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Effect of functional group polarity on the antimalarial activity of spiro and dispiro-1,2,4-trioxolanes

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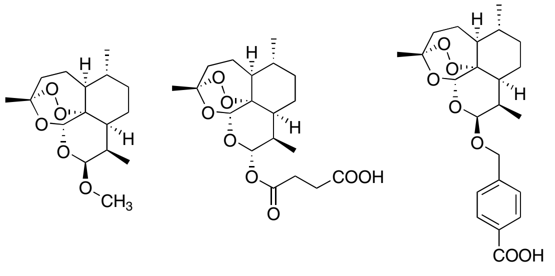
Abstract—Based on the structures of several lipophilic trioxolane antimalarial prototypes, we set out to determine which functional groups were associated with good antimalarial profiles and identify more polar (lower Log *P*/Log *D*) lead compounds with good physicochemical properties. More lipophilic trioxolanes tended to have better oral activities than their more polar counterparts. Trioxolanes with a wide range of neutral and basic, but not acidic, functional groups had good antimalarial profiles.

The semisynthetic artemisinins artemether and artesunate are important drugs in malaria chemotherapy;[1] however, the artemisinins have relatively poor biopharmaceutical properties that limit their therapeutic potential.[2] Many potent semisynthetic artemisinins and synthetic antimalarial peroxides have been prepared[3] but it has been difficult[4] to identify peroxide structures which maintain optimal activity and at the same time have the requisite physicochemical and metabolic properties to ensure good absorption and bioavailability following oral administration. It is well accepted that oral absorption requires a balance between good aqueous solubility, which is enhanced for more polar structures, and good membrane permeability, which is favored for less polar compounds.[5–7] Another factor that often limits oral bioavailability is extensive first-pass metabolism which typically increases for more lipophilic substrates.[8,9]



We recently described[10] the discovery of spiro and dispiro-1,2,4-trioxolanes (secondary ozonides) as a promising class of synthetic antimalarial peroxides, but most of these early lead compounds (**1**–**6**) were highly lipophilic and had limited oral bioavailability due to poor aqueous solubility and high metabolic lability.

In this paper, we describe the synthesis, physicochemical and antimalarial properties of 43 diversely functionalized derivatives of these early trioxolane prototypes with

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Keywords: 1,2,4-Trioxolane; Secondary ozonide; Antimalarial; Artemisinin.

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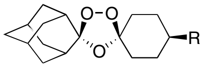
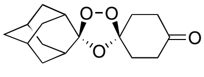
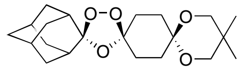


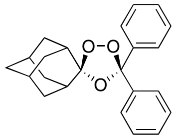
1, R = OH, log P 3.9
2, R = *n*-propyl, log P 8.1
3, R = phenyl, log P 8.6



4, log P 3.8



5, log P 6.1



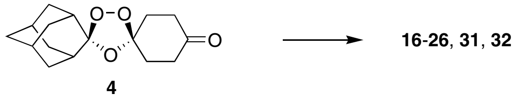
6, log P 7.3

a wide polarity spectrum. Our intent was to identify which functional groups were associated with good antimalarial profiles and identify lead compounds with an appropriate balance between lipophilicity (Log *P*/Log *D*) and aqueous solubility. Our emphasis was on the carboxylic acid functional group, not only because of its potential to form water-soluble salts, but because of the precedent set with the carboxylic acid-containing semisynthetic artemisinins, artesunate, and artelinate.[11]

1. Chemistry

Trioxolanes **46** (50%), **47** (18%), **49** (25%), **51** (45%), and **54** (49%) were obtained directly by Griesbaum coozonolysis[12,13] reactions between *O*-methyl 2-adamantanone oxime **7** and the appropriate 4-substituted cyclohexanones **8** or benzophenones **9** (Scheme 1). Symmetrical oxime ethers such as **7** preclude the *syn-anti* isomerism of the resulting carbonyl oxide intermediates, and ensure that the stereochemistry of the cycloaddition is only a function of the starting material ketones. For achiral benzophenones, the trioxolane products are achiral; for 4-substituted cyclohexanones, the major trioxolane isomers are uniformly *cis* with the substituent and peroxo groups at the equatorial and axial positions, respectively.[10,14] Assuming that the stereochemistry of the cycloaddition follows the same course for other 4-substituted cyclohexanones, we have assigned *cis* configurations for the new trioxolanes described herein. Trioxolane carboxylic acids **15** (58%), **48** (84%), **52** (90%), diol **14** (46%), alcohol **30** (87%), and diamine **53** (29% overall) were obtained by aq KOH hydrolysis of their precursor trioxolane esters;[15] the latter were obtained directly by coozonolysis (25–63%). The synthesis of **53** required three additional post-ozonolysis transformations (lithium borohydride/lithium triethylborohydride[16] reduction, phthalimide formation (Mitsunobu), and hydrazine deprotection).

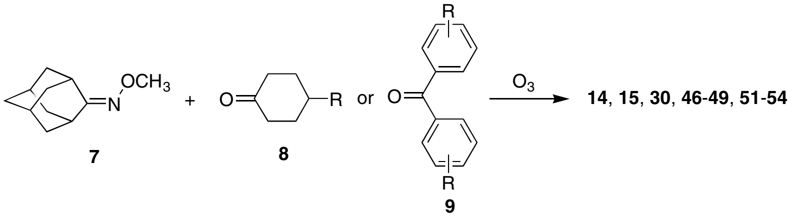
The ketone functional group of **4** provided a convenient means for functional group transformation (Scheme 2). Ketal **18** (56%) was obtained by ketalization of **4**.



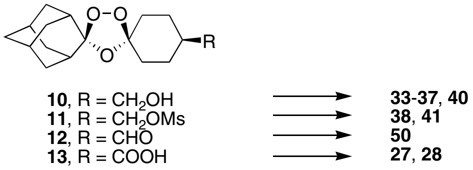
Scheme 2.

