **13**, and **14**, respectively (Scheme 4) with yields ranging from 47 to 70%. In each case, the coupling between the two moieties was ascertained by the ^{1}H and ^{13}C NMR resonance of the cyclohexyl –CH directly linked to the N2. In trioxaquantel **13**, for instance, the chemical shift of H9′ was 3.87–3.82 ppm, and the resonance of C9′ was detected at δ = 67.2 ppm, these values being consistent with an amine-linked –CH moiety.

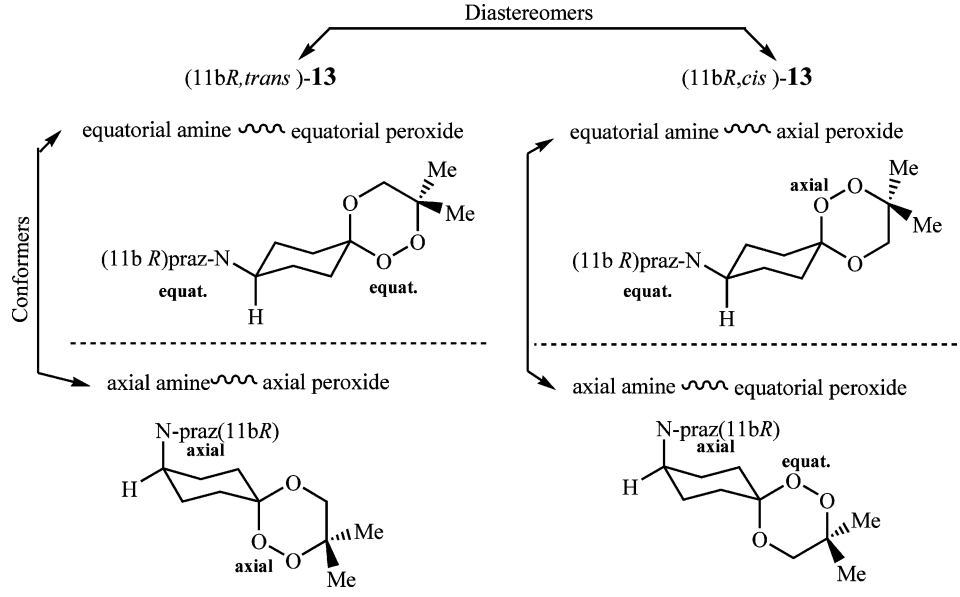


Scheme 4. Structures of trioxaquantel series **A**: compounds **12** (four diastereomeric racemates), **13**, and **14** (two diastereomeric racemates for each compound).

It should be noted that H9′ appeared as a complex pattern of overlapped multiplets, due to the fact that **13** was a mixture of two diastereomeric racemates. In fact, the common elements of symmetry of these three trioxaquantels are: i) the configuration of the carbon atom at the C11b position, and ii) the relative arrangement of the amine and peroxide functions, being either *cis* or *trans* with respect to the cyclohexyl ring. Reductive amination of **3** with a nonchiral trioxane or trioxolane (**9** or **11**) thus provided trioxaquantels **13** and **14**, each of them a mixture of two diastereomeric racemates. As an example, the stereoisomers of **13** are depicted in Scheme 5. Isomers (11b*R*,*trans*)-**13** and (11b*S*,*trans*)-**13** are enantiomers; similarly, (11b*R*,c*is*)-**13** and (11b*S*,c*is*)-**13** are also enantiomers. There is a diastereomeric relationship between these two racemates. As assessed by HPLC, they were obtained in 70:30 ratio. In addition, each stereoisomer can adopt two possible conformations: when piperazine and peroxide substituents are *trans* with respect to the cyclohexane mean plane, they can be either in equatorial-equatorial or in axial-axial positions. When piperazine and peroxide substituents are *cis*, equatorial–axial or axial–equatorial conformations also occur. These conformers could not be identified by NMR spectroscopy.

More complicated is the case of trioxaquantel **12**. The reductive amination of **3** with the chiral trioxane **7**, which is a racemate of the 5′*R*,10′*S* or 5′*S*,10′*R* configurations, provided trioxaquantel **12** as a mixture of four diastereomeric racemates. Furthermore, the interconversion of the cyclohexyl residue, with its chair conformation, allows each stereoisomer to exist as two conformers. Whatever the trioxaquantel (**12**, **13**, or **14**), it was not possible to separate the diastereomers, and NMR assignments were performed on mixtures.

A complex stereochemical status is a serious drawback to the development of putative drugs. We therefore developed a new series of trioxaquantels (**B**, Scheme 1) containing a smaller number of stereoisomers, by using an achiral trioxane. In addition, because the acyl function at the 2-

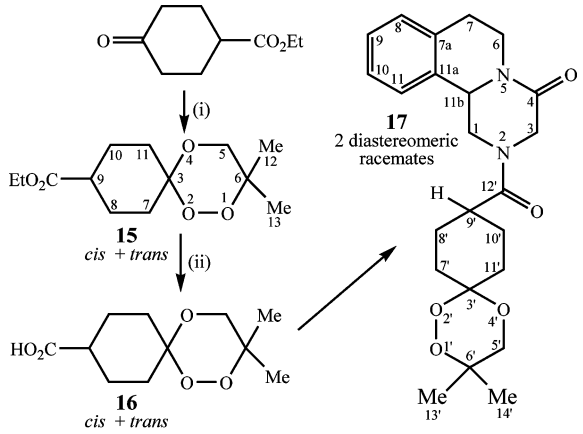


Scheme 5. Structures of diastereomers and conformers of trioxaquantel (11b*R*)-**13** [for clarity, (11b*S*,c*is*)-**13** and (11b*S*,*trans*)-**13**, which are enantiomers of (11b*S*,c*is*)-**13** and (11b*S*,*trans*)-**13**, respectively, are not depicted].

position in praziquantel is considered necessary for its biological activity,[5,12] we introduced this function in the structure of trioxaquantels of series **B**.

Trioxaquantels B

This series of trioxaquantels, each bearing an acyl function at the 2-position, was prepared by peptide coupling between **3** and a nonchiral 6,6-dimethyltrioxane. We thus prepared trioxane **15** by cyclization of silyl peroxide **8** (Scheme 3) with the commercially available ethyl 4-oxocyclohexanecarboxylate, in the presence of *p*-toluenesulfonic acid (Scheme 6). Compound **15** was obtained as a mixture of two *cis*/*trans* isomers in 1:2 or 2:1 ratio (undetermined). In the *trans* isomer, the ethyl carboxylate and peroxide substituents were on opposite sides of the mean plane of the cyclohexyl residue. In the *cis* isomer, both substituents were on the same side of the mean plane. Isomers *cis*-**15** and *trans*-**15** can be distinctly observed by ^{1}H NMR at 293K, with two different ethyl ester resonances [(4.13, 1.25 ppm) and (4.11, 1.24 ppm)] being detectable. Because of the fluxionality of the trioxane ring, the NMR spectrum at room temperature was considerably broadened. The two isomers were separated by column chromatography and were individually characterized by NMR at low temperature (263 K). Under these conditions, their corresponding spectra exhibited significant differences for the resonance of H9 (at δ = 2.38 and 2.35 ppm). The two isomers were also distinguishable by the resonance of one of the protons of the methylene group at C5 (doublet at 3.76 and 3.88, respectively). These differences in chemical shifts (0.2–0.3 ppm) may seem to be too low to be significant. However, at a given temperature, such differences between the *cis* and *trans* isomers of a trioxane, or between the diastereoisomers of a trioxaquantel, were highly reproducible, from one experiment to another, and under different conditions of concentration and purity (see Supporting Information for ^{1}H NMR spectra of trioxanes *cis*-**21**, *trans*-**21**, and a mixture of both).

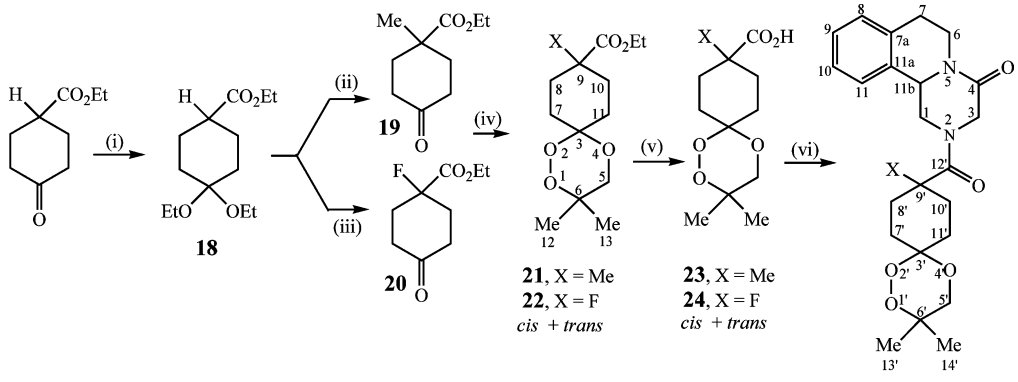


Reagents: (i) **8**, *p*-toluenesulfonic acid; (ii) NaOH; (iii) **3**, PyBOP, NMM

Scheme 6. Synthesis of trioxaquantel **17** (series **B**) (two diastereomeric racemates).

The ethyl ester function of **15** was quantitatively saponified to give the acid derivative **16**, which was then coupled to **3** in the presence of PyBOP (benzotriazol-1-yloxy-tris-pyrrolidinophosphonium hexafluorophosphate) and *N*-methylmorpholine to afford trioxaquantel **17** as a mixture of two diastereomeric racemates, due to i) the configuration at the C11b carbon atom, and ii) the *cis*/*trans* stereochemistry of the peroxide and amide functions with respect to the cyclohexyl ring. HPLC analysis of the diastereomeric mixture gave two peaks in 1:1 ratio, whereas a ratio of 1:2 was observed for the starting trioxane **15**. This result suggests the possible epimerization of the C9′-center, α to the acyl function. To inhibit the equilibration at this position, we decided to introduce either a methyl or a fluoro group at C9′.

The methyl or fluoro substituents were introduced α to the carboxylate function of the ethyl 4-oxocyclohexanecarboxylate (Scheme 7). Firstly, the ketone function was protected as the diethyl acetal **18** by treatment with triethyl orthoformate in absolute ethanol in the presence of hydrochloric acid (in solution in 2-propanol). Compound **18** was



Reagents: (i) $HC(OEt)_3$, HCl; (ii) a: $NH(iPr)_2$, *n*BuLi, Me_2SO_4; b: HCl; (iii) $NH(iPr)_2$, *n*BuLi, $(PhSO_2)_2NF$; b: HCl; (iv) **8**, *p*-toluenesulfonic acid; (v) NaOH; (vi) PyBOP, NMM.

Scheme 7. Synthesis of trioxaquantels **25** and **26** (series **B**) (two diastereomeric racemates).

then deprotonated with lithium diisopropylamide (generated in situ from diisopropylamine and *n*-butyllithium). Dimethylsulfate was then added to provide the methyl derivative. Similarly, treatment with *N*-fluorobenzenedisulfonimide afforded the fluorinated derivative. Addition of aqueous hydrochloric acid (10 vol.-%) then achieved the deprotection of the ketone function, and compounds **19** and **20** were obtained in 73% or 67% yields, respectively.

Ketones **19** and **20** were quantitatively cyclized into trioxanes **21** and **22**, by treatment with the silyl peroxide derivative **8** in the presence of *p*-toluenesulfonic acid. As already discussed for **15**, each of the trioxanes **21** and **22** was a mixture of *cis* and *trans* isomers, with the ethyl ester and the peroxide either on opposite sides or on the same side of the mean plane of the cyclohexyl ring, as assessed by NMR at 263 K. In trioxane **21**, the methylene group of the ethyl substituent appeared as two separate sets of resonances at δ = 4.16 and 4.15 ppm. Two different methyl-C9 groups were detectable at δ = 1.20 and 1.17 ppm, allowing the *cis*/*trans* isomer ratio to be determined as 3:2. The identification of *cis* or *trans* geometry was possible by X-ray diffraction on their anilide derivatives (see below; compounds *cis*-**34** and *trans*-**34**). Similarly, the ^{19}F NMR ($CDCl_3$, 293K) of trioxane **22** showed two singlets at –91.3 and –92.0 ppm for the *cis* and *trans* isomers.

Ester derivatives **21** and **22** were saponified to provide carboxylic acids **23** and **24**, which were then coupled with praziquanamine **3** in the presence of PyBOP and *N*-methylmorpholine to afford trioxaquantels **25** and **26**. As expected, compounds **25** and **26** were both mixtures of two diastereomeric racemates, because of i) the configuration at the chiral center C11b, and ii) the *cis*/*trans* relationship of the peroxide and the amide with respect to the cyclohexyl residue. In both cases, the proportions of diastereomers were 3:2, as expected from the proportions of the starting trioxanes **21** and **22**.

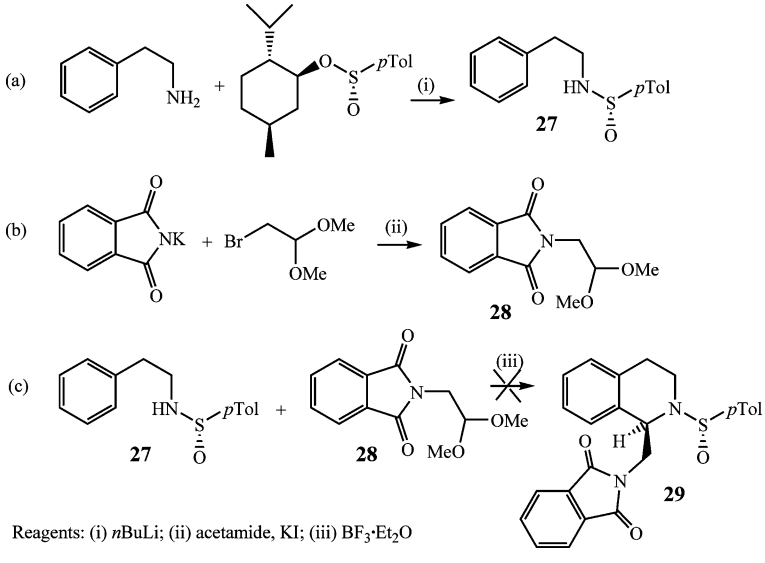
Synthesis of the Four Stereoisomers of Trioxaquantel 25

To synthesize all the four stereoisomers of the C9′-methyl-trioxaquantel **25**, the two enantiomers of praziquanamine **3** had to be obtained separately, and the *cis* and *trans* isomers of trioxane **21** were also separated.

Synthesis of Enantiopure Praziquanamine 3

Different methods were tried to prepare both enantiomers of **3**. An enantioselective synthesis, through the grafting of a chiral fragment derived from Andersen's reagent, has been reported by Ma et al.[41] We first tried to use this method. Enantiopure *N*-(*p*-tolylsulfinyl)phenethylamine **27** was then prepared by treatment of the corresponding phenethylamine with *n*-butyllithium (Scheme 8, a). Treatment of the anion of phenylethylamine with the commercially available Andersen's reagent [(1*S*,2*R*,5*S*)-menthyl (*R*)-*p*-toluenesulfinate] afforded enantiopure (*S*)-**27** in 79% yield {$[a]_D$ = –70 (*c* = 0.04, CH_2Cl_2), compared with the value reported in reference 37: $[a]_D$ = –63.1 (*c* = 0.5, acetone)}. The synthesis of *N*-(2,2,-dimethoxyethyl)phthalimide **28** (Scheme 8, b) was not reproducible under the conditions described by Ma et al. Compound **28** was therefore prepared from a mixture of potassium phthalimide, potassium iodide, and bromoacetaldehyde dimethyl acetal in acetamide at 140–150 °C (Scheme 8, b).[42] Unlike as reported,[41] however, treatment of compounds **27** and **28** (Scheme 8, c) in the presence of boron trifluoride failed to afford the desired ring-closed product **29**. Despite many attempts under different conditions (acid catalyst, solvent, temperature, and reaction time), the starting materials were usually recovered unchanged.