Unsaturated ketal **16** (63%) was obtained by transketalization of **4** dimethyl ketal. Ketal ketone **17** (57%) was obtained by ozonolysis of **16** at −78 °C followed by a reductive (triphenylphosphine) workup. Oxime **19** and oxime ethers **20–22** were obtained by reaction of **4** with the appropriate hydroxylamine or *O*-alkyl hydroxylamine in yields ranging from 73% to 86%. Semicarbazone **23** (90%), tosylhydrazone **24** (58%), *N*-pyridiniumhydrazone **25** (31%), and guanidinehydrazone **26** (64%) were obtained by reaction of **4** with 4-phenylsemicarbazide, 4-toluenesulfonylhydrazide, Girard's reagent P, and aminoguanidine bicarbonate, respectively. C=N containing trioxolanes **19–26** with chiral axes were isolated as their racemates. Carbinols **31** (37%) and **32** (41%) were obtained by addition of the lithium salts of thiazole and 2-picoline to **4**. Carbinol **31** was formed and isolated as a 1:1 mixture of achiral diastereomers; **32** was formed as a mixture of achiral diastereomers, but was isolated as a single achiral diastereomer. In the absence of X-ray data, the *cis* and *trans* configurations of **31** and **32** could not be assigned.

Trioxolane alcohol **10**, mesylate **11**, aldehyde **12**, and carboxylic acid **13**[14] provided the means to synthesize the remaining target trioxolanes (Scheme 3). Sodium sulfate **33** (41%) was obtained by treatment of **10** with sulfur trioxide pyridine complex in pyridine[17] to form the pyridinium sulfate of **10** that, in turn, was converted to **33** with aq sodium carbonate. Carbamate **35** (91%) was obtained by treatment of **10** and carbonyldiimidazole.[18] Acid **34** (75%) was obtained by hydrolysis of its corresponding ethyl ester.[14] Ethers **36** (37%) and **37** (57%) were formed via Mitsunobu reactions with **10**. Sulfones **38** (23%) and **41** (15%) were obtained in a



Scheme 1. Griesbaum Coozonolysis.



Scheme 3.

two-step procedure by treatment of **11** with sodium thiomethoxide and 2-mercapto-1-methylimidazole to form the sulfides; the latter were oxidized to the sulfones with *m*-CPBA. Imidazole **50** (73%) was formed by treatment of **12** with glyoxal and ammonia. Hydroxamic acid **27** (36%) was obtained from **13** by way of the mixed anhydride (ethyl chloroformate followed by hydroxylamine); hydroxy amide **28** (46%) was obtained from the HOBt active ester of **13**. Trioxolanes **1**, **3**, **4**, **6**, **10–13**, **29**, and **42–45** were obtained as previously described.[10,14]

Values for polar surface area (PSA)[19] and $\text{Log}\,P/\text{Log}\,D_{\text{pH 7.4}}$ were calculated for each of the trioxolanes. Experimental $\text{Log}\,P/\text{Log}\,D_{\text{pH 7.4}}$ values for 11 selected trioxolanes were determined by a rapid chromatographic method.[20]

2. Antimalarial activity

In vitro and in vivo antimalarial activities were measured using the chloroquine-resistant K1 and chloroquine-sensitive NF54 strains of *Plasmodium falciparum*, and *Plasmodium berghei*-infected mice, respectively. In vivo data were obtained using single 10 mg/kg oral doses of the trioxolanes administered on day 1 post-infection in a non-solubilizing, standard suspension vehicle (SSV) formulation comprising 0.5% w/v carboxymethyl cellulose, 0.5% v/v benzyl alcohol, 0.4% v/v Tween 80, and 0.9% w/v sodium chloride in water.

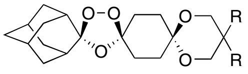
Relative to prototype ketal **5**, the more polar ketal diol **14** had an antimalarial profile similar to **5**, whereas the ketal diacid **15** was completely inactive following oral dosing (Table 1). In contrast, **16–18**, three similarly lipophilic ketals, had antimalarial profiles similar to prototype **5**. Oxime **19** and oxime ethers **20** and **21** were as potent as their parent ketone **4** in vitro (Table 2), whereas in vivo activities improved for **19** and **20**, but weakened for the more lipophilic **21**. We note that **22**, a carboxylic acid analog of **20**, was much less active than its parent oxime ether. Similarly, the relatively polar carbon–nitrogen double bond derivatives **23–26** were quite potent in vitro, but had poor to minimal activities in vivo.

Carboxylic acid **13** and its more lipophilic hydroxamic acid (**27**) and hydroxyethyl amide (**28**) derivatives are shown in Table 3. Although **13** was not very potent in vitro, it had quite good activity in vivo; the more weakly acidic **27** was similarly active in vivo and was 3-fold more potent in vitro. The in vitro potency for amide **28** was midway between that of **13** and **27** but it was much less active in vivo.

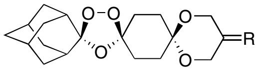
Analogs of **1**, the potent secondary alcohol metabolite of ketone **4**, are shown in Table 4. Primary alcohol **10** was as potent as **1**, but it had much higher activity in vivo. Tertiary carbinols **29** and **30** were designed as analogs of **1** with potentially enhanced metabolic stabilities;[21] **29** and **1** had very similar antimalarial profiles, and although **30** had good potency in vitro, it was much less active than **1** in vivo. The antimalarial profiles of heterocyclic weak-base carbinols **31** and **32** were no better than that of the more lipophilic 4-fluorophenyl carbinol **30**.

As **10** had a much better antimalarial profile than did **1**, and as it is readily synthesized[14] as a single *cis* isomer (unlike **1**), this alcohol was the logical choice for further derivatization (Table 5). Sodium sulfonate **33**, a poten-

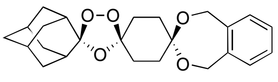
Table 1. Activity of trioxolane ketals against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo



5, **14**, **15**



16, **17**



18

Compound	R	$\text{Log}\,P/\text{Log}\,D_{\text{pH 7.4}}$	PSA (Å^2)	IC$_{50}$[a] (ng/ml) K1/NF54	Activity[b] (%)
NONE	—	—	—	—	0
4	—	3.8[c]	49.3	0.48/0.73[d]	74
5	CH_3	6.1[c]	38.4	1.5/2.7[d]	98
14	CH_2OH	3.6	100.3	0.96/0.41	98
15	COOH	0.18	142.1	>100/>100	3
16	CH_2	6.5	42.8	0.59/1.1	99.95
17	O	5.3	66.3	0.62/0.94	98.9
18	—	7.4	42.2	3.0/3.0	90
AM	—	3.3[c]	62.2	0.74/1.2	99.36
AS	—	3.5	111.5	1.3/1.6	67

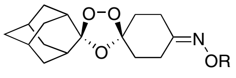
[a] Mean from $n = 2$–3.

[b] Groups of three *P. berghei*-infected MORO mice were treated orally 1 day post-infection with trioxolanes dissolved or suspended in SSV. Antimalarial activity was measured by percent reduction in parasitemia on day 3 post-infection compared to an untreated control group.

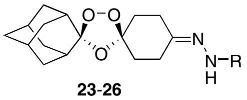
[c] Measured e Log *P* value.

[d] Data from Dong et al.[10]

Table 2. Activity of trioxolane oxime ethers and C=N derivatives against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo



19-22



23-26

Compound	R	$\log P/\log D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
19	H	4.1[a]	70.6	0.45/0.67	83
20	CH_3	5.1[a]	50.2	0.60/1.0	88
21	$CH_2C_6H_5$	7.2[a]	48.1	1.3/2.7	56
22	CH_2COOH	3.1[b]	103.6	32/35	85[c]
23	$CONHC_6H_5$	3.5	91.7	0.65/1.3	0[c]
24	Tosyl	4.0	93.0	1.4/1.8	61[c]
25[d]	$COCH_2$*N*-pyridinium	1.7	89.6	0.49/0.60	45[c]
26[e]	C=NH (NH_2)	−1.0	121.2	3.5/5.0	82

[a] Measured e Log *P* value.

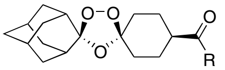
[b] Measured e Log *D* value.

[c] In vivo data from administration in a 3% ethanol and 7% Tween 80 vehicle.

[d] Chloride salt.

[e] Hydrochloride salt.

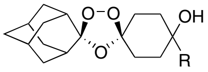
Table 3. Activity of trioxolane acid **13** and its derivatives against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo



Compound	R	$\log P/\log D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
13	OH	2.8	71.2	15/13	97[a]
27	NHOH	4.3	98.2	4.2/3.3	96
28	$NH(CH_2)_2OH$	4.3	87.3	8.0/6.2	53

[a] In vivo data from administration in a 3% ethanol and 7% Tween 80 vehicle.

Table 4. Activity of trioxolane alcohols against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo



29-32

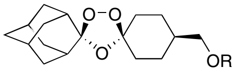
Compound	R	$\log P/\log D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
1	—	3.9[a]	52.9	0.25/0.51[b]	93
10	—	5.1	58.4	0.83/0.20	99.15
29	CH_3	4.5	50.5	0.44/0.84	95
30	4-FC_6H_5	6.6	46.4	1.7/3.0	49[c]
31	2-Thiazolyl	5.1	62.5	1.8/2.3	27
32	2-Picolyl	5.2	57.3	0.66/0.74	68

[a] Measured e Log *P* value.

[b] Data from Dong et al.[10].

[c] In vivo data from administration in a 3% ethanol and 7% Tween 80 vehicle.

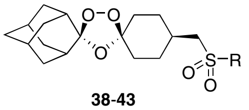
Table 5. Activity of derivatives of trioxolane alcohol **10** against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo

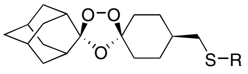


Compound	R	$\log D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
33	SO_3Na	1.8	99.7	100/110	0
34	4-$COOHC_6H_5$	4.8	85.7	25/35	18
35	COIm[a]	5.6	71.9	1.7/1.9	97
36	4-Pyridyl	6.7	50.1	2.1/2.8	>99.99
37	2-Pyrimidinyl	6.0	62.9	0.62/1.4	99.43

[a] Carbonylimidazole.

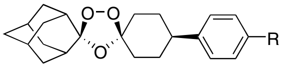
Table 6. Activity of trioxolane sulfides and sulfones against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo

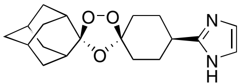

38-43


44, 45

Compound	R	Log*P*/Log$D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
38	CH_3	4.6	65.3	0.62/0.88	98
39	C_6H_5	6.3	61.5	1.4/1.6	77
40	2-Pyridinyl	4.9	89.3	6.8/6.3	36
41	1-Me-2-imidazole	5.2	78.7	0.82/1.1	81
42	2-Pyridyl *N*-oxide	2.9	84.2	2.4/3.4	60
43	1-Me-2-tetrazolyl	5.8	111.5	1.7/2.5	8
44	2-Pyridyl *N*-oxide	5.1	51.5	1.4/3.0	99.77
45	1-Me-2-tetrazolyl	6.0	79.0	0.50/1.2	99.47

Table 7. Activity of aryl trioxolanes against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo


3, 46-49


50

Compound	R	Log*P*/Log$D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
3	H	8.6[a]	19.9	2.2/4.8[b]	96
46	F	8.2[a]	26.2	3.5/4.6	81
47	SO_2CH_3	6.7	66.3	21/27	23
48	COOH	5.0	74.6	36/38	3
49[c]	4,4-Dimethyl-2-oxazyl	8.1	45.7	3.7/2.8	97
50	—	5.1	55.2	0.60/0.35	6

[a] Measured eLog*P* value.
[b] Data from Dong et al.[10].
[c] Hydrochloride salt.

tial phase II metabolite of **10**, was two-orders of magnitude less potent than the parent alcohol and it was completely inactive in vivo. The phenyl ether carboxylic acid **34** was similarly inactive. Imidazole carbamate **35** had good potency in vitro, but its oral activity was substantially less than that of **10**. The relatively lipophilic weak-base ethers **36** and **37** had the best antimalarial profiles of this group of derivatives of **10**.

As shown in Table 6, we explored trioxolanes containing the metabolically stable and relatively polar sulfone functional group. These sulfones (and two sulfide analogs) had IC_{50}s between 0.50 and 6.8 ng/mL, but their in vivo activities varied widely. This was especially evident in the dramatic increase in activity seen for sulfides **44** and **45** versus their more polar sulfone counterparts **42** and **43**.

Analogs of **3** functionalized at the *para* position are shown in Table 7. In vitro potencies decreased significantly for the more polar sulfone **47** and carboxylic acid **48**. Only the weak-base oxazoline **49** (a potential prodrug of **48**) was as active in vivo as **3**. Unlike the similarly polar **48**, weak-base imidazole **50** was the most potent compound of this group of trioxolanes, although it was nearly inactive in vivo.