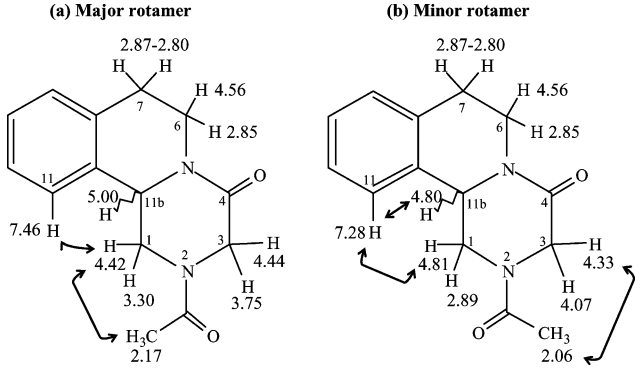
In a second approach, we decided to perform the resolution of praziquanamine **3** through the crystallization of diastereomeric chiral ammonium salts prepared from enantiopure acids, such as tartaric acid, camphorsulfonic acid,



Scheme 8. Scheme of the enantioselective synthesis of **29**, modified from Reference 38.

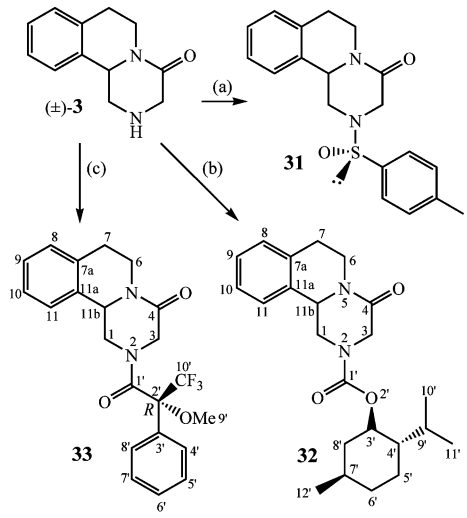
mandelenic acid, and Mosher's acid. The use of many different solvent mixtures (methanol, ethanol/water, acetone, acetonitrile, ethyl acetate, acetone/water, dichloromethane/hexane, acetone/hexane) resulted in the co-precipitation of diastereoisomers, whatever the **3**/acid stoichiometry was. The separation of the diastereomeric salts by HPLC (C18 column) also failed. We did not succeed in the direct resolution of **3** by chiral HPLC chromatography (Chiralcel OD column), despite the fact that this stationary phase allows the separation of the enantiomers of the parent drug praziquantel.[43,44]

Kinetic resolution of **3** by an enzymatic acylation reaction was also tried. The stereospecific acylation of the secondary amines of piperidine derivatives in the presence of porcine pancreatic lipase (PPL) in ethyl acetate was reported by Asensio et al.[45] Different lipases (*Pseudomonas cepacia* lipase, *Candida antarctica* lipase B, *Candida cylindracea* lipase, PPL), different acylating agents (ethyl acetate, acetic anhydride, isopropenyl acetate, and vinyl acetate) and many solvents (diisopropyl ether, THF, DMSO/H_2O, chloroform, ethyl acetate) were tried. In all cases, when ethyl acetate was used as acylating agent, no acylation of **3** was observed, while the other acylating agents gave racemic acylpraziquanamine (±)-**30**. As expected, ^{1}H NMR spectra of (±)-**30** showed two rotamers, because of the slow rotation of the amide bond at room temperature (Scheme 9). In [D_6]DMSO, two singlets at δ = 2.17 and 2.06 ppm were observed for the acyl-CH_3 groups of the major and minor rotamers, respectively. When ^{1}H NMR spectra was recorded at 313 K, coalescence of these singlets occurred. In the major rotamer, the acyl-CH_3 is in the close vicinity of *H*C1, giving rise to a strong NOE effect (Scheme 9, a). In the minor rotamer, the main NOE effect is observed between the acyl-CH_3 and one of the protons at C3 (Scheme 9, b)



Scheme 9. Strong NOE (2–3 Å) of the two rotamers of acylpraziquanamine **30**.

In the last approach to obtaining optically active praziquanamine, we decided to transform racemic **3** into covalent diastereomers. In a first attempt, treatment of (±)-**3** with (*R*)-Andersen's reagent gave two diasteromeric sulfinate derivatives **31** (Scheme 10, a). The deprotonation of **3** in solution in dry THF was achieved by addition of *n*-butyllithium at –78 °C, and monitored by the blood-red coloration characteristic of the deprotonation of the amine. However, after addition of Andersen's reagent and standard workup, sulfinates were only obtained in poor yields ranging from 3 to 10%. Use of many different conditions did not allow this poor yield to be improved, and **3** was mainly recovered unchanged (30–90%). Nevertheless, the formation of sulfinate **31** in good yield, followed by its rapid degradation, cannot be definitively ruled out.[46,47] In any case, this method was abandoned.



Scheme 10. Synthesis of **31**, **32**, and **33**.

In a next attempt, (±)-**3** was quantitatively transformed into diastereomeric carbamates **32** by treatment with (–)-menthyl chloroformate in the presence of triethylamine (Scheme 10,b). ^{1}H NMR spectra showed that diastereomers were obtained in 50:50 ratio (as expected) and that each diastereomer appeared as two rotamers in 70:30 ratio. Unfortunately, it was not possible to separate the two diastereomers, either by TLC (silica or aluminium oxide) or by HPLC.

The last attempt was made with Mosher's acid, usually used to determine enantiomeric compositions of chiral alcohols and amines.[48] Treatment of (±)-**3** with (*R*)-Mosher's acid [(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, (*R*)-MTPA] in the presence of PyBOP and *N*-methylmorpholine provided the amide **33** as a mixture of two racemic diastereomers in 71% yield (Scheme 10, c). Separation of the two diastereomers (11b*R*,2′*R*)-**33** and (11b*S*,2′*R*)-**33** was successfully accomplished on a silica column with diethyl ether as eluent, and each diastereomer was obtained, with diastereomeric excesses higher than 97% for (11b*R*,2′*R*)-**33** (the first eluted from the column) and in the 91–95% range for (11b*S*,2′*R*)-**33** (the second one). The determination of the configuration at C11b was possible through X-ray diffraction analysis of the first eluted diastereomer {$[a]_D$ = –25 (c = 5.10^{-3}, CH_2Cl_2)}. Given the *R* configuration of the C2′ center in the (*R*)-Mosher's acid moiety, the configuration of the C11b carbon could also

be determined as *R*. This less polar enantiomer was thus (11b*R*,2′*R*)-**33** (Figure 2). A pseudo-chair conformation for the piperazine ring was also noted. Currently, no monocrystal of the second diastereomer suitable for X-ray diffraction has been obtained. By deduction, though, the 11b*S*,2′*R* configuration was assigned to this diastereoisomer. As in the case of compound **30**, two rotamers were identified by ^{1}H NMR for each diastereomer of **33**. The slow rotation of the tertiary amide bond gave a pair of equienergetic rotamers, and the differences in chemical shifts were higher than 0.9 ppm for some specific protons. For diastereomer (11b*R*,2′*R*)-**33**, strong NOE effects (2–3 Å) were observed between the methoxy group and one of the H3-protons of the pyrazino-isoquinoline system of the major rotamer. In the minor rotamer, strong NOE effects were observed between the methoxy group and H1 and H11b.

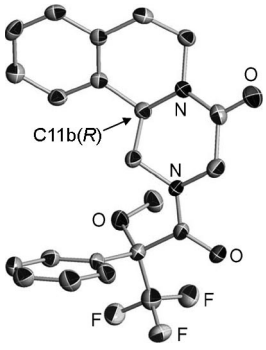
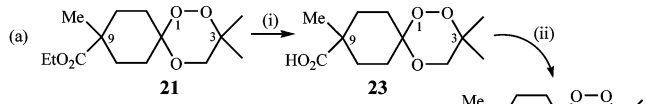


Figure 2. X-ray structure of the Mosher's amide (11b*R*,2′*R*)-**33**.

The next required step was the hydrolysis of the amide bond of **33**, which in fact was a very stable bond. Under basic conditions, only the degradation of the product could be achieved. Furthermore, epimerization at the C11b-benzylic position may occur under such conditions. In concentrated H_2SO_4 at 100 °C for 24 hours, compound **33** was recovered unchanged, while it was degraded after 13 hours at 150 °C. A clean hydrolysis was finally achieved in concentrated H_3PO_4 at 100 °C for 3 days, conditions described by Pohlke et al. for the hydrolysis of benzoylamide derivatives.[49] Specific rotations of (*R*)-**3** and (*S*)-**3** were $[\alpha]_D$ = –152 (c = 4.10^{-3}, CH_2Cl_2) and $[\alpha]_D$ = +146 (c = 5.10^{-3}, CH_2Cl_2) for enantiomeric excesses higher than 95 and 91%, respectively. During the writing of the present work, the first enantioselective synthesis of (*R*)-(–)-praziquantel was reported.[50]

Separation of the cis and trans Isomers of Trioxane 21

The *cis* and *trans* isomers of trioxane **21** were separated, with excellent diastereoselectivity (de > 98%), on a chromatographic column filled with aluminium oxide, with use of a hexane/dichloromethane gradient. The *cis* or *trans* stereochemistry of the carboxylate and peroxide substituents was determined by derivatizing trioxane **21** into crystallizable amide derivatives **34** (Scheme 11, a). After saponification of the ethyl ester of each stereoisomer of **21** to provide the corresponding carboxylic acid derivative **23**, treatment with aniline in the presence of PyBOP and *N*-methylmorpholine provided the *cis* and *trans* amides **34**, respectively.



(b)

	d(H$_3$C–C9) [ppm]		
Compound	**21**	**23**	**34**
cis-trioxanes	1.18	1.26	1.30
trans-trioxanes	1.16	1.25	1.28

Scheme 11. a) Synthesis of anilides *cis*-**34** and *trans*-**34** of trioxanes *cis*-**21** and *trans*-**21**; b) ^{1}H NMR chemical shifts of the methyl-C9, according to *cis* or *trans* stereochemistry.

Amides **34** were crystallized in a dichloromethane/hexane mixture and the stereochemistry of each of them was determined by X-ray diffraction (Figure 3). In *cis*-**34**, the amide function is in an axial position and the peroxide in an equatorial position, these two substituents being on the same side of the mean plane of the cyclohexyl ring (Figure 3, a). In *trans*-**34**, the amide and peroxide functions are both in equatorial positions, on one side and on the other of the mean plane of the cyclohexyl (Figure 3, b). In addition, in the ^{1}H NMR spectra, the resonance of the methyl-C9 was, slightly but significantly, shielded for *trans* trioxanes **21**, **23**, and **34** with respect to their *cis* isomers (Scheme 11, b). This feature allows the identification of the *cis* or *trans* stereochemistries of compounds **21**, **23**, and **34** by NMR analysis.

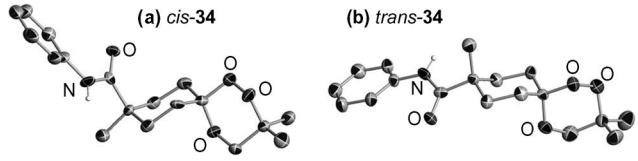


Figure 3. X-ray structures of the amide derivatives *cis*-**34** (a) and *trans*-**34** (b).

Amide Coupling Between Enantiopure 3 and Separated Isomers of 23

Through the coupling of each of the enantiomers of **3** with each of the isomers of **23**, the four stereoisomers of trioxaquantel **25** were separately synthesized, by the method described above for the diastereomeric racemates. Yields of this reaction were good, ranging from 60 to 70% after purification (chromatography and precipitation). As expected, NMR spectra were identical for (*R*,*cis*)-**25** and (*S*,*cis*)-**25**, which are enantiomers {$[\alpha]_D$ = –95 for (*R*,*cis*)-**25**, and +90 for (*S*,*cis*)-**25**}. Similarly, (*R*,*trans*)-**25** and (*S*,*trans*)-**25** also had the same NMR signature {$[\alpha]_D$ = –100 for (*R*,*trans*)-**25**, and +96 for (*S*,*trans*)-**25**}.

Diastereomers could also easily be distinguished by ^{1}H NMR in $CDCl_3$ at 293 K for routine analysis. The two enantiomers (*R*,*trans*)-**25** and (*S*,*trans*)-**25** each showed a singlet at δ = 1.31 ppm for the 13′-methyl resonance and a

doublet at δ = 3.99 ppm for one of the H3-protons ($^2J_{HH}$ = 17.8 Hz), whereas the two enantiomers (*R*,*cis*)-**25** and (*S*,*cis*)-**25** each have a singlet at δ = 1.34 ppm for the 13′-methyl and a doublet at δ = 3.96 ppm for one of the H3-protons. At low temperature (263 K), significant differences were also detectable in the aromatic regions of the ^{1}H spectra. Enantiomers (*R*,*trans*)-**25** and (*S*,*trans*)-**25** each have a distinct doublet at δ = 7.22 ppm for H8 ($^3J_{HH}$ = 7.5 Hz) and a complex pattern at 7.29–7.23 ppm for H9, H10, and H11. In contrast, in (*R*,*cis*)-**25** and (*S*,*cis*)-**25**, the aromatic protons were detectable as two doublets at δ = 7.32 and 7.22 ppm for the resonances of H11 and H8, respectively, together with the overlapped signals of H9 and H10 at 7.30–7.27 ppm. Then, with the four stereoisomers of **25** to hand, the interpretation of NMR spectra allows the *cis* or *trans* stereochemistry to be determined, while the sign of the specific rotation allows the configuration at carbon 11b to be determined.

A preliminary evaluation of these trioxaquantel molecules as antischistosomial drugs is reported below. Because of the possible heme alkylation by these trioxane-based drugs,[51–54] their potential antimalarial activity has also been evaluated.

Antischistosomiasis Activity

Mice were infected by the transcutaneous route[55] with cercariae of a Brazilian strain of *S. mansoni*. After 7 weeks, mice were treated by the oral route, for five consecutive days, with trioxaquantels dispersed in a mixture of Tween 80® in methylcellulose (0.5 vol.-%). At 10 weeks post-infection (PI), they were anesthetized with pentobarbital to allow the release of the schistosomes from the mesenteric capillary endothelium, and perfused. The blood was filtered, and the liver, the digestive system, and the lungs were removed and dilacerated to recover all the worms. Pure excipient was administered to control mice. The absence of any specific parasiticidal activity of these excipients has been checked.

Infected mice were treated with trioxaquantels **17**, **25**, or **26** (with either H, CH_3, or F substituents, respectively, at C9′), each of them as a mixture of the two diastereomeric racemates. Praziquantel (PZQ) and artemether (Artm) were used as reference drugs, and the doses of trioxaquantel were in the range of active doses of PZQ and Artm (100–400 mg kg^{-1} of body weight/d). Results are reported in Table 1.