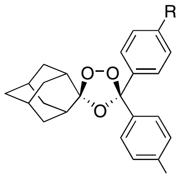
Symmetrically substituted analogs of **6** are shown in Table 8. In vitro potencies decreased significantly for the more polar dicarboxylic acid **52**[22] and dipyridine **54**, both of which were completely inactive in vivo. The more lipophilic difluoro **51** had much better activity in vivo than its unsubstituted parent **6** suggesting that the latter may be converted to inactive hydroxylated metabolites although this was not investigated. The diamine **53**, while 2- to 3-fold less potent than **6**, is considerably less lipophilic (Log*D* 2.4) and had good activity in vivo.

3. Discussion

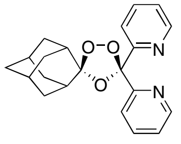
Most of the new trioxolanes depicted in Tables 1–8 were quite potent against *P. falciparum* with IC_{50}s less than 5 ng/ml. Of the 26 most potent trioxolanes with IC_{50}s (against K1) < 2 ng/mL, only five had Log*P*/Log*D* values < 4 consistent with the previous observation[4] that moderately high lipophilicity is required for good antimalarial potency. Of the 10 trioxolanes with IC_{50}s > 10 ng/mL, seven were carboxylic or sulfonic acids; conversely, with two exceptions (**53** and **54**), weak-base trioxolanes had good potency.

Far fewer trioxolanes had good oral activities in the *P. berghei* model. Consistent with the trends for in vitro potency, those with oral activities ⩾99% (**10**, **16**, **36**, **37**, **44**, **45**, **51**) were quite lipophilic with Log*P*/

Table 8. Activity of diaryl trioxolanes against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo



6, **51-53**



54

Compound	R	Log*P*/Log$D_{pH\ 7.4}$	PSA (Å^2)	IC_{50} (ng/ml) K1/NF54	Activity (%)
6	H	7.3[b]	22.9	2.3/2.6[c]	68[a]
51	F	8.1[b]	22.9	2.5/2.3	99.3[a]
52	COOH	2.7	124.2	>100/>100	0
53[d]	CH_2NH_2	2.4	79.7	11/5.6	98
54	—	2.4	48.4	>100/>100	0[a]

[a] In vivo data from administration in a 3% ethanol and 7% Tween 80 vehicle.

[b] Measured e Log*P* value.

[c] Data from Dong et al.[10].

[d] Dimesylate salt.

Log*D* values ranging from 5.1 to 8.1. Of the 20 trioxolanes with activities ⩾90%, only six (diol ketal **14**, alcohols **1** and **29**, carboxylic acid **13**, hydroxamic acid **27**, and diamine **53)** had Log*P*/Log*D* values below 5. For compounds with good in vitro potency ($IC_{50} < 2$ ng/mL) but with reduced oral efficacy (activity < 90%), it is likely that poor aqueous solubility and/or high metabolic lability resulted in low oral bioavailability since each of these compounds had physicochemical properties consistent with good membrane permeability.

During this work, we made the transition from a solubilizing 3% ethanol and 7% Tween 80 (T/A) vehicle to a non-solubilizing SSV vehicle for oral dosing. We observed that the activity of 7/30 trioxolanes was significantly lower (25- to 1000-fold)[23] in the SSV versus T/A vehicle (data not shown); significantly these seven trioxolanes were the highly lipophilic (Log*P*/Log*D* 5.1–8.6) compounds **3**, **5**, **18**, **20**, **21**, **46**, and **49**, all of which had good in vitro potency. These data supported the hypothesis that poor solubility and dissolution severely restricted the oral absorption of these lipophilic trioxolanes. In addition, these data showed that the use of the non-solubilizing SSV vehicle for assessment of oral activity kept the focus on those trioxolanes that might be expected to have reasonable oral bioavailability and made certain that our SAR would not be skewed by the very high oral activities seen for highly lipophilic trioxolanes in the solubilizing T/A vehicle.

4. Summary

From these data, it is evident that in vitro potency is not a reliable predictor of in vivo activity and that the more lipophilic trioxolanes tend to have better oral activities than their more polar counterparts, an outcome consistent with that seen for other classes of synthetic peroxides.[4] Trioxolanes with a wide range of neutral and basic, but not acidic, functional groups had good antimalarial profiles.

5. Experimental

5.1. General

Melting points are uncorrected. Using $CDCl_3$, CD_3OD, or DMSO-*d*$_6$ as solvents, ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer for **19**–**21** and on a 500 MHz spectrometer for the remaining compounds. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^1H and $CDCl_3$ (77.0 ppm), CD_3OD (49.0 ppm), or DMSO-*d*$_6$ (39.7 ppm) for ^{13}C NMR.

5.2. Starting material synthesis

4,4′-Benzophenonedicarboxylic acid was obtained in 80% yield by $KMnO_4$ oxidation of 4,4′-dimethylbenzophenone; esterification of the diacid in refluxing toluene/EtOH with concd H_2SO_4 catalyst afforded diethyl 4,4′-benzophenonedicarboxylate in 90% yield.[24] 4-[4-(methylsulfonyl)phenyl]cyclohexanone was obtained in a five-step sequence.[24] The first step was addition of the Grignard reagent formed from 4-bromothioanisole to the monoethylene ketal of 1,4-cyclohexanedione to produce the tertiary benzylic alcohol. Oxidation to the sulfone alcohol with oxone[25] followed by dehydration with methanesulfonyl chloride/triethylamine[26] cleanly afforded the corresponding olefin. Hydrogenation of the olefin over Pd–C and deprotection with TFA afforded the desired keto sulfone. As indicated below, the remaining starting materials cyclohexanones and benzophenones were commercially available or were prepared according to known procedures.

5.2.1. Diethyl 4,4′-benzophenonedicarboxylate. ^1H NMR ($CDCl_3$) δ 1.42 (t, $J = 7.5$ Hz, 6H), 4.43 (q, $J = 7.0$ Hz, 4H), 7.84 (d, $J = 8.5$ Hz, 4H), 8.18 (d, $J = 8.5$ Hz, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 14.26, 61.45, 129.89, 129.74, 134.18, 140.63, 165.66, 195.25.