At 10 weeks post-infection, control mice have on average 42 worms (Entry 1). Administration of praziquantel at the dose of 100 mg kg^{-1} d^{-1} resulted in a reduction in the total worm burden of 73% with respect to untreated animals (Entry 8). This result, suggesting an ED_{50} value slightly lower than 100 mg kg^{-1} d^{-1}, was consistent with that previously reported (81 mg kg^{-1} d^{-1}).[56] On the other hand, the activity of Artm (41% reduction of worms at 400 mg kg^{-1} d^{-1}, Entry 11) was in the expected range (51% with Cremophor EL®[22,57]). Surprisingly, none of the trioxaquantels **17** and **25** induced a significant reduction in the worm burden at 100 and 200 mg kg^{-1} d^{-1}. Conversely, the fluorinated trioxaquantel **26** induced a moderate worm burden reduction at 200 mg kg^{-1} d^{-1} (27%, Entry 7). Such activity was not as high as expected; however, one should keep in mind that praziquantel is 35–40 times more active in humans than in mice.[58] The low solubilities of this first generation of trioxaquantel molecules might be responsible for these rather low activities, due to poor absorption of these derivatives. Modification of these trioxaquantels in order to increase their solubilities is now in progress. In addition, artemether has been reported to be much more active on juvenile parasites than on adults.[59]

Antimalarial Activity

The trioxaquantels **13** (series A) and **25** (series B) exhibited moderate in vitro antimalarial activities on the chloroquine-resistant strains of *P. falciparum*. The IC_{50} values of **13** and **25** on the FcB1-Columbia strain were 1196 and 895 nM, respectively. The activities on the FcM29-Indochina strain were better, with IC_{50} values of 570 and 258 nM for **13** and **25**, respectively. However, the trioxaquines, designed by covalent coupling of an aminoquinoline and a trioxane are more efficient by one or two orders of magnitude (IC_{50} = 2–20 nM).[8,33]

Table 1. Total worm burden reduction in mice infected with *S. mansoni* after oral treatment on five consecutive days at 49 days PI (post-infection).

Entry	Drug	Daily dose [mg kg^{-1}]	Mean total worm burden			% Total worm burden reduction[a]
			x[b]	σ_{n-1}[c]	n[d]	
1	–[e]	–	42.0	6.3	5	control
2	17	100	35.2	10.2	5	16
3	17	200	37.2	5.5	5	11
4	25	100	41.8	5.4	5	0
5	25	200	37.0	10.6	5	12
6	26	100	40.2	8.7	5	4
7	26	200	30.6	9.0	5	27
8	(±)-PZQ	100	11.2	7.4	5	73
9	(±)-PZQ	200	1.0	1.4	5	98
10[f]	Artm	400	21.7	2.1	3	41

[a] Total worm burden reduction = 100 – (mean total worm burden of treated mice/mean total worm burden of the control) × 100. [b] x = Mean worm burden for n mice. [c] σ_{n-1} = standard deviation. [d] n = number of mice. [e] Excipient alone. [f] Test performed in a different experiment, where the mean total worm burden of the control mice was 37.3.

Experimental Section

Antischistosomiasis Testing

Parasites and Hosts: A Brazilian strain of *S. mansoni* was maintained at the laboratory, with use of *Biomphalaria glabrata* as the intermediate host and female albino mice for the development of mammalian stages. For infestation, anesthetized mice shaved on abdomen (9 cm^2) were laid down on small glass crystallizing dishes containing 120 cercariae freely swimming in water at 25 °C, so that the skin was in close contact with water and parasites.[55] The parasite–mouse contact lasted for 45 min, allowing the penetration of 40 ± 4 cercariae.

Treatment: PZQ, Tween 80® and methylcellulose were purchased from Sigma Aldrich. Artm was a gift from Rhône–Poulenc Rohrer Doma (Antony, F.). Animals were treated 7 weeks post-infestation by the oral route. The drugs were dissolved in Tween 80® (0.5 vol.-%) in an aqueous solution of methylcellulose (0.6% wt./vol.). Pure excipient was administered to control mice.

Dissection of Mice and Determination of the Worm Burden: Ten weeks after the infestation, mice were sacrificed and perfused by the method of Duvall et al.[60] The blood was filtered, and the liver, the digestive system, and the lungs were removed and dilacerated in order to count the worms.

Antimalarial Activities: The antiplasmodial activities of the trioxaquantels were evaluated by the radioactive microdilution method, as reported previously for trioxaquines with stock solutions of trioxaquantels prepared in dimethyl sulfoxide.[33]

Chemistry

Materials and Methods: Reactants were purchased from Aldrich Chemical Co. and Acros Organics. The synthesis of trioxane **7** has been reported in ref.[31]. *Pseudomonas cepacia* lipase (PSL, 40 u mg^{-1}), *Candida cylindracea* lipase (CCL, 25 u mg^{-1}), and *Candida antartica B* lipase, (CALB recombinant from *Aspergillus orizae*, 11 u mg^{-1}) were purchased from Fluka. Porcine pancreatic lipase type II (PPL) was purchased from Sigma.

NMR spectra were recorded on Bruker spectrometers working at 250 and 500 MHz for ^1H, with tetramethylsilane as an external reference. ^{19}F NMR spectra were recorded on Bruker spectrometers at 188.3 and 376.5 MHz, with CF_3CO_2H 10% in C_6D_6 and trifluoroethanol, respectively, as external references. ES mass spectra and DCI mass spectra were acquired on an API 365 Sciex Perkin–Elmer and a Nermag R10–10H instrument, respectively. All crystal data for structures given in this paper were collected at low temperatures from an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer with Mo-K_α radiation (λ = 0.71073 Å). The structures were solved by direct methods,[61] and all non-hydrogen atoms were refined anisotropically by the least-squares method on F^2.[62]

Melting points were measured on an Electrothermal Digital melting point apparatus. Ozone was generated in a steam of oxygen with an LI1981 type ozonizer from Trailigaz, the flow of molecular oxygen being 180 L h^{-1} (pressure 1.55 bar, power O_3 = 0.3 arbitrary unit). Chromatographic columns were performed on silica gel (60 ACC Chromagel, 70–230 mesh) and on basic aluminium oxide 90, 63–200 μm. TLC analyses were performed on Merck Kieselgel 60 F254 precoated silica gel plates with development by i) UV-fluorescence or ii) treatment with a solution of phosphomolybdic acid (5 g) and sulfuric acid (2 mL) in ethanol (95%, 20 mL), followed by heating the plate at 150 °C.

HPLC analysis of trioxaquantel **13** (series **A**) was performed with a 10 μm C18 Nucleosil column (250 × 4.6 mm). The eluent was CH_3CN/H_2O (40:60, v/v), and the flow rate was 1 mL min^{-1}. Detection was monitored at 254 nm. The retention times for the two diastereomers were 17.9 min (70%) and 19.9 min (30%).

HPLC analysis of trioxaquantels **17**, **25**, and **26** was performed with a 5 μm C18 Uptisphere column (250 × 4.6 mm). The eluent solutions were A) CH_3CN, and B) H_2O/HCO_2H (100:1, v/v). Flow rate 1 mL min^{-1}, detection at 262 nm. Elution of **17** was obtained with an A/B isocratic ratio of 40:60, v/v; retention times of the two diastereomers were 19.5 min (50%) and 22.0 min (50%). Elution of **25** and **26** was isocratic A/B 45:55, v/v. The retention time for **25** was 23.5 min (no separation of the diastereomers). The retention times of the two diastereomers of **26** were 24.6 min (40%) and 28.2 min (60%).

HPLC analysis of chiral ammonium salts of praziquanamine **3** and of carbamate **32** were performed with a 10 μm C18 Nucleosil column (250 × 4.6 mm). Flow rate was 1 mL min^{-1}. The eluent solutions were A) CH_3CN, and B) H_2O. In the case of ammonium salts, elution was a linear gradient from A/B 15:85, v/v to A/B 40:60, v/v in 15 min, followed by 10 min at A/B 40:60, v/v; detection of the product was monitored at 254 nm and the retention time was 17.7 min (one broad peak whatever the counterion was). In the case of **32**, elution was isocratic A/B 65:35, v/v; detection at 262 nm and retention time 27.0 min (a single peak for two diastereomers).

Chiral HPLC analysis of compound **3** was performed with a Chiralcel OD column (250 × 4.6 mm). Flow rate 1 mL min^{-1}. Detection at 254 nm. Eluent: hexane/2-propanol/diethylamine 80:20:0.1, v/v/v. Retention time: 13.9 min (1 broad peak).

CCDC-638938 [for (11b*R*,2′*R*)-**33**], -638939 (for *cis*-**34**), and -638940 (for *trans*-**34**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk).

Supporting Information (see also the footnote on the first page of this article): Tables with the main data (experimental data, distances and angles) for the three crystal structure determinations. ^1H NMR spectra of *cis*-**21** and *trans*-**21**.

Syntheses

***N*-(2-Phenylethyl)chloroacetamide (4):** Phenethylamine (6.0 mL, 48 mmol, 1 equiv.) and $NaHCO_3$ (4.0 g, 48 mmol, 1 equiv.) were dissolved under argon in CH_2Cl_2 (82 mL) at room temperature. The mixture was cooled to 0 °C and chloroacetyl chloride (4.6 mL, 57 mmol, 1.2 equiv.) was added. The reaction mixture was stirred at room temperature for 3 h, and water (60 mL) was carefully added. The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The organic layers were combined, washed with an aqueous solution of HCl (10%, 50 mL), dried with $MgSO_4$, filtered, concentrated, and dried under vacuum. A white powder was obtained (8.9 g, 91% yield). R_f = 0.83 (CH_2Cl_2/MeOH/NEt_3 90:10:0.5, v/v/v), m.p. 65 °C. ^1H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.33–7.19 (m, 5 H, $H_{aromatic}$), 6.62 (br. s, 1 H, NH), 4.03 (s, 2 H, CH_2Cl), 3.57 (m, ^3J = 7.0 Hz, 2 H, CH_2N), 2.85 (t, ^3J = 7.0 Hz, 2 H, Ph–CH_2) ppm. ES^+-MS: *m*/*z* (%) = 198.2 (55) $[M + H]^+$, 200.1 (18), 220.3 (100) $[M + Na]^+$, 222.2 (33), 236.4 (6) $[M + K]^+$, 238.4 (2).

***N*-(2-Phenylethyl)-2-[(2,2-dimethoxyethyl)amino]acetamide (5):** Chloroacetamide **4** (29.4 g, 149 mmol, 1 equiv.) was dissolved under argon in toluene (350 mL). Dimethoxyethylamine (32.5 mL, 298 mmol, 2 equiv.) was added, and the solution was stirred at reflux for 2 h. The mixture was cooled to 0 °C. Dimethoxyethylamine hydrochloride precipitated spontaneously and was obtained as a

white powder (20.9 g, quantitative yield). The solution was concentrated and dried under vacuum. A brownish oil corresponding to compound **5** was obtained (37 g, 93% yield). R_f = 0.63 (CH_2Cl_2/MeOH/NEt_3, 90:10:0.5, v/v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.33–7.16 (m, 5 H, $H_{aromatic}$), 4.29 [t, ^3J = 5.3 Hz, 1 H, $CH(OMe)_2$], 3.55 (td, ^3J = 7.0 Hz, 2 H, CH_2NHCO), 3.34 (s, 6 H, 2 × OCH_3), 3.25 (s, 2 H, $COCH_2NH$), 2.83 (t, ^3J = 7.0 Hz, 2 H, Ph–CH_2), 2.64 [d, ^3J = 5.3 Hz, 2 H, $CH_2CH(OMe)_2$]; ES$^+$-MS$^+$: *m*/*z* (%) = 235.2 (73) [M + H – CH_3OH]$^+$, 267.2 (100) [M + H]$^+$, 289.2 (46) [M + Na]$^+$.

2-[(2,2-Dimethoxyethyl)amino]-*N*-(2-phenylethyl)acetamide Hydrochloride (6): Compound **5** (14.7 g, 55 mmol, 1 equiv.) was dissolved in dichloromethane (90 mL). The solution was cooled to 0 °C and a solution of hydrochloric acid in diethyl ether (1 M, 61 mL, 61 mmol, 1.2 equiv.) was added. The hydrochloride **6** precipitated spontaneously and was filtered off, washed (15 mL each of diethyl ether and hexane), and dried under vacuum. A white powder was obtained (12.0 g, 73% yield), m.p. 153 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 9.00 (br. s, 2 H, NH_2^+), 8.58 (br. s, 1 H, NHCO), 7.29–7.19 (m, 5 H, $H_{aromatic}$), 4.88 [t, ^3J = 5.1 Hz, 1 H, $CH(OMe)_2$], 4.03 (s, 2 H, $COCH_2$), 3.52 (m, 2 H, CH_2NHCO), 3.41 (s, 6 H, 2 × OCH_3), 3.18 [d, ^3J = 5.1 Hz, 2 H, $CH_2CH(OMe)_2$], 2.88 (t, ^3J = 7.9 Hz, 2 H, Ph–CH_2) ppm. MS (DCI/NH_3): *m*/*z* (%) = 267 (100) [M + H]$^+$.

Praziquanamine 3

Synthesis of (±)3: Compound **6** (1.0 g, 3.30 mmol, 1 equiv.) was dissolved at 0 °C in concentrated H_2SO_4 (3.0 mL). The reaction mixture was stirred at room temperature for 3.5 h, and then poured into crushed ice (20 mL). An aqueous solution of NaOH (20 wt.-%) was added until pH 12. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, concentrated, and dried under vacuum. A white crystalline product was obtained (508 mg, 76% yield). R_f = 0.48 (CH_2Cl_2/MeOH/NEt_3, 90:10:0.5, v/v/v), m.p. 116–118 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.24 (m, 1 H, HC9), 7.23 (m, 1 H, HC10), 7.19 (m, 1 H, HC8), 7.15 (m, 1 H, HC11), 4.88 (m, ^2J = 12.5 Hz, 1 H, HC6), 4.82 (m, 1 H, HC11b), 3.75 (m, 1 H, HC1), 3.68 (AB, ^2J = 17.0 Hz, 1 H, HC3), 3.54 (AB, ^2J = 17.0 Hz, 1 H, HC3), 3.00 (m, 1 H, HC7), 2.90 (m, 1 H, HC1), 2.85 (m, 1 H, HC6), 2.77 (m, 1 H, HC7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 293 K): δ = 167.3 (C4), 134.9 (C7a), 134.2 (C11a), 129.4 (C8), 127.1 (C9), 126.7 (C10), 124.7 (C11), 56.8 (C11b), 50.0 (C3), 49.8 (C1), 38.8 (C6), 28.8 (C7) ppm. UV/Vis (CH_2Cl_2): λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 264 (400). MS (DCI/NH_3): *m*/*z* (%) = 203 (100) [M + H]$^+$, 220 (20) [M + NH_4]$^+$.

Synthesis of Enantiopure Praziquanamine 3 by Hydrolysis of Diastereomers of Mosher's Amides 33: A single stereomer of Mosher's amide **33** (see below; 208 mg, 498 μmol, 1 equiv.) was dissolved in H_3PO_4 (4 mL) and stirred at 100 °C for 3.5 days. The mixture was cooled to 0 °C and poured into crushed ice (30 mL), and an aqueous solution of NaOH (4.4 M) was added until pH 12. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH gradient from 100:0, v/v to 90:10, v/v). A white powder, corresponding to enantiopure praziquanamine was obtained (73 mg, 73% yield). Hydrolysis of (11b*R*,2′*R*)-**33** gives (11b*R*)-**3**, $[\alpha]_D$ = –152 (*c* = 4.0.10^{-3}, CH_2Cl_2), (*ee* > 95%). Hydrolysis of (11b*S*,2′*R*)-**33** gives (11b*S*)-**3**, $[\alpha]_D$ = +146 (*c* = 3.1.10^{-3}, CH_2Cl_2), (*ee* > 91%).