5.3. 4-[4-(Methylsulfonyl)phenyl]cyclohexanone

^{1}H NMR ($CDCl_3$) δ 1.92–2.02 (m, 2H), 2.22–2.28 (m, 2H), 2.52–2.56 (m, 4H), 3.06 (s, 3H), 3.10–3.18 (m, 1H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.91 (d, $J = 8.5$ Hz, 2H).

5.4. General procedure for the preparation of 1,2,4-trioxolanes

Ozone was produced with an OREC ozone generator (0.6 L/min O_2, 60 V), passed through an empty gas washing bottle that was cooled to −78 °C, and bubbled through a solution of an 2-adamantanone *O*-methyl oxime and a ketone in pentane or pentane/CH_2Cl_2 at 0 °C. The oxime ether was consumed within 3 min. After completion, the solution was flushed with oxygen for 5 min before being concentrated in vacuo at rt to give a residue that was purified by flash chromatography. Although we encountered no difficulties in working with these 1,2,4-trioxolanes (secondary ozonides), routine precautions such as the use of shields, fume hoods, and avoidance of metal salts should be observed whenever possible. Differential scanning calorimetry experiments revealed that these 1,2,4-trioxolanes had good thermal stabilities; decomposition occurred at 127–175 °C with enthalpies ranging from 300 to 650 J/g.

5.5. Adamantane-2-spiro-3′-11′,11′-bis(hydroxymethyl)-1′,2′,4′,9′,13′-pentaoxadispiro[4.2.5.2]pentadecane (14)

Step 1. A solution of *O*-methyl 2-adamantanone oxime[27] (2.69 g, 15 mmol) and 3,3-bis(ethoxycarbonyl)-1,5-dioxaspiro[5.5]undecan-9-one[28] (4.71 g, 15 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in petroleum ether) to afford adamantane-2-spiro-3′-11′,11′-bis(ethoxycarbonyl)-1′,2′,4′,9′,13′-pentaoxadispiro[4.2.5. 2]pentadecane (3.60 g, 50%) as a colorless solid. Mp 74–77 °C (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, $J = 7.1$ Hz, 6H), 1.61–2.18 (m, 22H), 4.24 (q, $J = 7.2$ Hz, 4H), 4.28 (s, 4H).

Step 2. A solution of adamantane-2-spiro-3′-11′,11′-bis(ethoxycarbonyl)- 1′,2′,4′,9′,13′-pentaoxadispiro[4.2.5. 2]pentadecane (1.00 g, 2.18 mmol), lithium borohydride (2.10 ml, 4.20 mmol, 2 M in THF), and lithium triethylborohydride (0.42 ml, 0.42 mmol, 1 M in THF) in ether (5 ml) was stirred at rt for 3 h. The reaction mixture was diluted with ether (10 ml) and washed with 3 M aq NaOH (2× 10 ml), water (2× 10 ml), and brine (10 ml). The combined aqueous layers were extracted with $CHCl_3$ (3× 50 ml), and the chloroform extract was washed with water (2× 50 ml) and brine (50 ml). The ether extract and chloroform extract were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 5% methanol in chloroform) to afford **14** (0.40 g, 46%) as a colorless solid. Mp 146–148 °C (ethanol/H_2O 3:2). ^{1}H NMR (DMSO-d_6) δ 1.60–2.15 (m, 22H), 3.36 (d, $J = 4.9$ Hz, 4H), 3.61 (s, 2H), 3.62 (s, 2H), 4.49 (t, $J = 5.4$ Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 25.86, 26.26, 29.34, 30.21, 34.27, 34.36, 35.77, 36.13, 39.07, 60.69, 61.44, 61.48, 96.00, 108.15, 110.84. Anal. Calcd for $C_{21}H_{32}O_7$·0.077 $CHCl_3$: C, 62.40; H, 7.97. Found: C, 62.76; H, 7.77.

5.6. Adamantane-2-spiro-3′-11′,11′-dicarboxy-1′,2′,4′,9′,13′-pentaoxadispiro[4.2.5.2]pentadecane (15)

A solution of adamantane-2-spiro-3′-11′, 11′-bis(ethoxycarbonyl)-1′,2′,4′,9′,13′-pentaoxadispiro[4.2.5.2]pentadecane (0.73 g, 1.5 mmol), 15% aq KOH (4.2 ml) in methanol (30 ml) was heated at 50 °C for 2 h. After being cooled to rt, the reaction mixture was concentrated to 5 ml, acidified with concd HCl, and extracted with $CHCl_3$ (5× 50 ml). The combined organic layers were washed with water (2× 50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated to afford **15** (0.38 g, 58%) as a colorless solid. Mp 151–153 °C (water). ^{1}H NMR (DMSO-d_6) δ 1.51–2.14 (m, 22H), 4.13 (s, 2H), 4.15 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 25.86, 26.26, 29.16, 30.16, 34.27, 34.37, 35.77, 36.13, 52.89, 61.65, 96.49, 107.99, 110.92, 169.11. Anal. Calcd for $C_{21}H_{28}O_9$: C, 59.43; H, 6.65. Found: C, 59.42; H, 6.66.

5.7. Adamantane-2-spiro-3′-11′-methylene-1′, 2′,4′,9′,13′-pentaoxadispiro[4.2.5.2]pentadecane (16)

Step 1. A mixture of **4**[10] (1.12 g, 4 mmol), TFA (0.70 ml), CH_2Cl_2 (10 ml), and methanol (70 ml) was stirred at rt for 16 h. The reaction was quenched with $NaHCO_3$ (2.0 g) and stirred for an additional 1 h before evaporation to dryness. The residue was dissolved in CH_2Cl_2 (20 ml), washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to afford dimethyl ketal of **4** (1.31 g, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$) *d* 1.66–2.02 (m, 22H), 3.18 (s, 3H), 3.19 (s, 3H).

Step 2. A mixture of the above ketal (1.30 g, 4 mmol), 2-methylene-1,3-propanediol (0.70 g, 8 mmol), and *p*-TsOH (0.5 g) in CH_2Cl_2 (70 ml) and THF (10 ml) was stirred at rt for 16 h. The reaction was quenched with $NaHCO_3$ (1.0 g), stirred for an additional 1 h, and diluted with water (70 ml). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2× 50 ml). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 8% ether in hexanes) to afford **16** (0.87 g, 63%) as a colorless solid. Mp 58–59 °C (hexanes). ^{1}H NMR ($CDCl_3$) δ 1.59–2.21 (m, 22H), 4.31 (s, 4H), 4.86 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 26.60, 27.02, 29.97, 30.69, 34.84, 34.94, 36.49, 36.90, 63.63, 97.60, 107.92, 108.38, 111.59, 141.15. Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.77; H, 7.93.

5.8. Adamantane-2-spiro-3′-11′-oxo-1′,2′,4′,9′,13′-pentaoxadispiro[4.2.5.2]pentadecane (17)

A solution of **16** (0.65 g, 1.9 mmol) in CH_2Cl_2 (80 ml) at −78 °C was treated with ozone for 10 min, flashed with oxygen for 5 min before addition of triphenylphosphine

(0.49 g, 1.9 mmol). The reaction mixture was warmed up to rt and stirred at rt for 1 h before evaporation to dryness. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford **17** (0.37 g, 57%) as a colorless solid. Mp 76–79 °C (hexanes). ^{1}H NMR (CDCl$_3$) δ 1.61–2.21 (m, 22H), 4.17 (s, 4H). ^{13}C NMR (CDCl$_3$) δ 26.61, 27.03, 29.80, 30.81, 34.85, 34.96, 36.52, 36.89, 66.92, 66.94, 99.14, 107.96, 111.82, 207.00. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.38; H, 7.58.

5.9. Adamantane-2-spiro-3′-11′,12′-benzo-1′,2′,4′,9′,14′-pentaoxadispiro[4.2.6.2]hexadecane (18)

To a solution of **4**[10] (0.28 g, 1.0 mmol) in 1,2-dimethoxyethane (10 ml) were added 1,5-dihydro-3-methoxy-2,4-benzodioxepin (0.20 g, 1.1 mmol) and *p*-toluenesulfonic acid monohydrate (38 mg), and the reaction mixture was stirred at rt for 30 min before being quenched by addition of saturated NaHCO$_3$ solution (1.0 ml). The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations from ethanol/H$_2$O (15 ml, 2:1) and from ethanol (10 ml) to give **18** (0.22 g, 56%) as a colorless solid. Mp 149–151 °C (ethanol). ^{1}H NMR (CDCl$_3$) δ 1.60–2.20 (m, 22H), 4.80–4.94 (m, 4H), 7.02–7.09 (m, 2H), 7.13–7.22 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 26.53, 26.94, 29.46, 31.12, 34.81, 34.91, 36.42, 36.84, 64.65, 101.38, 108.42, 111.65, 126.09, 126.15, 126.75, 138.01, 138.09. Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.51; H, 7.70.

5.10. Adamantane-2-spiro-3′-8′-hydroxyimino-1′,2′,4′-trioxaspiro[4.5]decane (19)

To a solution of **4**[10] (0.557 g, 2.0 mmol) in CH$_2$Cl$_2$ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and hydroxylamine hydrochloride (0.210 g, 3.0 mmol), and the reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallization from ethanol/H$_2$O (20 ml, 1:1) to give **19** (0.43 g, 73%) as a colorless solid. Mp 137–139 °C (ethanol/H$_2$O 1:1). ^{1}H NMR (CDCl$_3$) δ 1.62–2.10 (m, 18H), 2.32–2.88 (m, 4H), 8.60–8.95 (br s, 1H). ^{13}C NMR (CDCl$_3$) δ 20.97, 26.41, 26.81, 28.72, 32.48, 33.74, 34.74, 34.80, 34.84, 36.29, 36.70, 107.91, 112.06, 157.94. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.65; H, 7.96; N, 4.75.

5.11. Adamantane-2-spiro-3′-8′-methoxyimino-1′,2′,4′-trioxaspiro[4.5]decane (20)

To a solution of **4**[10] (0.557 g, 2.0 mmol) in CH$_2$Cl$_2$ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and methoxylamine hydrochloride (0.250 g, 3.0 mmol), and the reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations from ethanol/H$_2$O (20 ml, 1:1) and from ethanol/H$_2$O (15 ml, 2:1) to give **20** (0.51 g, 83%) as a colorless solid. Mp 97–99 °C (ethanol/H$_2$O 2:1). ^{1}H NMR (CDCl$_3$) δ 1.60–2.10 (m, 18H), 2.30–2.81 (m, 4H), 3.84 (s, 3H). ^{13}C NMR (CDCl$_3$) δ 21.54, 26.40, 26.81, 28.74, 32.59, 33.85, 34.72, 34.77, 34.84, 36.28, 36.70, 61.15, 107.92, 112.00, 156.93. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.58; H, 8.29; N, 4.41.

5.12. Adamantane-2-spiro-3′-8′-benzyloxyimino-1′,2′,4′-trioxaspiro[4.5]decane (21)

To a solution of **4**[10] (0.56 g, 2.0 mmol) in CH$_2$Cl$_2$ (5 ml) and methanol (5 ml) were added pyridine (0.30 ml) and *O*-benzylhydroxylamine hydrochloride (0.48 g, 3.0 mmol), and the reaction mixture was stirred at rt for 24 h. The reaction mixture was concentrated in vacuo to provide a crude residue that was purified by recrystallizations from ethanol/H$_2$O (20 ml, 1:1) and from ethanol/H$_2$O (15 ml, 2:1) to give **21** (0.66 g, 86%) as a colorless solid. Mp 62–64 °C (ethanol/H$_2$O 2:1). ^{1}H NMR (CDCl$_3$) δ 1.60–2.10 (m, 18H), 2.32–2.50 (m, 2H), 2.53–2.67 (m, 1H), 2.72–2.86 (m, 1H), 5.08 (s, 2H), 7.25–7.42 (m, 5H). ^{13}C NMR (CDCl$_3$) δ 21.87, 26.41, 26.81, 28.76, 32.61, 33.87, 34.72, 34.74, 34.79, 34.85, 36.29, 36.70, 75.36, 107.94, 111.99, 127.67, 127.90, 128.31, 137.99, 157.57. Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 72.30; H, 7.49; N, 3.77.