2-Methyl-2-[(triethylsilyl)dioxy]-1-propanol (8): 2-Methylprop-2-en-1-ol (10 mL, 119 mmol, 1 equiv.), cobalt acetylacetonate [Co(acac)$_2$, 1.53 g, 5.94 mmol, 0.05 equiv.], and triethylsilane (29 mL, 178 mmol, 1.5 equiv.) were mixed under argon in anhydrous ethanol stabilized with methyl ethyl ketone (2%). The inert atmosphere was replaced by 1.2 bar of molecular oxygen and the mixture was vigorously stirred for 4 h. Solvents were removed under vacuum. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 80:20, v/v). A colorless oil was obtained (9.4 g, 36% yield). R_f = 0.61 (hexane/AcOEt, 80:20, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 3.60 (d, ^3J = 6.0 Hz, 2 H, CH_2), 2.37 (m, 1 H, OH), 1.19 (s, 6 H, 2 × CH_3), 1.00 (t, ^3J = 8.3 Hz, 9 H, 3 × $SiCH_2CH_3$), 0.70 (q, ^3J = 8.3 Hz, 6 H, 3 × $SiCH_2CH_3$) ppm. MS (DCI/NH_3): *m*/*z* (%) = 221 (29) [M + H]$^+$, 238 (100) [M + NH_4]$^+$.

3,3-Dimethyl-1,2,5-trioxaspiro[5.5]undecan-9-one (9): Silyl peroxide **8** (1.7 g, 7.73 mmol, 1 equiv.) and cyclohexane-1,4-dione (2.6 g, 23.2 mmol, 3 equiv.) were dissolved under argon in chloroform (40 mL). *p*-Toluenesulfonic acid monohydrate was added (1.03 mg, 5.41 mmol, 0.7 equiv.), and the reaction mixture was stirred at room temperature for 45 min. Solvents were removed and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/Et_2O, gradient from 100:0, v/v to 95:5, v/v). A white powder was obtained (881 mg, 57% yield). R_f = 0.42 (CH_2Cl_2/Et_2O, 95:5, v/v), m.p. 68–69 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 3.79 and 3.52 (2× br. s, 2 H, O–CH_2), 2.70–1.95 (m, 8 H, $H_{cyclohexanone}$), 1.53 and 1.13 (2× br. s, 6 H, 2 × CH_3) ppm. MS (DCI/NH_3): *m*/*z* (%) = 218 (100) [M + NH_4]$^+$, 235 (18) [M + NH_3 + NH_4]$^+$.

***O*-Methyladamantan-2-one Oxime (10):** Pyridine (3 mL, 36.6 mmol, 2.2 equiv.) and *O*-methylhydroxylamine hydrochloride (2.2 mg, 26.6 mmol, 1.6 equiv.) were added, under argon, to a solution of adamantan-2-one (2.5 g, 16.6 mmol, 1 equiv.) in methanol (17 mL). The mixture was stirred at room temperature for 48 h and concentrated under vacuum. The white residue was diluted in water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with an aqueous solution of $CuSO_4$ (10 wt.-%), dried with $MgSO_4$, filtered, concentrated, and dried under vacuum. A white powder was obtained (2.34 g, 79% yield). R_f = 0.80 (hexane/AcOEt, 80:20, v/v). ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 3.81 (s, 3 H, $NOCH_3$), 3.46 (br. s, 1 H, adamantyl), 2.53 (br. s, 1 H, adamantyl), 1.99–1.63 (m, 12 H, adamantyl) ppm. ES$^+$-MS: *m*/*z* (%) = 180 (100) [M + H]$^+$.

Dispiro Compound 11: Oxime **10** (2.3 g, 12.8 mmol, 1 equiv.) and cyclohexane-1,4-dione (2.8 g, 27 mmol, 2 equiv.) were dissolved in a solution of pentane and CH_2Cl_2 (60:40, v/v). A flow of ozone was passed through the mixture for 5 min. The solution was concentrated and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate gradient from 100:0, v/v to 90:10, v/v). A powder was obtained and recrystallized from warm absolute ethanol. White crystals were obtained (1.02 g, 37% yield). R_f = 0.53 (hexane/AcOEt, 80:20, v/v), m.p. 71–72 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 2.53 (t, ^3J = 7.2 Hz, 4 H, 2 × $CH_{2\ cyclohexanone}$), 2.14 (t, ^3J = 7.2 Hz, 4 H, 2 × $CH_{2\ cyclohexnone}$), 2.03–1.70 (m, 14 H, adamantyl) ppm. MS (DCI/NH_3): *m*/*z* (%) = 296 (100) [M + NH_4]$^+$.

Trioxaquantel 12 (Series A): Racemic praziquanamine **3** (26 mg, 128 μmol, 1 equiv.) and trioxane **7** (36 mg, 128 μmol, 1 equiv.) were dissolved under argon in dichloroethane (2 mL). Sodium triacetoxyborohydride [$BH(OAc)_3Na$, 40 mg, 188 μmol, 1.4 equiv.] was added and the reaction mixture was stirred at room temperature for 72 h. An aqueous solution of NaOH (1 M) was added until pH 12. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography

(SiO_2, CH_2Cl_2/MeOH gradient from 100:0, v/v to 92:8, v/v). A yellow pale oil, containing four diastereomeric racemates, was obtained (28 mg, 47% yield). R_f = 0.75 (CH_2Cl_2/MeOH/NEt_3, 90:10:0.5, v/v/v, single spot). ^{1}H NMR (500 MHz, $CDCl_3$, 253 K): δ = 7.26–7.23 (m, 1 H, HC9), 7.25–7.23 (m, 1 H, HC10), 7.19–7.16 (m, 2 H, HC8, HC11), 5.47–5.38 (m, 1 H, HC6′), 4.88–4.80 (m, 1 H, HC11b), 4.81–4.78 (m, 1 H, HC6), 4.44–4.00 (m, 1 H, HC5′), 3.91–3.75 (m, 1 H, HC17′), 3.66–3.52 (m, 1 H, HC3), 3.62–3.52 (m, 1 H, HC1), 3.24–3.09 (m, 1 H, HC3), 2.97–2.94 (m, 1 H, HC7), 2.90–2.86 (m, 1 H, HC6), 2.77–2.76 (m, 1 H, HC7), 2.73–2.63 (m, 1 H, HC9′), 2.47–2.37 (m, 1 H, HC1), 2.24 (m, 1 H, HC12′), 2.29–2.14 (m, 1 H, HC8′), 2.17–2.05 (m, 1 H, HC8′), 1.87 (m, 2 H, HC15′, HC19′), 1.85–1.80 (m, 2 H, HC16′, HC18′), 1.70–1.51 (m, 2 H, HC16′, HC18′), 1.64–1.51 (m, 2 H, HC15′, HC19′), 1.72–1.49 (m, 1 H, HC9′), 1.07–1.00 (m, 6 H, H_3C13', H_3C14'), 1.00–0.91 (m, 3 H, H_3C11') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 253 K): δ = 167.1–167.0 (C4), 135.0–134.9 (C7a), 134.2 (C11a), 129.5 (C8), 127.2 (C9), 126.7 (C10), 124.9 (C11), 102.2–101.6 (C3′), 150.4–144.5 (C7′), 118.8–115.7 (C6′), 80.8–78.7 (C10′), 67.5–67.0 (C17′), 67.3–64.3 (C5′), 56.0–55.1 (C11b), 54.1–52.9 (C3), 53.8–52.2 (C1), 38.7 (C6), 34.9–34.6 (C12′), 32.7–32.4 (C15′, C19′), 30.9–29.9 (C16′, C18′), 28.8 (C7), 21.5–21.2 (C13′, C14′), 21.4–17.7 (C11′) ppm. ES$^+$-MS: *m*/*z* (%) = 467.3 (100) $[M + H]^+$, 483.3 (19) $[M + Na]^+$.

Trioxaquantel 13 (Series A): Racemic praziquanamine **3** (38.4 mg, 190 μmol, 1 equiv.) and trioxane **9** (38 mg, 190 μmol, 1 equiv.) were dissolved under argon in CH_2Cl_2 (3 mL). $BH(OAc)_3Na$ (60 mg, 285 μmol, 1.5 equiv.) was added, and the mixture was stirred at room temperature for 96 h. An aqueous solution of NaOH (1 M) was added until pH 12. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2/MeOH gradient from 100:0, v/v to 90:10, v/v) provided a pale yellow powder, containing two diastereomeric racemates (43 mg, 59% yield). R_f = 0.59 (CH_2Cl_2/MeOH/NEt_3, 90:10:0.5, v/v/v, one spot), m.p. 131–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 253 K): δ = 7.49–7.21 (m, 4 H, phenyl), 4.87 (m, 1 H, HC11b), 4.75 (m, 1 H, HC6), 3.87–3.82 (m, 1 H, HC9′), 3.80 (m, 1 H, HC5′), 3.60 (m, 1 H, HC3), 3.59 (m, 1 H, HC1), 3.40 (m, 1 H, HC5′), 3.20 (m, 1 H, HC3), 2.95 (m, 1 H, HC7), 2.90 (m, 1 H, HC6), 2.77 (m, 1 H, HC7), 2.46 (m, 1 H, HC1), 2.00 (m, 2 H, HC8′, HC10′), 1.85 (m, 2 H, HC7′, HC11′), 1.60 (m, 2 H, HC8′, HC10′), 1.50 (m, 2 H, HC7′, HC11′), 1.48 (s, 3 H, H_3C12'), 1.08 (s, 3 H, H_3C13') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 253 K): δ = 168.6 (C4), 135.1 (C7a), 134.2 (C11a), 129.5 (C8), 127.1 (C9), 126.7 (C10), 124.9 (C11), 100.9 (C3′), 77.3 (C6′), 67.2 (C9′), 66.5 (C5′), 55.7 (C11b), 53.1 (C3), 52.4 (C1), 39.0 (C6), 33.5 (C8′, C10′), 32.2 (C7′, C11′), 29.0 (C7), 22.6 (C13′), 21.4 (C12′) ppm. ES$^+$-MS: *m*/*z* (%) = 387.3 (100) $[M + H]^+$. Anal. for ($C_{22}H_{30}N_2O_4$) C,H,N.

Trioxaquantel 14 (Series A): (±)-Praziquanamine **3** (25 mg, 124 μmol, 1 equiv.) and trioxolane **11** (34.4 mg, 124 μmol, 1 equiv.) were dissolved under argon in CH_2Cl_2 (2 mL). $BH(OAc)_3Na$ (39.3 mg, 186 μmol, 1.5 equiv.) was added, and the mixture was stirred at room temperature for 72 h. An aqueous solution of NaOH (1 M) was added until pH 12. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, gradient from 100:0, v/v to 92:8, v/v), providing a pale yellow oil containing two diastereomeric racemates (34.5 mg, 70% yield). R_f = 0.71 (CH_2Cl_2/MeOH/NEt_3, 90:10:0.5, v/v/v, one spot). ^{1}H NMR (500 MHz, $CDCl_3$, 273 K): δ = 7.26 (m, 1 H, HC10), 7.25 (m, 1 H, HC9), 7.19 (m, 2 H, HC8, HC11), 4.87–4.83 (m, 1 H, HC11b), 4.81 (m, 1 H, HC6), 3.85–3.80 (m, 1 H, HC8′), 3.65–3.57 (m, 1 H, HC3), 3.61–3.55 (m, 1 H, HC1), 3.18–3.13 (m, 1 H, HC3), 2.97 (m, 1 H, HC7), 2.89 (m, 1 H, HC6), 2.81 (m, 1 H, $H_{adamantyl}$), 2.76 (m, 1 H, HC7), 2.45–2.43 (m, 1 H, HC1), 1.97–1.96 (m, 2 H, HC6′, HC10′), 1.92–1.89 (m, 2 H, HC7′, HC9′), 1.73–1.65 (m, 2 H, HC7′, HC9′), 1.71–1.69 (m, 2 H, HC6′, HC10′), 1.98–1.60 (m, 11 H, $H_{adamantyl}$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 166.9 (C4), 135.1 (C7a), 134.2 (C11a), 129.5 (C8), 127.1 (C9), 126.7 (C10), 124.9 (C11), 111.7–111.0 (C5′), 108.1 (C3′), 68.1–67.4 (C8′), 55.9 (C11b), 53.6–53.3 (C3), 53.7–52.8 (C1), 39.5 (3 × $C_{adamantyl}$), 38.7 (C6), 36.4–36.2 (4 × $C_{adamantyl}$), 35.2–34.7 (7 × $C_{adamantyl}$), 32.1–31.5 (C7′, C9′), 31.3–30.7 (C6′, C10′), 28.8 (C7) ppm. MS (DCI/NH_3): *m*/*z* (%) = 465 (100) $[M + H]^+$.

Ethyl 3,3-Dimethyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxylate (15): Silyl peroxide **8** (216 mg, 980 μmol, 1 equiv.), ethyl 4-oxocyclohexanecarboxylate (500 mg, 2.94 mmol, 3 equiv.), and *p*-toluenesulfonic acid monohydrate (130 mg, 686 μmol, 0.7 equiv.) were dissolved under argon in $CHCl_3$ (3 mL). The mixture was stirred at room temperature for 3 h. Solvent was removed and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/Et_2O, gradient from 100:0, v/v to 95:5, v/v). A colorless oil was obtained (156 mg, 62% yield); *cis*/*trans* isomers in 1:2 or 2:1 ratio. $R_{f\ average}$ = 0.42 (CH_2Cl_2/Et_2O, 95:5, v/v, two poorly resolved spots). MS (DCI/NH_3): *m*/*z* (%) = 259 (5) $[M + H]^+$, 276 (100) $[M + NH_4]^+$.

Separation of the *cis*/*trans* isomers of trioxane **15** (90 mg) was performed by column chromatography on basic alumina (1.2 × 35 cm, hexane/CH_2Cl_2 from 80:20, v/v to 60:40, v/v). Isomer 1 (30 mg) was eluted first, followed by a mixture of both (20 mg), and then pure isomer 2 (30 mg). Separation was monitored by TLC on SiO_2 (CH_2Cl_2/Et_2O, 95:5, v/v), visualized with a phosphomolybdic acid solution and heating at 150 °C.

Isomer 1 (*cis*-15 or *trans*-15): R_f = 0.40 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (500 MHz, $CDCl_3$, 263 K): δ = 4.13 (q, ^3J = 7.3 Hz, 2 H, CO_2CH_2), 3.76 (d, ^2J = 11.5 Hz, 1 H, HC5), 3.42 (d, ^2J = 11.5 Hz, 1 H, HC5), 2.38 (m, 1 H, HC9), 1.50 (s, 3 H, H_3C13), 1.25 (t, ^3J = 7.3 Hz, 3 H, $CO_2CH_2CH_3$), 1.09 (s, 3 H, H_3C12), 1.67 and 2.63 (2 H, H_2C7 or H_2C11), 1.68 and 1.88 (2 H, H_2C8 or H_2C10), 1.51 and 1.77 (2 H, H_2C10 or H_2C8), 1.82 and 1.88 (2 H, H_2C11 or H_2C7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 263 K): δ = 172.2 (CO), 101.2 (C3), 77.1 (C6), 66.4 (C5), 60.6 (CO_2CH_2), 41.7 (C9), 32.9 (C10 or C8), 26.5 (C7 or C11), 24.6 (C8 or C10), 24.3 (C11 or C7), 22.9 (C12), 21.9 (C13), 14.3 ($CO_2CH_2CH_3$) ppm. In addition, as assessed by COSY ^{1}H–^{1}H correlations, the carbon atoms whose chemical shifts are 24.6 and 26.5 ppm are in α positions. Similarly, the carbon atoms with resonances at δ = 24.3 and 32.9 ppm are in α positions.

Isomer 2 (*cis*-15 or *trans*-15): R_f = 0.44 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (500 MHz, $CDCl_3$, 253 K): δ = 4.11 (q, ^3J = 7.3 Hz, 2 H, CO_2CH_2), 3.88 (d, ^2J = 12.2 Hz, 1 H, HC5), 3.42 (d, ^2J = 12.2 Hz, 1 H, HC5), 2.35 (tt, ^3J = 11.0 Hz and ^3J = 3.7 Hz, 1 H, HC9), 1.51 (s, 3 H, H_3C13), 1.24 (t, ^3J = 7.3 Hz, 3 H, $CO_2CH_2CH_3$), 1.11 (s, 3 H, H_3C12), 1.42 and 2.85 (2 H, H_2C7 or H_2C11), 1.73 and 1.92 (2 H, H_2C8 or H_2C10), 1.59 and 1.87 (2 H, H_2C10 or H_2C8), 1.71 and 1.87 (2 H, H_2C11 or H_2C7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 253 K): δ = 175.4 (CO), 101.2 (C3), 77.1 (C6), 66.7 (C5), 60.6 (CO_2CH_2), 42.1 (C9), 33.8 (C10 or C8), 26.9 (C7 or C11), 24.9 (C8 or C10), 24.6 (C11 or C7), 22.9 (C12), 21.9 (C13), 14.4 ($CO_2CH_2CH_3$) ppm. In addition, as assessed by COSY ^{1}H–^{1}H correlations, the carbon atoms with chemical shifts 24.9 and 26.9 ppm are in α positions, and the carbon atoms at δ = 24.6 and 33.8 ppm are in α positions.

3,3-Dimethyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxylic Acid (16): Trioxane **15** (600 mg, 2.33 mmol, 1 equiv.) was dissolved in absolute ethanol (10 mL) and an aqueous solution of NaOH (4.4 M, 1.1 mL, 4.66 mmol, 2 equiv.) was added. The mixture was heated at 60 °C for 2 h, then cooled to 0 °C and a solution of concentrated hydrochloric acid was added until pH 3. NaCl spontaneously precipitated and was filtered off. The solution was concentrated and precipitated by addition of hexane (15 mL). The precipitate was filtered, washed with hexane, and dried under vacuum. A white powder was obtained (535 mg, quantitative yield), m.p. 120–122 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 3.80 and 3.47 (2× br. s, 2 H, O–CH_2), 2.45 (m, 1 H, $CHCO_2$), 1.91–1.52 (m, 8 H, $H_{cyclohexanone}$), 1.49 and 1.13 (2× br. s, 6 H, 2 × CH_3) ppm. MS (DCI/NH_3): *m*/*z* (%): 160 (8) $[M' + NH_4]^+$, M′ corresponding to the cleavage of the trioxane ring and the formation in the spectrometer of 4-oxocyclohexane-1-carboxylic acid), 231 (5) $[M + H]^+$, 248 (100), $[M + NH_4]^+$.

Trioxaquantel 17 (Series B): (±)-Praziquanamine **3** (255 mg, 1.26 mmol, 1 equiv.), trioxane **16** (290 mg, 1.26 mmol, 1 equiv.), PyBOP (787 mg, 1.51 mmol, 1.2 equiv.), and *N*-methylmorpholine (NMM, 692 µL, 6.30 mmol, 5 equiv.) were mixed under argon in dry DMF (10 mL). The mixture was stirred at room temperature for 8.5 h and then poured into a separating funnel, and CH_2Cl_2 (50 mL) was added. The organic layer was washed with an aqueous saturated solution of $NaHCO_3$ (50 mL) and with water (5 × 30 mL), dried with $MgSO_4$, filtered, concentrated, and dried under vacuum. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, from 100:0, v/v to 96:4, v/v). A colorless oil was obtained and precipitated in CH_2Cl_2/hexane, 1:6, v/v. A white powder, dried under vacuum, was obtained (306 mg, 59% yield), containing two diastereomeric racemates in 3:2 ratio, as determined by ^{1}H NMR spectroscopy. R_f = 0.67 (CH_2Cl_2/MeOH/NEt_3 90:10:0.5, v/v/v), m.p. 178–180 °C. MS (DCI/NH_3): *m*/*z* (%): 327 (9) $[M' + H]^+$ (M′ corresponding to the cleavage of the trioxane ring in the spectrometer, and subsequent formation of a ketone function on the cyclohexyl residue), 344 (18) $[M' + NH_4]^+$, 415 (50) $[M + H]^+$, 432 (100, $[M + NH_4]^+$. UV/Vis (CH_2Cl_2): λ_{max}, nm (ε, $M^{-1}\,cm^{-1}$): 262 (560). Anal. for ($C_{23}H_{30}N_2O_5$) C,H,N.

NMR analysis was performed with the mixture of diastereomers. For clarity, the resonances of both stereomers are given separately.

Diastereomer 1-17: ^{1}H NMR (500 MHz, $CDCl_3$, 253 K): δ = 7.32 (m, 1 H, HC10), 7.29 (m, 1 H, HC11), 7.27 (m, 1 H, HC9), 7.21 (m, 1 H, HC8), 5.22 (dd, ^2J = 15.0, ^3J = 5.0 Hz, 1 H, HC1), 4.85 (m, 1 H, HC6), 4.83 (m, 1 H, HC11b), 4.50 (AB, ^2J = 17.5 Hz, 1 H, HC3), 4.12 (AB, ^2J = 17.5 Hz, 1 H, HC3), 3.91 (d, ^2J = 10 Hz, 1 H, HC5′), 3.44 (d, ^2J = 10 Hz, 1 H, HC5′), 3.04 (m, 1 H, HC7′ or HC11′), 3.00 (m, 1 H, HC7), 2.91 (m, 1 H, HC6), 2.82 (m, 1 H, HC7), 2.80 (m, 1 H, HC1), 2.50 (m, 1 H, HC9′), 1.99 (m, 1 H, HC7′ or HC11′), 1.79 (m, 2 H, HC8′, HC10′), 1.70 (m, 2 H, HC8′, HC10′), 1.62 (m, 1 H, HC7′ or HC11′), 1.53 (s, 3 H, H_3C13′), 1.35 (m, 1 H, HC7′ or HC11′), 1.12 (s, 3 H, H_3C14′) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 253 K): δ = 173.5 (C12′), 164.3 (C4), 134.7 (C7a), 132.5 (C11a), 129.5 (C8), 125.5 (C11), 127.6 (C9), 127.1 (C10), 100.9 (C3′), 77.1 (C6′), 66.8 (C5′), 55.0 (C11b), 49.0 (C3), 45.0 (C1), 39.9 (C9′), 39.1 (C6), 34.1 (C11′), 28.7 (C7), 27.3 (C7′), 25.0 (C10′, C8′), 22.9 (C14′), 21.9 (C13′) ppm.

Diastereomer 2-17: ^{1}H NMR (500 MHz, $CDCl_3$, 253 K): δ = 7.32 (m, 2 H, HC10, HC9), 7.25 (m, 1 H, HC8), 7.19 (m, 1 H, HC11), 4.93 (m, 1 H, HC11b), 4.89 (m, 1 H, HC6), 4.80 (AB, ^2J = 17.5 Hz, 1 H, HC3), 4.34 (m, 1 H, HC1), 3.89 (AB, ^2J = 17.5 Hz, 1 H, HC3), 3.77 (d, ^2J = 10 Hz, 1 H, HC5′), 3.45 (d, ^2J = 10 Hz, 1 H, HC5′), 3.30 (m, 1 H, HC1), 2.99 (m, 1 H, HC7), 2.96 (m, 1 H, HC7′ or HC11′), 2.87 (m, 1 H, HC6), 2.82 (m, 1 H, HC7), 2.65 (m, 1 H, HC9′), 1.87 (m, 1 H, HC7′ or HC11′), 1.79 (m, 2 H, HC8′, HC10′), 1.70 (m, 2 H, HC8′, HC10′), 1.53 (s, 3 H, H_3C13′), 1.49 (m, 2 H, H7′, H11′), 1.12 (s, 3 H, H_3C14′) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 253 K): δ = 173.0 (C12′), 165.6 (C4), 134.5 (C7a), 131.7 (C11a), 129.4 (C8), 127.9 (C9), 127.1 (C10), 125.6 (C11), 100.9 (C3′), 77.1 (C6′), 66.4 (C5′), 55.7 (C11b), 49.6 (C3), 39.7 (C9′), 38.6 (C6), 33.1 (C11′), 28.8 (C7), 26.7 (C7′), 25.0 (C10′, C8′), 22.9 (C14′), 21.9 (C13′) ppm.

Ethyl 4,4-Diethoxycyclohexane-1-carboxylate (18): Ethyl 4-oxocyclohexane-1-carboxylate (2 g, 11.8 mmol, 1 equiv.) was dissolved under argon in absolute ethanol (20 mL). Triethyl orthoformate (3 mL, 16.5 mmol, 1.4 equiv.) and a solution of hydrochloric acid (5 M) in 2-propanol (471 µL, 2.35 mmol, 0.2 equiv.) were added. The reaction mixture was stirred at 80 °C for 4 h and then cooled at room temperature. CH_2Cl_2 (30 mL) and an aqueous saturated solution of K_2CO_3 (10 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10, v/v). A colorless oil was obtained (2.9 g, quantitative). R_f = 0.70 (hexane/AcOEt, 80:20, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 4.11 (q, ^3J = 7.2 Hz, 2 H, CO_2CH_2), 3.47 (q, ^3J = 7.1 Hz, 2 H, 4$COCH_2$), 3.37 (q, ^3J = 7.1 Hz, 2 H, 4$COCH_2$), 2.25 (tt, ^3J = 10.4, ^3J = 3.7 Hz, 1 H, HC1), 1.99 (dt, ^2J = 12.6, $^3J_{eq-eq}$ = $^3J_{ax-eq}$ = 4.4 Hz, 2 H, H_{eq}C3, H_{eq}C5), 1.88–1.60 (m, 4 H, H_2C2, H_2C6), 1.42 (ddd, 2 H, ^2J = 12.6, $^3J_{ax-ax}$ = 12.0, $^3J_{ax-eq}$ = 4.4 Hz, 2 H, H_{ax}C3, H_{ax}C5), 1.24 (t, ^3J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.17 (t, ^3J = 7.1 Hz, 3 H, 4-$COCH_2CH_3$), 1.15 (t, ^3J = 7.1 Hz, 3 H, 4-$COCH_2CH_3$) ppm. The protons with chemical shifts at 3.47 and 1.15 made up an ethyl group, the other ethyl being constituted by the signals at δ = 3.37 and 1.17 ppm. MS (DCI/NH_3): *m*/*z* (%) = 199 (100) $[M + H - CH_3CH_2OH]^+$, 244 (31) $[M]^+$, 262 (21) $[M + NH_4]^+$.

Ethyl 1-Methyl-4-oxocyclohexane-1-carboxylate (19): A solution of *n*-butyllithium (1.6 M in hexane, 5.63 mL, 9.02 mmol, 2 equiv.) was added at 0 °C under argon to a solution of diisopropylamine (1.26 mL, 9.02 mmol, 2 equiv.) in dry diethyl ether (12 mL). The mixture was stirred at 0 °C for 1 h. Diethyl acetal **18** (1.0 g, 4.09 mmol, 1 equiv.) in solution in dry diethyl ether (2 mL) was then added, and the temperature was raised. The reaction mixture was stirred at room temperature for 2 h. Dimethylsulfate (760 µL, 8.18 mmol, 2 equiv.) was then added and the mixture was stirred for a further 14 h. The reaction was quenched and the ketone function was deprotected in situ by the addition of an aqueous solution of hydrochloric acid (10%, 10 mL). The reaction mixture was vigorously stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 80:20, v/v). A colorless oil was obtained (551 mg, 73% yield). R_f = 0.45 (hexane/AcOEt, 80:20, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 4.22 (q, ^3J = 7.1 Hz, 2 H, CO_2CH_2), 2.51–2.28 (m, 6 H, 3 × $CH_{2\ cyclohexyl}$), 1.74–1.60 (m, 2 H, $CH_{2\ cyclohexyl}$), 1.29 (s, 3 H, C–CH_3), 1.28 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. MS (DCI/NH_3): *m*/*z* (%) = 185 (85) $[M + H]^+$, 202 (100) $[M + NH_4]^+$.

Ethyl 1-Fluoro-4-oxocyclohexane-1-carboxylate (20): A solution of *n*-butyllithium (1.6 M in hexane, 5.6 mL, 9.02 mmol, 2.2 equiv.) was added at 0 °C under argon to a solution of diisopropylamine (1.26 mL, 9.02 mmol, 2.2 equiv.) in dry THF (5 mL). The reaction mixture was stirred at 0 °C for 1 h and diethyl acetal **18** (1.0 g, 4.10 mmol, 1 equiv.) in solution in dry THF (5 mL) was added.

The mixture was stirred at 0 °C for 45 min. A solution of *N*-fluorobenzenesulfonimide (1.94 g, 6.15 mmol, 1.5 equiv.) in dry THF (10 mL) was added and the mixture was stirred at room temperature for 3 h. An aqueous solution of hydrochloric acid (10%, 10 mL) was added, and the reaction mixture was stirred for 1h. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified on a column chromatography (SiO_2, hexane/AcOEt, 80:20, v/v) to provide a pale yellow oil (517 mg, 67% yield). R_f = 0.35 (hexane/AcOEt, 80:20, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 4.31 (q, ^3J = 7.1 Hz, 2 H, CO_2CH_2), 2.80–2.61 (m, 2 H, $CH_{2\ cyclohexyl}$), 2.51–2.33 (m, 6 H, 3 × $CH_{2\ cyclohexyl}$), 1.32 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$) ppm. ^{19}F NMR (188.3 MHz, $CDCl_3$, 293 K): δ = –92.0 (s) ppm. MS (DCI/NH_3): *m*/*z* (%) = 206 (100) $[M + NH_4]^+$.

Ethyl 3,3,9-Trimethyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxylate (21): Silyl peroxide **8** (223 mg, 1.01 mmol, 1 equiv.), ketone **19** (559 mg, 3.04 mmol, 3 equiv.), and *p*-toluensulfonic acid monohydrate (133 mg, 699 μmol, 0.7 equiv.) were mixed under argon in $CHCl_3$ (5 mL) and stirred for 3.5 h at room temperature. Solvents were removed under vacuum and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/Et_2O, from 100:0, v/v to 95:5, v/v). Trioxane **21** (275 mg, quantitative yield) was obtained as a colorless oil. The excess of ketone **19** was also recovered and recycled (239 mg, 1.3 equiv.). The *cis*/*trans* isomers of **21** were in 3/2 ratio. $R_{f\ average}$ = 0.50 (CH_2Cl_2/Et_2O, 95:5, v/v). MS (DCI/NH_3): *m*/*z* (%): 185 (36) $[M' + H]^+$ (M′ corresponding to the opening of the trioxane and the formation of a ketone function on the cyclohexyl residue), 202 (19) $[M' + NH_4]^+$, 290 (100) $[M + NH_4]^+$.

Separation of the *cis*/*trans* isomers of trioxane **21** (330 mg) was performed by column chromatography on basic alumina (2.5 × 35 cm, hexane/CH_2Cl_2, from 80:20, v/v to 60:40, v/v). Isomer *trans*-**21** was eluted first (120 mg, *de* > 98%), followed by a mixture of *cis* and *trans* isomers (20 mg), and then by *cis*-**21** (190 mg, *de* > 98%). Separation was monitored by TLC on SiO_2 (CH_2Cl_2/Et_2O, 95:5, v/v), visualized by treatment with a phosphomolybdic acid solution and heating at 150 °C (R_f = 0.48 and 0.51 for *cis*-**21** and *trans*-**21**, respectively).