5.13. Adamantane-2-spiro-3′-8′-carboxymethoxyimino-1′,2′,4′-trioxaspiro[4.5]decane (22)

To a solution of **4**[10] (0.278 g, 1.0 mmol) in methanol (5 ml) were added pyridine (0.16 g, 2.0 mmol) and carboxymethoxylamine hemihydrochloride (0.262 g, 1.2 mmol). The reaction was stirred at rt for 4 h. After the solvent was removed in vacuo, the crude residue was acidified with 2 M HCl (25 ml) and extracted with CH$_2$Cl$_2$ (3× 20 ml). The combined extracts were dried over Na$_2$SO$_4$ and concentrated to give a residue that was triturated in hexanes to afford **22** (0.30 g, 85%) as a colorless solid. Mp 126–128 °C (hexanes). ^{1}H NMR (CDCl$_3$) δ 1.60–2.10 (m, 18H), 2.33–2.50 (m, 2H), 2.59–2.70 (m, 1H), 2.72–2.90 (m, 1H), 4.62 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 22.08, 26.52, 26.92, 28.55, 32.54, 33.76, 34.80, 34.87, 34.92, 36.41, 36.79, 69.71, 107.77, 112.15, 160.04, 174.84. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.48; H, 7.16; N, 3.84.

5.14. Adamantane-2-spiro-3′-1′,2′,4′-trioxaspiro[4.5]decan-8′-one 4-phenylsemicarbazone (23)

To a solution of **4**[10] (0.28 g, 1.0 mmol) in ethanol (5 ml) and CH$_2$Cl$_2$ (1.5 ml) was added a solution of 4-phenylsemicarbazide (0.17 g, 1.1 mmol) in ethanol (5 ml) and CH$_2$Cl$_2$ (2 ml), and the reaction mixture was stirred at rt for 1 h before being heated to 50 °C for 30 min. The solution was cooled to rt and the resulting precipitate was filtered, washed with ethanol, and dried to afford **23** (0.37 g, 90%) as a colorless solid. Mp 161–163 °C dec (ethanol). ^{1}H NMR (CDCl$_3$) δ 1.62–2.10 (m, 18H), 2.48–2.61 (m, 3H), 2.62–2.69 (m, 1H), 7.02–7.09 (m, 1H), 7.23–7.35 (m, 2H), 7.48–7.54 (m, 2H), 8.24 (s, 1H), 9.11 (s, 1H). ^{13}C NMR (CDCl$_3$) δ 23.17, 26.46, 26.87, 31.88, 32.57, 33.92, 34.75, 34.79, 34.93, 36.35, 36.37, 36.75, 107.75, 112.17, 119.33, 123.10, 128.84, 138.26, 150.83, 154.31. Anal. Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 66.86; H, 6.92; N, 10.04.

5.15. Adamantane-2-spiro-3′-1′,2′,4′-trioxaspiro[4.5]decan-8′-one tosylhydrazone (24)

To a solution of **4**[10] (0.28 g, 1.0 mmol) and *p*-toluenesulfonhydrazide (0.21 g, 1.1 mmol) in CH_2Cl_2 (5 ml) and ethanol (5 ml) was added acetic acid (0.5 ml), and the reaction mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to rt and concentrated in vacuo. The residue was purified by recrystallization from ethanol/H_2O (15 ml, 2:1) to give **24** (0.26 g, 58%) as a colorless solid. Mp 137 °C dec (ethanol/H_2O 2:1). ^{1}H NMR (DMSO-d_6) δ 1.52–2.10 (m, 18H), 2.15–2.65 (m, 4H), 2.38 (s, 3H), 7.39 (d, $J = 7.8$ Hz, 2H), 7.72 (d, $J = 7.8$ Hz, 2H), 10.23 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 20.92, 23.84, 25.72, 26.12, 31.05, 31.80, 33.09, 34.17, 34.29, 35.58, 35.97, 107.55, 111.19, 127.44, 129.31, 136.28, 143.01, 158.63. Anal. Calcd for $C_{23}H_{30}N_2O_5S$: C, 61.86; H, 6.77; N, 6.27. Found: C, 61.71; H, 6.81; N, 6.53.

5.16. Adamantane-2-spiro-3′-1′,2′,4′-trioxaspiro[4.5]decan-8′-one pyridinioacetylhydrazone chloride (25)

To a solution of **4**[10] (278 mg, 1 mmol) in ethanol (10 ml) and acetic acid (1 ml) was added Girard's reagent P (190 mg, 1 mmol). The mixture was stirred at 25 °C for 24 h. The solvent was removed in vacuo, and the residue was purified by recrystallization from ether/methanol (95:5) to afford **25** (140 mg, 31%, 2:1 mixture of two tautomers) as a yellowish solid. Mp 88–90 °C (ether/methanol 9:1). ^{1}H NMR (CD_3OD) δ 1.58–2.39 (m, 18H), 2.43–2.92 (m, 4H), 5.72 (s, minor isomer), 5.94 (s, major isomer), 8.10–8.28 (m, 2H), 8.61–8.78 (m, 1H), 8.90–9.14 (m, 2H). ^{13}C NMR (CD_3OD) δ 21.36, 24.51, 25.72, 27.88, 28.29, 29.00, 29.08, 31.93, 32.59, 32.80, 32.87, 33.58, 33.68, 33.89, 34.83, 35.73, 35.77, 35.92, 36.63, 37.22, 37.72, 38.78, 39.02, 40.18, 40.25, 41.08, 61.72 (m), 62.77 (m), 108.80, 108.92, 113.21, 128.86, 129.00, 129.20, 147.46, 147.66, 157.71, 163.30, 167.86, 175.75. Anal. Calcd for $C_{23}H_{30}ClN_3O_4{\cdot}H_2O$: C, 59.28; H, 6.92; N, 9.02. Found: C, 58.88; H, 7.24; N, 8.83.