Isomer *trans*-21: R_f = 0.48 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (500 MHz, $CDCl_3$, 263 K): δ = 4.15 (q, ^3J = 7.0 Hz, 2 H, CO_2CH_2), 3.87 (d, ^2J = 12.1 Hz, 1 H, HC5), 3.40 (d, ^2J = 12.1 Hz, 1 H, HC5), 1.51 (s, 3 H, H_3C13), 1.26 (t, ^3J = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.17 (s, 3 H, H_3C-C9), 1.09 (s, 3 H, H_3C12), 1.64 and 1.74 (2 H, H_2C7 or H_2C11), 1.40 and 2.08 (2 H, H_2C8 or H_2C10), 1.45 and 2.11 (2 H, H_2C10 or H_2C8), 1.45 and 2.70 (2 H, H_2C11 or H_2C7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 263 K): δ = 177.0 (CO), 101.5 (C3), 77.1 (C6), 66.6 (C5), 60.6 (CO_2CH_2), 42.8 (C9), 32.3 (C7 or C11), 31.5 (C10 or C8), 31.1 (C8 or C10), 26.8 (*C*-C9), 25.3 (C11 or C7), 22.9 (C12), 21.9 (C13), 14.3 ($CO_2CH_2CH_3$) ppm. In addition, as assessed by COSY ^{1}H–^{1}H correlations, the carbon atoms with chemical shifts 31.1 and 32.3 ppm are in α positions. Similarly, the carbon atoms with chemical shifts 25.3 and 31.5 ppm are in α positions.

Isomer *cis*-21: R_f = 0.51 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (500 MHz, $CDCl_3$, 263 K): δ = 4.16 (q, ^3J = 7.0 Hz, 2 H, CO_2CH_2), 3.78 (d, ^2J = 11.8 Hz, 1 H, HC5), 3.43 (d, ^2J = 11.8 Hz, 1 H, HC5), 1.51 (s, 3 H, H_3C13), 1.26 (t, ^3J = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.20 (s, 3 H, H_3C-C9), 1.10 (s, 3 H, H_3C12), 1.70 and 2.49 (2 H, H_2C7 or H_2C11), 1.37 and 2.09 (2 H, H_2C8 or H_2C10), 1.55 and 1.65 (2 H, H_2C10 or H_2C8), 1.52 and 2.11 (2 H, H_2C11 or H_2C7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 263 K): δ = 177.1 (CO), 101.5 (C3), 77.2 (C6), 66.6 (C5), 60.6 (CO_2CH_2), 42.8 (C9), 31.4 (C10 or C8), 31.2 (C8 or C10), 30.7 (C11 or C7), 25.9 (*C*-C9), 24.9 (C7 or C11), 22.9 (C12), 21.9 (C13), 14.3 ($CO_2CH_2CH_3$). COSY ^{1}H–^{1}H correlations indicate that the carbon atoms whose resonances are at δ = 24.9 and 31.2 ppm are in α positions, and the carbon atoms with shifts δ = 30.7 and 31.4 ppm are in α positions.

Ethyl 9-Fluoro-3,3-dimethyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxylate (22): Silyl peroxide **8** (218 mg, 993 μmol, 1 equiv.), ketone **20** (560 mg, 2.98 mmol, 3 equiv.), and *p*-toluenesulfonic acid (130 mg, 685 μmol, 0.7 equiv.) were dissolved under argon in chloroform (5 mL) and the mixture was stirred at room temperature for 3.5 h. Solvents were removed under vacuum and the residue was purified by chromatography (SiO_2, CH_2Cl_2/Et_2O, from 100:0, v/v to 95:5, v/v) to yield a colorless oil (273 mg, quantitative). The *cis*/*trans* isomers were in 3:2 or 2:3 ratio (undetermined). $R_{f\ average}$ = 0.82 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 4.23 (q, ^3J = 7.0 Hz, 2 H, CO_2CH_2), 3.70 and 3.45 (2× br. s, 2 H, O–CH_2), 2.22–1.01 (m, 14 H, 4 × $CH_{2\ cyclohexyl}$ + 2 × CH_3), 1.29 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3) ppm. ^{19}F NMR (188.3 MHz, $CDCl_3$, 293 K): δ = –91.3 (s, 60%) and –92.0 (s, 40%) ppm. MS (DCI/NH_3): *m*/*z* (%): 206 (35) $[M' + NH_4]^+$ (M′ corresponding to the cleavage of the trioxane and the formation of a ketone function on the cyclohexyl residue), 294 (100) $[M + NH_4]^+$.

3,3,9-Trimethyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxylic Acid (23): Trioxane *cis*-**21** or *trans*-**21** (320 mg, 1.18 mmol, 1 equiv.) was dissolved in absolute ethanol (5 mL). An aqueous solution of NaOH (4.4 M,535 μL, 2.36 mmol, 2 equiv.) was added, and the mixture was stirred at 60 °C for 2 h, then cooled to 0 °C, and concentrated hydrochloric acid was added until pH 3. NaCl precipitated and was filtered. The solution was concentrated, and compound **23** precipitated on addition of hexane at 0 °C (5 mL). It was filtered off, washed with hexane, and dried under vacuum. A white powder was obtained (290 mg, quantitative), m.p. 148–150 °C. MS (DCI/NH_3): *m*/*z* (%): 174 (12) $[M' + NH_4]^+$ (M′ corresponding to the opening of the trioxane and the formation of a ketone function on the cyclohexyl residue), 262 (100) $[M + NH_4]^+$.

Isomer *trans*-23: ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 3.81 and 3.41 ppm (2× br. s, 2 H, O–CH_2), 2.12–2.02 (m, 2 H), 1.78–1.02 (m, 12 H, 3 × $CH_{2\ cyclohexyl}$ + 2 × CH_3), 1. 25 (s, 3 H, CH_3).

Isomer *cis*-23: ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 3.71 and 3.45 ppm (2× br. s, 2 H, O–CH_2), 2.11–2.05 (m, 2 H), 1.82–1.03 (m, 12 H, 3 × $CH_{2\ cyclohexyl}$ + 2 × CH_3), 1. 26 (s, 3 H, CH_3).

9-Fluoro-3,3-dimethyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxylic Acid (24): Unseparated *cis* and *trans* isomers of trioxane **22** (400 mg, 1.45 mmol, 1 equiv.) were dissolved in absolute ethanol (4 mL). An aqueous solution of NaOH (4.4 M, 659 μL, 2.90 mmol, 2 equiv.) was added and the mixture was stirred at 60 °C for 2 h, then cooled to 0 °C, and concentrated hydrochloric acid was added until pH 3. NaCl precipitated and was filtered off. The solution was concentrated and precipitated by addition of hexane (5 mL) at 0 °C. Product **24** precipitated; it was filtered, washed with hexane, and dried under vacuum (359 mg, quantitative, white powder). The *cis*/*trans* isomers were in 3:2 or 2:3 ratio (undetermined), m.p. 128–129 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 3.86 and 3.45 ppm (2× br. s, 2 H, O–CH_2), 2.98–2.41 (m, 1 H, cyclohexyl), 2.27–1.65 (m, 7 H, cyclohexyl), 1.49 (br. s, 3 H, CH_3), 1.15 (br. s, 3 H, CH_3) ppm. ^{19}F NMR (188.3 MHz, $CDCl_3$, 293 K): δ = –91.0 (s, 60%) and –92.0 (s, 40%) ppm. MS (DCI/NH_3): *m*/*z* (%): 160 (7) $[M' + H]^+$ (M′ corresponding to the cleavage of the trioxane and the formation of a ketone on the cyclohexyl), 266 (100) $[M + NH_4]^+$.

Trioxaquantel 25 (Series B): Enantiopure (*R*)- or (*S*)-praziquanamine **3** (112 mg, 553 μmol, 1 equiv.), trioxane *cis*-**23** or *trans*-**23** (135 mg, 553 μmol, 1 equiv.), PyBOP (345 mg, 664 μmol, 1.2 equiv.), and NMM (304 μL, 2.77 mmol, 5 equiv.) were dissolved under argon in dry DMF (1 mL), and the mixture was stirred at room temperature for 7.5 h. The mixture was poured into a funnel and CH_2Cl_2 (30 mL) was added. The organic layer was washed with a saturated aqueous solution of K_2CO_3 (30 mL) and with water (3 × 30 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2/MeOH from 100:0, v/v to 96:4, v/v). A colorless oil was obtained and precipitated with CH_2Cl_2/hexane, 1:6, v/v to yield a white powder (140 mg, 59% yield). The four stereoisomers of **25** were then separately obtained and analyzed. R_f = 0.78 (CH_2Cl_2/MeOH/NEt_3 90:10:0.5, v/v/v), m.p. 200–201 °C. MS (DCI/NH_3): *m*/*z* (%) = 341 (42) $[M' + H]^+$ (M′ corresponding to the cleavage of the trioxane and the formation of a ketone on the cyclohexyl), 429 (100) $[M + H]^+$, 446 (10) $[M + NH_4]^+$. UV/Vis (CH_2Cl_2): λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 262 (610). Anal. for ($C_{24}H_{32}N_2O_5$ $^1/_8$ H_2O) C,H,N.

Enantiomers (*R*,*trans*)-25 *and* (*S*,*trans*)-25: $[\alpha]_D$ = –95 (*c* = 2.9.10^{-3}, CH_2Cl_2), *ee* > 95%, *de* > 98% for (*R*,*trans*)-**25**. $[\alpha]_D$ = +90 (*c* = 2.5.10^{-3}, CH_2Cl_2), *ee* > 90%, *de* > 98% for (*S*,*trans*)-**25**. ^{1}H NMR (500 MHz, $CDCl_3$, 273 K): δ = 7.29–7.23 (m, 3 H, HC9, HC10, HC11), 7.22 (d, ^3J = 7.5 Hz, 1 H, HC8), 5.09 (br. s, 1 H, HC1), 4.88–4.80 (m, 3 H, HC3, HC6, HC11b), 4.02 (d, ^2J = 17.5 Hz, 1 H, HC3), 3.83 (d, ^2J = 12.1 Hz, 1 H, HC5′), 3.42 (d, ^2J = 12.1 Hz, 1 H, HC5′), 3.05–2.84 (m, 3 H, HC1, HC6, HC7), 2.80 (dd, ^2J = 15.3, ^3J = 4.1 Hz, 1 H, HC7), 2.57 (dt, ^2J = 17.5, ^3J = 6.6 Hz, 1 H, HC7′ or HC11′), 2.25–2.15 (m, 2 H, H_2C8′ or H_2C10′), 1.87–1.72 (m, 3 H, H_2C8′ or H_2C10′, HC7′ or HC11′), 1.68–1.56 (m, 2 H, HC7′ or HC11′), 1.52 (d, ^4J = 4.1 Hz, 3 H, H_3C13′), 1.34 (s, 3 H, H_3C-C9′), 1.11 (s, 3 H, H_3C14′) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 174.7 (C12′), 164.6 (C4), 134.9 (C7a), 132.5 (C11a), 129.6 (C8), 127.6 (C9), 127.0 (C10), 125.4 (C11), 101.3 (C3′), 77.1 (C6′), 66.6 (C5′), 55.0 (C11b), 50.0 (C3), 48.6 (C1), 42.7 (C9′), 39.0 (C6), 33.4 (C8′ or C10′), 32.0 (C8′ or C10′), 28.8 (C7), 25.2 (C7′ or C11′), 25.1 (C7′ or C11′), 24.8 (*C*-C9′), 22.9 (C14′), 21.9 (C13′) ppm.

Enantiomers (*R*,*cis*)-25 *and* (*S*,*cis*)-25: $[\alpha]_D$ = –100 (*c* = 3.0.10^{-3}, CH_2Cl_2), *ee* > 95%, *de* > 98% for (*R*,*cis*)-**25**. $[\alpha]_D$ = +96 (*c* = 2.1.10^{-3}, CH_2Cl_2), *ee* > 90%, *de* > 98% for (*S*,*cis*)-**25**. ^{1}H NMR (500 MHz, $CDCl_3$, 273 K): δ = 7.32 (d, ^3J = 7.2 Hz, 1 H, HC11), 7.30–7.27 (m, 2 H, HC9, HC10), 7.22 (d, ^3J = 7.6 Hz, 1 H, HC8), 5.13 (dd, ^2J = 12.9, ^3J = 5.7 Hz, 1 H, HC1), 4.89–4.81 (m, 3 H, HC3, HC6, HC11b), 4.00 (d, ^2J = 16.4 Hz, 1 H, HC3), 3.82 (d, ^2J = 10.9 Hz, 1 H, HC5′), 3.46 (d, ^2J = 10.9 Hz, 1 H, HC5′), 3.05–2.86 (m, 3 H, HC1, HC6, HC7), 2.81 (dd, ^2J = 16.4, ^3J = 2.7 Hz, 1 H, HC7), 2.30–2.15 (m, 4 H, H_2C7′ or H_2C11′, H_2C8′ or H_2C10′), 1.90–1.68 (m, 2 H, H_2C8′ or H_2C10′), 1.68–1.49 (m, 2 H, H_2C7′ or H_2C11′), 1.54 (s, 3 H, H_3C13′), 1.36 (s, 3 H, H_3C-C9′), 1.12 (s, 3 H, H_3C14′) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 175.0 (C12′), 164.7 (C4), 134.9 (C7a), 132.5 (C11a), 129.5 (C8), 127.5 (C9), 127.0 (C10), 125.6 (C11), 101.3 (C3′), 77.0 (C6′), 66.7 (C5′), 55.1 (C11b), 50.0 (C3), 48.7 (C1), 42.5 (C9′), 39.0 (C6), 31.2 (C8′ or C10′), 28.8 (C8′ or C10′), 28.5 (C7), 24.7 (*C*-C9′), 24.0 (C7′ or C11′), 23.7 (C7′ or C11′), 22.9 (C14′), 22.0 (C13′) ppm.

Trioxaquantel 26 (Series B): Racemic praziquanamine **3** (244 mg, 1.21 mmol, 1 equiv.), trioxane **24** (*cis* + *trans* isomers, 300 mg, 1.21 mmol, 1 equiv.), PyBOP (755 mg, 1.45 mmol, 1.2 equiv.), and NMM (664 μL, 6.05 mmol, 5 equiv.) were dissolved under argon in DMSO (7 mL) and the mixture was stirred at room temperature for 7 h. The mixture was poured into a funnel and CH_2Cl_2 (30 mL) was added. The organic layer was washed with an aqueous saturated solution of Na_2CO_3 (30 mL) and with water (5 × 15 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH from 100:0, v/v to 96:4, v/v). A colorless oil was obtained and precipitated in CH_2Cl_2/hexane, 1:6, v/v to yield a white powder containing **26** as two diastereomeric racemates (330 mg, 63% yield). R_f = 0.73 (CH_2Cl_2/MeOH/NEt_3 90:10:0.5 v/v/v), m.p. 179–181 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 264 K): δ = 7.33–7.29 (m, 1 H, HC9), 7.31–7.30 (m, 1 H, HC10), 7.29–7.20 (m, 1 H, HC11), 7.27–7.21 (m, 1 H, HC8), 5.12–5.00 (m, 1 H, HC1), 4.97–4.87 (m, 1 H, HC11b), 4.95–4.91 (AB, ^2J = 17.5 Hz, 1 H, HC3), 4.92–4.83 (m, 1 H, HC6), 4.19–3.82 (AB, ^2J = 17.5 Hz, 1 H, HC3), 3.93–3.74 (m, 1 H, HC5′), 3.45 (m, 1 H, HC5′), 3.18–2.87 (m, 1 H, HC1), 3.00–2.98 (m, 1 H, HC7), 2.98–1.71 (m, 4 H, H_2C8′, H_2C10′), 2.92–2.85 (m, 1 H, HC6), 2.81 (m, 1 H, HC7), 2.52–1.79 (m, 4 H, H_2C7′, H_2C11′), 1.54 (m, 3 H, H_3C13′), 1.13 (m, 3 H, H_3C14′) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 264 K): δ = 170.0–169.1 (C12′, $^2J_{CF}$ = 22 Hz), 164.8–164.5 (C4), 135.2–134.8 (C7a), 132.4–131.9 (C11a), 129.5–129.7 (C8), 127.6 (C9), 127.1 (C10), 125.6 (C11), 97.5–96.7 (C9′, $^1J_{CF}$ = 186 Hz), 100.3 (C3′), 77.2 (C6′), 66.8–66.7 (C5′), 56.1–54.6 (C11b), 50.2–46.9 (C1), 49.8–47.9 (C3, $^4J_{CF}$ = 16 and 9 Hz), 39.0–38.7 (C6), 30.0–29.0 (C8′, C10′), 28.9–28.7 (C7), 22.9–22.5 (C7′, C11′), 22.9 (C14′), 21.9 (C13′) ppm. MS (DCI/NH_3): *m*/*z* (%) = 345 (63) $[M' + H]^+$ (M′ corresponding to the cleavage of the trioxane and formation of a ketone on the cyclohexyl), 362 (16) $[M' + NH_4]^+$, 433 (100) $[M + H]^+$, 450 (10) $[M + NH_4]^+$. UV/Vis (CH_2Cl_2): λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 262 (340). Anal. for ($C_{23}H_{29}FN_2O_5$·4/5 CH_2Cl_2) C,H,N.

(*S*)-4-Methyl-*N*-(2-phenylethyl)benzenesulfinamide (27): A solution of *n*-butyllithium (1.6 M in hexane, 1.16 mL, 1.87 mmol, 1.1 equiv.) was added under argon at –78 °C to a solution of phenylethylamine (213 μL, 1.7 mmol, 1 equiv.) in freshly distilled THF (17 mL), and the mixture was warmed to room temperature. This solution was added under argon to a solution of (1*S*,2*R*,5*S*)-menthyl (5*R*)-*p*-toluenesulfinate (500 mg, 1.7 mmol, 1 equiv.) dissolved in freshly distilled THF (1 mL). The mixture was then stirred at room temperature for 3 h, and the reaction was quenched by the addition of an aqueous solution of Na_2HPO_4 (1 M, 50 mL). The mixture was diluted with water (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 98:2, v/v). A colorless oil was obtained and precipitated with CH_2Cl_2/hexane. A white powder was obtained (348 mg, 79% yield). R_f = 0.75 (CH_2Cl_2/MeOH/NEt_3, 90:10:0.5, v/v/v). $[\alpha]_D$ = –70 (*c* = 0.04, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.53 [d, ^3J = 8.2 Hz, 2 H, =CH–C(SO)], 7.27 [d, ^3J = 8.2 Hz, 2 H, =C*H*–C(CH_3)], 7.24–6.84 (m, 5 H, phenyl), 4.02 (br. t, ^3J = 5.6 Hz, 1 H, NH), 3.36 (m, 1 H, C*H*HNH), 3.07 (m, 1 H, CH*H*NH), 2.78 (t, ^3J = 6.9 Hz, 2 H, Ph–CH_2) ppm. ES$^+$-MS: *m*/*z* (%) = 260.1 (100) $[M + H]^+$, 282.2 (49) $[M + Na]^+$.

2-(2,2-Dimethoxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (28): Acetamide (2.60 g, 44 mmol, 8 equiv.), potassium phthalimide (1.02 g, 5.5 mmol, 1 equiv.), and potassium iodide (750 mg, 4.5 mmol, 0.8 equiv.) were mixed under argon at 150 °C. When a suspension in melted acetamide was obtained, bromoacetaldehyde dimethyl acetal (843 μL, 7.14 mmol, 1.3 equiv.) was added. The mixture was stirred at 110 °C for 40 min, then at 140 °C for 2 h 45, and was finally cooled to room temperature. Water (5 mL) was added and the precipitate was filtered. A white powder was obtained (1.3 g, quantitative). R_f = 0.75 (hexane/AcOEt, 50:50, v/v). ^{1}H NMR

(250 MHz, $CDCl_3$, 293 K): δ = 7.89–7.83 (m, 2 H, $H_{aromatic}$), 7.77–7.68 (m, 2 H, $H_{aromatic}$), 4.77 [t, ^3J = 5.8 Hz, 1 H, $CH(OMe)_2$], 3.83 (d, ^3J = 5.8 Hz, 2 H, CH_2), 3.38 (s, 6 H, 2 × OCH_3) ppm. ES^+-MS: *m/z* (%) = 204.2 (43) $[M + H - CH_3OH]^+$, 236.2 (6) $[M + H]^+$, 258.2 (100) $[M + Na]^+$, 274.3 (4) $[M + K]^+$.

Acylpraziquanamine (30): (±)-Praziquanamine **3** (500 mg, 2.48 mmol, 1 equiv.) was dissolved in $CHCl_3$ (5 mL), and CH_3COOH (2.3 mL, 24.8 mmol, 10 equiv.) was added. The mixture was stirred at room temperature for 8 h. Solvents were removed under vacuum, and the residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, from 100:0, v/v to 93:7, v/v). A pale brown powder was obtained (675 mg, quantitative). R_f = 0.63 (CH_2Cl_2/MeOH 90:10, v/v). MS (DCI/NH_3): *m/z* (%) = 245.3 (3) $[M + H]^+$, 262.2 (100) $[M + NH_4]^+$, 279.3 (6) $[M + NH_4 + NH_3]^+$. For clarity, the NMR spectra of the two rotamers are described separately.

Major Rotamer of 30: ^1H NMR (500 MHz, [D_6]DMSO, 293 K): δ = 7.46 (d, ^3J = 5 Hz, 1 H, HC11), 7.31–7.20 (m, 3 H, HC8, HC9, HC10), 5.00 (dd, ^3J = 10.0, ^3J = 5.0 Hz, 1 H, HC11b), 4.56 (m, 1 H, HC6), 4.44 (d, ^2J = 20.0 Hz, 1 H, HC3), 4.42 (dd, ^2J = 16.5, ^3J = 5.0 Hz, 1 H, HC1), 3.75 (d, ^2J = 20.0 Hz, 1 H, HC3), 3.30 (dd, ^2J = 16.5, ^3J = 10.0 Hz, 1 H, HC1), 2.87–2.80 (m, 2 H, H_2C7), 2.85 (m, 1 H, HC6), 2.17 (s, 3 H, CH_3).

Minor Rotamer of 30: ^1H NMR (500 MHz, [D_6]DMSO, 293 K): δ = 7.28 (m, 1 H, HC11), 7.31–7.20 (m, 3 H, HC8, HC9, HC10), 4.81 (m, 1 H, HC1), 4.80 (m, 1 H, HC11b), 4.56 (m, 1 H, HC6), 4.33 (d, ^2J = 18.5 Hz, 1 H, HC3), 4.07 (d, ^2J = 18.5 Hz, 1 H, HC3), 2.89 (m, 1 H, HC1), 2.87–2.80 (m, 2 H, H_2C7), 2.85 (m, 1 H, HC6), 2.06 (s, 3 H, CH_3).

(*R*)-Sulfinate of (±)-Praziquanamine 31: (±)-Praziquanamine **3** (100 mg, 0.5 mmol, 1 equiv.) was dissolved under argon in freshly distilled THF (5 mL). The solution was cooled to –78 °C, and a solution of *n*-butyllithium (1.6 M in hexane, 344 µL, 0.55 mmol, 1.1 equiv.) was added. The mixture was warmed to room temperature and was added to a solution of (1*S*,2*R*,5*S*)-menthyl (5*R*)-*p*-toluenesulfinate (147 mg, 0.5 mmol, 1 equiv.) in freshly distilled THF (0.5 mL). The mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of an aqueous solution of Na_2HPO_4 (1 M, 15 mL), and then diluted with water (15 mL) and CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate from 100:0, v/v to 50:50, v/v). A yellow glassy compound was obtained (15 mg, 10% yield, two diastereomers). R_f = 0.53 (hexane/AcOEt, 50:50, v/v). $[\alpha]_D$ = –16 (c = 2.5.10^{-3}, CH_2Cl_2). ^1H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.43 (d, ^2J = 8.1 Hz, 2 H, =C*H*–CSO_2), 7.25–7.04 [m, 6 H, H_{phenyl} + 2 × = C*H*–$C(CH_3)$], 4.96 (dd, J = 10.2, J = 4.4 Hz, 1 H), 4.80 (m, 1 H), 3.91–3.75 (m, 1 H), 3.83 (AB, ^2J = 16.6 Hz, 1 H, HC3), 3.43 (AB, ^2J = 16.6 Hz, 1 H, HC3), 2.86–2.67 (m, 4 H), 2.34 (s, 3 H, $CH_{3\ tolyl}$) ppm. MS (DCI/NH_3): *m/z* (%) = 325 (100) $[M - O + H]^+$, 342 (38) $[M - O + NH_4]^+$, 358 (7) $[M + H]^+$.

Menthyl Carbamate of (±)-Praziquanamine 32: (±)-Praziquanamine **3** (50 mg, 248 µmol, 1 equiv.) and triethylamine (38 µL, 495 µmol, 2 equiv.) were dissolved under argon in THF (1.3 mL). The solution was cooled to 0 °C, and (–)-menthyl chloroformate (105 µL, 495 µmol, 2 equiv.) was added. The slurry mixture was stirred at room temperature for 1 h and then diluted with water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, diethyl ether 100%). A white powder was obtained (91 mg, quantitative). $R_{f\ average}$ = 0.57 (100% Et_2O), m.p. 70–73 °C. UV/Vis (CH_2Cl_2): λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 262 (420). MS (DCI/NH_3): *m/z* (%) = 385 (40) $[M + H]^+$, 402 (100) $[M + NH_4]^+$. Compound **32** is a mixture of two diastereomeric racemates, each of them existing as two rotamers that were identified at 273 K. For clarity, the NMR spectra of the diastereomers and rotamers are described separately.

Diastereomer 1-32, Major Rotamer: ^1H NMR (500 MHz, $CDCl_3$, 273 K): δ = 7.30 (m, 1 H, HC10), 7.29 (m, 1 H, HC11), 7.28 (m, 1 H, HC9), 7.22 (m, 1 H, HC8), 4.91 (m, 1 H, HC11b), 4.89 (m, 1 H, HC6), 4.78 (m, 1 H, HC1), 4.62 (m, 1 H, HC3′), 4.57 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.92 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.00 (m, 1 H, HC7), 2.95 (m, 1 H, HC1), 2.91 (m, 1 H, HC6), 2.81 (m, 1 H, HC7), 2.10 (m, 1 H, HC8′), 1.93 (m, 1 H, HC9′), 1.70 (m, 2 H, HC5′, HC6′), 1.52 (m, 1 H, HC7′), 1.40 (m, 1 H, HC4′), 1.07 (m, 1 H, HC5′), 1.00 (m, 1 H, HC8′), 0.93 (s, 3 H, H_3C12'), 0.92 (m, 3 H, H_3C11'), 0.89 (m, 1 H, HC6′), 0.79 (d, ^3J = 7.1 Hz, 3 H, H_3C10') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 65.1 (C4), 157.4 (C1′), 139.9 (C7a), 132.6 (C11a), 129.4 (C8), 127.5 (C9), 127.0 (C10), 125.6 (C11), 76.2 (C3′), 55.3 (C11b), 47.5 (C3), 47.2 (C4′), 46.9 (C1), 41.3 (C8′), 38.8 (C6), 34.2 (C6′), 31.4 (C7′), 28.8 (C7), 26.2 (C9′), 23.3 (C5′), 22.2 (C12′), 21.0 (C11′), 16.4 (C10′) ppm.

Diastereomer 2-32, Major Rotamer: ^1H NMR (500 MHz, $CDCl_3$, 273 K): δ = 7.30 (m, 1 H, HC10), 7.29 (m, 1 H, HC11), 7.28 (m, 1 H, HC9), 7.22 (m, 1 H, HC8), 4.91 (m, 1 H, HC11b), 4.89 (m, 1 H, HC6), 4.78 (m, 1 H, HC1), 4.62 (m, 1 H, HC3′), 4.58 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.93 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.00 (m, 1 H, HC7), 2.95 (m, 1 H, HC1), 2.91 (m, 1 H, HC6), 2.81 (m, 1 H, HC7), 2.10 (m, 1 H, HC8′), 1.93 (m, 1 H, HC9′), 1.70 (m, 2 H, HC5′, HC6′), 1.52 (m, 1 H, HC7′), 1.40 (m, 1 H, HC4′), 1.07 (m, 1 H, HC5′), 1.00 (m, 1 H, HC8′), 0.93 (s, 3 H, H_3C12'), 0.91 (m, 3 H, H_3C11'), 0.89 (m, 1 H, HC6′), 0.78 (d, ^3J = 7.1 Hz, 3 H, H_3C10') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 165.1 (C4), 154.6 (C1′), 134.9 (C7a), 132.6 (C11a), 129.4 (C8), 127.5 (C9), 127.0 (C10), 125.6 (C11), 76.1 (C3′), 55.3 (C11b), 47.4 (C3), 47.2 (C4′), 46.8 (C1), 41.3 (C8′), 38.8 (C6), 34.1 (C6′), 31.4 (C7′), 28.8 (C7), 26.2 (C9′), 23.1 (C5′), 22.2 (C12′), 20.9 (C11′), 16.3 (C10′) ppm.

Diastereomer 1-32, Minor Rotamer: ^1H NMR (500 MHz, $CDCl_3$, 273 K): δ = 7.32 (m, 1 H, HC10), 7.27 (m, 1 H, HC9), 7.22 (m, 2 H, HC8, HC11), 4.83 (m, 1 H, HC11b), 4.89 (m, 1 H, HC6), 4.85 (m, 1 H, HC1), 4.62 (m, 1 H, HC3′), 4.58 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.94 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.07 (m, 1 H, HC1), 3.00 (m, 1 H, HC7), 2.91 (m, 1 H, HC6), 2.81 (m, 1 H, HC7), 2.11 (m, 1 H, HC8′), 1.98 (m, 1 H, HC9′), 1.72 (m, 1 H, HC5′), 1.70 (m, 1 H, HC6′), 1.52 (m, 1 H, HC7′), 1.49 (m, 1 H, HC4′), 1.12 (m, 1 H, HC5′), 1.03 (m, 1 H, HC8′), 0.97 (d, ^3J = 7.0 Hz, 3 H, H_3C11'), 0.93 (s, 3 H, H_3C12'), 0.89 (m, 1 H, HC6′), 0.86 (d, ^3J = 7.0 Hz, 3 H, H_3C10') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 165.5 (C4), 154.4 (C1′), 135.3 (C7a), 132.5 (C11a), 129.6 (C8), 127.5 (C9), 126.9 (C10), 125.4 (C11), 76.2 (C3′), 55.6 (C11b), 47.7 (C3), 47.6 (C1), 47.3 (C4′), 41.6 (C8′), 38.8 (C6), 34.2 (C6′), 31.4 (C7′), 28.8 (C7), 27.0 (C9′), 23.8 (C5′), 22.2 (C12′), 20.8 (C11′), 17.0 (C10′) ppm.

Diastereomer 2-32, Major Rotamer: ^1H NMR (500 MHz,$CDCl_3$, 273 K): δ = 7.32 (m, 1 H, HC10), 7.27 (m, 1 H, HC9), 7.22 (m, 1 H, HC8), 7.17 (m, 1 H, HC11), 4.83 (m, 1 H, HC11b), 4.89 (m, 1 H, HC6), 4.85 (m, 1 H, HC1), 4.62 (m, 1 H, HC3′), 4.58 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.94 (d, ^2J = 17.6 Hz, 1 H, HC3), 3.07 (m, 1 H, HC1), 3.00 (m, 1 H, HC7), 2.91 (m, 1 H, HC6), 2.81 (m, 1 H,

HC7), 2.11 (m, 1 H, HC8′), 1.93 (m, 1 H, HC9′), 1.70 (m, 2 H, HC5′, HC6′), 1.52 (m, 1 H, HC7′), 1.49 (m, 1 H, HC4′), 1.07 (m, 1 H, HC5′), 1.03 (m, 1 H, HC8′), 0.93 (s, 3 H, H_3C12'), 0.92 (m, 3 H, H_3C11'), 0.89 (m, 1 H, HC6′), 0.79 (d, ^3J = 7.0 Hz, 3 H, H_3C10') ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 273 K): δ = 165.5 (C4), 154.3 (C1′), 135.3 (C7a), 132.5 (C11a), 129.6 (C8), 127.5 (C9), 126.9 (C10), 125.3 (C11), 76.2 (C3′), 55.6 (C11b), 47.6 (C3), 47.6 (C1), 47.3 (C4′), 41.6 (C8′), 38.8 (C6), 34.2 (C6′), 31.4 (C7′), 28.8 (C7), 26.3 (C9′), 23.4 (C5′), 22.2 (C12′), 21.0 (C11′), 16.5 (C10′) ppm.

Mosher's Amide of (±)Praziquanamine 33: (±)-Praziquanamine **3** (300 mg, 1.49 mmol, 1 equiv.), (*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid [(*R*)-Mosher's acid, 348 mg, 1.49 mmol, 1 equiv.), PyBOP (927 mg, 1.78 mmol, 1.2 equiv.), and NMM (815 μL, 7.43 mmol, 5 equiv.) were dissolved under argon in DMSO (5 mL) and the mixture was stirred at room temperature for 22 h. An aqueous saturated solution of $NaHCO_3$ (20 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was washed with water (3 × 20 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, diethyl ether 100%). A white powder containing two diastereomeric racemates was obtained (440 mg, 71% yield). $R_{f\ average}$ = 0.35 (100% Et_2O), m.p. 158–159 °C. UV/Vis (CH_2Cl_2): λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 262 (630). MS (DCI/NH_3): *m*/*z* (%) = 419.2 (7) $[M + H]^+$, 436.2 (100) $[M + NH_4]^+$.

Separation of the mixture of the two diastereomers (100 mg) was performed by column chromatography (1.2 × 35 cm, SiO_2, diethyl ether 100%). For each diastereomer, two rotamers were identified by NMR at room temperature.

Diastereomer (11b*R*,2′*R*)-33: R_f = 0.41 (100% Et_2O). $[\alpha]_D$ = –25 (c = 5.10^{-3}, CH_2Cl_2) with *de* > 97% (determined by NMR).

Major Rotamer: ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.57 (m, 2 H, HC4′, HC8′), 7.43 (m, 3 H, HC5′, HC6′, HC7′), 7.33 (m, 1 H, HC11), 7.32 (m, 1 H, HC10), 7.28 (m, 1 H, HC9), 7.18 (m, 1 H, HC8), 5.10 (dd, ^2J = 15.0, ^3J = 5.0 Hz, 1 H, HC1), 4.84 (dd, ^3J = 10.0, ^3J = 5.0 Hz, 1 H, HC11b), 4.60 (dt, ^2J = 18.0, ^3J = 5.0 Hz, 1 H, HC6), 4.22 (dd, ^2J = 18.0, J = 3.7 Hz, 1 H, HC3), 3.96 (dd, ^2J = 18.0, J = 3.7 Hz, 1 H, HC3), 3.65 (d, $^5J_{HF}$ = 1.3 Hz, 3 H, OCH_3), 3.11 (dd, ^2J = 15.0, ^3J = 10.0 Hz, 1 H, HC1), 2.93 (m, 1 H, HC7), 2.76 (m, 1 H, HC6), 2.74 (m, 1 H, HC7) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 293 K): δ = 164.9 (C1′), 163.4 (C4), 134.9 (C7a), 132.9 (C3′), 132.3 (C11a), 130.2 (C6′), 129.4 (C8), 128.7 (C7′, C5′), 127.7 (C9), 127.0 (C10), 126.3 (C4′, C8′), 125.4 (C11), 123.3 (CF_3), 84.6 (C2′), 55.5 (OCH_3), 54.4 (C11b), 48.8 (C3), 46.3 (C1), 39.0 (C6), 28.6 (C7) ppm. ^{19}F NMR (400 MHz, [D$_6$]DMSO, 333 K): δ = –69.8 (s, 60%) ppm.

Minor Rotamer: ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.55 (m, 2 H, HC4′, HC8′), 7.42 (m, 2 H, HC5′, HC7′), 7.41 (m, 1 H, HC6′), 7.23 (m, 2 H, HC9, HC10), 7.15 (m, 1 H, HC8), 6.89 (m, 1 H, HC11), 4.91 (d, ^2J = 18.0 Hz, 1 H, HC3), 4.88 (ddd, ^2J = 15.0, ^3J = 5.0, ^3J = 3 Hz, 1 H, HC6), 4.86 (m, 1 H, HC11b), 4.52 (dd, ^2J = 15.0, ^3J = 5.0 Hz, 1 H, HC1), 3.90 (d, $^5J_{HF}$ = 1.3 Hz, 3 H, OCH_3), 3.87 (d, ^2J = 18.0 Hz, 1 H, HC3), 2.86 (m, 1 H, HC7), 2.84 (m, 1 H, HC6), 2.74 (m, 1 H, HC7), 2.37 (dd, ^2J = 15.0, ^3J = 10.0 Hz, 1 H, HC1) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 293 K): δ = 164.3 (C1′), 164.2 (C4), 135.1 (C7a), 133.4 (C3′), 131.7 (C11a), 129.8 (C6′), 129.5 (C8), 128.8 (C7′, C5′), 127.6 (C9), 127.0 (C10), 126.2 (C4′, C8′), 125.0 (C11), 123.2 (CF_3), 84.9 (C2′), 56.6 (OCH_3), 55.4 (C11b), 49.4 (C1), 47.1 (C3), 38.5 (C6), 28.7 (C7) ppm. ^{19}F NMR (400 MHz, [D$_6$]DMSO, 333 K): δ = –69.3 (s, 40%) ppm. Crystal data: $C_{22}H_{21}F_3N_2O_3$, M = 418.41, orthorhombic, $P2_12_12_1$, a = 8.248(1) Å, b = 10.562(1) Å, c = 22.197(3) Å, V = 1933.7(4) Å^3, Z = 4, T = 173(2) K. 8644 reflections (2747 independent, R_{int} = 0.0849) were collected. Largest electron density residue: 0.158 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0473 and wR_2 = 0.0672 (all data) with $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR_2 = [\Sigma w (F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{0.5}$.

Diastereomer (11b*S*,2′*R*)-33: R_f = 0.32 (100% Et_2O). $[\alpha]_D$ = +95 (c = 6.10^{-3}, CH_2Cl_2); *de* > 90% (determined by NMR).

Major Rotamer: ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.71 (d, ^3J = 7.4 Hz, 2 H, HC4′, HC8′), 7.55 (t, ^3J = 7.4 Hz, 2 H, HC5′, HC7′), 7.48 (tt, ^3J = 7.4, ^4J = 1.1 Hz, 1 H, HC6′), 7.17 (m, 1 H, HC9), 7.10 (m, 2 H, HC8, HC10), 6.00 (d, ^2J = 7.5 Hz, 1 H, HC11), 5.06 (d, ^2J = 18.9 Hz, 1 H, HC3), 4.89 (m, 1 H, HC6), 4.54 (m, 1 H, HC1), 3.88 (d, ^2J = 18.9 Hz, 1 H, HC3), 3.77 (d, ^3J = 3.8 Hz, 1 H, HC11b), 3.69 (d, $^5J_{HF}$ = 1.4 Hz, 3 H, OCH_3), 2.97 (dd, ^2J = 13.7, ^3J = 3.8 Hz, 1 H, HC1), 2.84 (m, 1 H, HC7), 2.64 (m, 1 H, HC7), 2.61 (m, 1 H, HC6) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 293 K): δ = 164.2 (C4), 164.1 (C1′), 135.0 (C7a), 134.0 (C3′), 131.4 (C11a), 130.2 (C6′), 129.4 (C8), 128.8 (C5′, C7′), 127.3 (C9), 126.9 (C4′, C8′), 126.7 (C10), 125.5 (C11), 123.4 (CF_3), 84.5 (C2′), 54.6 (OCH_3), 54.3 (C11b), 48.9 (C1), 46.3 (C3), 38.3 (C6), 28.8 (C7) ppm. ^{19}F NMR (400 MHz, [D$_6$]DMSO, 333 K): δ = –70.3 (s, 70%) ppm.

Minor Rotamer: ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.43 (m, 2 H, HC4′, HC8′), 7.40 (m, 1 H, HC6′), 7.37 (m, 2 H, HC5′, HC7′), 7.35 (m, 1 H, HC11), 7.32 (m, 1 H, HC10), 7.29 (m, 1 H, HC9), 7.20 (m, 1 H, HC8), 5.15 (dd, ^2J = 13.6, ^3J = 4.2 Hz, 1 H, HC1), 4.87 (m, 1 H, HC11b), 4.78 (m, 1 H, HC6), 4.54 (d, ^2J = 18.0 Hz, 1 H, HC3), 3.75 (d, $^5J_{HF}$ = 1.4 Hz, 3 H, OCH_3), 3.22 (d, ^2J = 18.0 Hz, 1 H, HC3), 3.10 (dd, ^2J = 13.6, ^3J = 4.2 Hz, 1 H, HC1), 2.90 (m, 1 H, HC7), 2.89 (m, 1 H, HC6), 2.75 (m, 1 H, HC7) ppm. ^{19}F NMR (400 MH, [D$_6$]DMSO, 333 K): δ = –70.0 (s, 30%) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 293 K): δ = 164.2 (C1′), 163.6 (C4), 134.9 (C7a), 132.7 (C3′), 132.4 (C11a), 129.7 (C6′), 129.5 (C8), 128.7 (C5′, C7′), 127.7 (C9), 127.1 (C10), 126.6 (C4′, C8′), 125.4 (C11), 123.5 (CF_3), 84.7 (C2′), 55.6 (OCH_3), 55.3 (C11b), 48.6 (C1), 45.5 (C1), 39.4 (C6), 28.6 (C7) ppm.

Diastereomers (11b*S*,2′*S*)-33 and (11b*R*,2′*S*)-33 were obtained in a similar way, starting from (*S*)-Mosher's acid.

3,3,9-Trimethyl-*N*-phenyl-1,2,5-trioxaspiro[5.5]undecane-9-carboxamide (*cis*-34 and *trans*-34): Carboxylic acid **23** (*cis* or *trans*, 31 mg, 129 μmol, 1 equiv.) and PyBOP (80 mg, 155 μmol, 1.2 equiv.) were dissolved under argon in DMSO (1 mL). Aniline (11 μL, 129 μmol, 1 equiv.) and NMM (71 μL, 645 μmol, 5 equiv.) were added. The mixture was stirred at room temperature for 18 h. An aqueous saturated solution of $NaHCO_3$ (15 mL) and dichloromethane (15 mL) were added. The organic layer was washed with water (3 × 10 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/Et_2O, from 100:0, v/v to 97:3 v/v). A colorless oil was obtained and crystallized from CH_2Cl_2/hexane, 1:6, v/v (21 mg, 50% yield).

Isomer *trans*-34: Crystal data: $C_{18}H_{25}NO_4$, M = 319.39, orthorhombic, *Pbca*, a = 12.831(2) Å, b = 9.219(2) Å, c = 29.052(5) Å, V = 3436.2(10) Å^3, Z = 8, T = 173(2) K. 11122 reflections (1774 independent, R_{int} = 0.2701) were collected. Largest electron density residue: 0.182 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0614 and wR_2 = 0.0622 (all data). R_f = 0.35 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.52 (dd, ^3J = 8.5, ^4J = 1.3 Hz, 2 H, H_{ortho}), 7.33 (br. t, ^3J = 7.4 Hz, 2 H, H_{meta}), 7.29 (br. s, 1 H, NH), 7.12 (tt, ^3J = 7.4, ^4J = 1.3 Hz, 1 H, H_{para}), 3.80 and 3.44 (2× br. s, 2 H, H_2C5), 2.59 (br. s, 1 H), 2.10–1.99 (m, 2 H), 1.85–1.76 (m, 3 H), 1.67–1.41 (m, 5 H, 2H + CH_3), 1.28 (s, 3 H, H_3C-C9), 1.11 (br. s, 3 H, CH_3) ppm. MS (DCI/NH_3): *m*/*z* (%) = 232 (52) $[M' + H]^+$

(M' corresponding to the cleavage of the trioxane and formation of a ketone on the cyclohexyl), 249 (100) $[M' + NH_4]^+$, 266 (16) $[M' + NH_3 + NH_4]^+$, 320 (26) $[M + H]^+$, 337 (35) $[M + NH_4]^+$.

Isomer *cis*-34: Crystal data: $C_{18}H_{25}NO_4$, M = 319.39, orthorhombic, *Pbca*, a = 12.552(3) Å, b = 9.207(3) Å, c = 29.188(8) Å, V = 3373.3(16) Å^3, Z = 8, T = 173(2) K. 10803 reflections (1746 independent, R_{int} = 0.1804) were collected. Largest electron density residue: 0.219 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0530 and wR_2 = 0.1136 (all data). R_f = 0.32 (CH_2Cl_2/Et_2O, 95:5, v/v). ^{1}H NMR (250 MHz, $CDCl_3$, 293 K): δ = 7.48 (dd, ^3J = 8.3, ^4J = 1.2 Hz, 2 H, H_{ortho}), 7.35 (br. s, 1 H, NH), 7.31 (br. t, ^3J = 8.3 Hz, 2 H, H_{meta}), 7.10 (tt, ^3J = 7.8, ^4J = 1.2 Hz, 1 H, H_{para}), 3.75 and 3.47 (2× br. s, 2 H, H_2C5), 2.85–2.02 (m, 4 H), 1.94–1.40 (m, 7 H, 4H + CH_3), 1.30 (s, 3 H, H_3C-C9), 1.11 (br. s, 3 H, CH_3) ppm. MS (DCI/NH_3): *m/z* (%) = 232 (59) $[M' + H]^+$ (M′ corresponding to the cleavage of the trioxane and formation of a ketone on the cyclohexyl), 249 (100) $[M' + NH_4]^+$, 320 (18) $[M + H]^+$, 337 (52) $[M + NH_4]^+$ (with M′ corresponding to the opening of the trioxane and the formation of a ketone function on the cyclohexyl residue)

Enzymatic Resolution Attempts: (±)-Praziquanamine **3** (30 mg, 148 μmol, 1 equiv.) and the enzyme [*Pseudomonas cepacia* lipase, PSL (5.0 mg); *Candida cylindracea* lipase, CCL (4.2 mg); *Candida antartica B* lipase, CALB, recombinant from *Aspergillus orizae* (4.2 mg); or porcine pancreatic lipase type II, PPL (5.0 mg)] were dissolved in solvent (diisopropyl ether, THF, DMSO/H_2O, $CHCl_3$, or AcOEt). Acetylation reagent was then added (AcOEt, Ac_2O, isopropenyl acetate, vinyl acetate). The mixtures were stirred at room temperature for 3 to 6 h. Heterogeneous mixture were centrifuged: the supernatants were concentrated, dried under vacuum and analyzed by ^{1}H NMR spectroscopy. Homogenous mixture were diluted with water, extracted with CH_2Cl_2, dried with $MgSO_4$, and centrifuged. The supernatants were concentrated, dried under vacuum and analyzed by ^{1}H NMR spectroscopy.

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