5.17. Adamantane-2-spiro-3′-8′-oxo-1′,2′,4′-trioxaspiro[4.5]decaneamidinohydrazone hydrochloride (26)

To a solution of **4**[10] (555 mg, 2 mmol) in THF (11 ml), water (3 ml), and ethanol (3.5 ml) were added 2 M aq HCl (1.5 ml) and aminoguanidine bicarbonate (299 mg, 2.2 mmol). The mixture was stirred at rt for 30 h before removal of solvents. The residue was triturated with ethanol (10 ml) and the resulting precipitate was collected by filtration and washed with THF to give **26** (476 mg, 64%) as a colorless solid. Mp 150 °C dec (ethanol). ^{1}H NMR ($CDCl_3$) δ 1.46–2.27 (m, 18H), 2.42–2.61 (m, 2H), 2.62–2.83 (m, 2H), 6.34 (s, 1H), 7.63 (br s, 2H), 7.91 (s, 1H), 10.95 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 24.83, 26.37, 26.77, 31.72, 32.49, 33.62, 34.70, 34.74, 34.84, 36.23, 36.26, 36.65, 107.26, 112.27, 156.57, 157.93. Anal. Calcd for $C_{17}H_{27}ClN_4O_3$: C, 55.05; H, 7.34; N, 15.11. Found: C, 55.14; H, 7.51; N, 15.30.

5.18. *cis*-Adamantane-2-spiro-3′-8′-[(hydroxyamino)carbonyl]-1′,2′,4′-trioxaspiro[4.5]decane (27)

A solution of ethyl chloroformate (0.26 g, 2.4 mmol), **13**[14] (0.62 g, 2.0 mmol), and triethylamine (0.27 g, 2.6 mmol) in ether (6 ml) was stirred at 0 °C for 10 min. The solid was removed by filtration, and the filtrate was added to a freshly prepared solution of hydroxylamine. (To a suspension of KOH (168 mg, 3.0 mmol) in methanol (1 ml) at 0 °C was added a solution of hydroxylamine hydrochloride (0.20 g, 3 mmol) in methanol (3 ml). The reaction mixture was stirred at 0 °C for 15 min and filtered to remove solid by-products. The filtrate was used as such.) The resulting mixture was stirred at rt for 1 h and concentrated. The crude product was purified by flash chromatography (silica gel, 8% methanol in chloroform) to afford **27** (0.23 g, 36%) as a colorless solid. Mp 130–132 °C (ethanol/water 1:2). ^{1}H NMR (DMSO-d_6) δ 1.40–2.19 (m, 23H), 8.60 (s, 1H), 10.35 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 25.87, 26.27, 26.50, 33.03, 34.28, 34.30, 35.84, 36.15, 39.04, 107.85, 110.64, 171.30. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.97; H, 7.57; N, 4.26.

5.19. *cis*-Adamantane-2-spiro-3′-8′-[[(2′-hydroxyethyl)amino]carbonyl]-1′,2′,4′-trioxaspiro[4.5]decane (28)

A solution of **13**[14] (0.31 g, 1.0 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.29 g, 1.5 mmol), HOBT (0.20 g, 1.5 mmol), and 2-aminoethanol (0.09 g, 1.5 mmol) in DMF (10 ml) was stirred at rt for 18 h before being quenched with 2 M aq HCl (30 ml). The mixture was extracted with ethyl acetate (4× 30 ml), and the combined extracts were washed with water (2× 30 ml) and brine (30 ml), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (silica gel, 5% methanol in CH_2Cl_2) to afford **28** (0.16 g, 46%) as a colorless solid. Mp 114–116 °C (ether/CH_2Cl_2 2:1). ^{1}H NMR ($CDCl_3$) δ 1.59–2.08 (m, 22H), 2.17 (br s, 1H), 3.38–3.45 (m, 2H), 3.71 (t, $J = 4.8$ Hz, 2H), 6.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.44, 26.84, 26.99, 33.58, 34.75, 34.78, 36.35, 36.75, 42.27, 43.58, 62.31, 107.77, 111.53, 176.04. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found: C, 64.68; H, 8.11; N, 3.93.

5.20. Adamantane-2-spiro-3′-8′-(4′-fluorophenyl)-8′-hydroxy-1′,2′,4′-trioxaspiro[4.5]decane (30)

Step 1. A solution of *O*-methyl 2-adamantanone oxime[27] (0.36 g, 2 mmol) and 4-acetoxy-4-(4-fluorophenyl)cyclohexanone[24,29] (0.50 g, 2 mmol) in pentane (100 ml) and CH_2Cl_2 (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 5% ether in petroleum ether) to afford adamantane-2-spiro-3′-8′-acetoxy-8′-(4′-fluorophenyl)-1′,2′,4′-trioxaspiro[4.5]decane

(0.44 g, 53%) as a colorless solid. Mp 147–149 °C (ethanol/H_2O 1:1). ^1H NMR ($CDCl_3$) δ 1.62–2.19 (m, 20H), 2.07 (s, 3H), 2.53 (app d, $J = 12.2$ Hz, 2H), 6.96–7.04 (m, 2H), 7.27–7.33 (m, 2H).

Step 2. A mixture of adamantane-2-spiro-3′-8′-acetoxy-8′-(4′-fluorophenyl)-1′,2′,4′-trioxaspiro[4.5]decane (2.40 g, 5.76 mmol), methanol (56 ml), and 17 % aq KOH (5.6 ml) was heated at 50 °C for 2 h. The reaction mixture was cooled to rt, concentrated to 10 ml, diluted with water (40 ml), and extracted with chloroform (40× 3 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by crystallization from ethanol/H_2O (1:1) to give **30** (1.87 g, 87%) as a colorless solid. Mp 122–124 °C (ethanol/H_2O 1:1). ^1H NMR ($CDCl_3$) δ 1.60–2.18 (m, 20H), 2.25 (td, $J = 13.7$, 4.4 Hz, 2H), 6.98–7.14 (m, 2H), 7.38–7.56 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.54, 26.94, 30.25, 34.84, 36.49, 36.53, 36.84, 71.85, 108.22, 111.62, 115.02 (d, $J = 21.1$ Hz), 126.17 (d, $J = 7.8$ Hz), 144.03 (d, $J = 3.2$ Hz), 161.87 (d, $J = 245.4$ Hz). Anal. Calcd for $C_{22}H_{27}FO_4$: C, 70.57; H, 7.27. Found: C, 70.37; H, 7.27.

5.21. Adamantane-2-spiro-3′-8′-hydroxy-8′-(2′-thiazolyl)-1′,2′,4′-trioxaspiro[4.5]decane (31)

To a stirred solution of 2-bromothiazole (246 mg, 1.5 mmol) in dry THF (4 ml) under N_2 at −78 °C was added *n*-BuLi (1.6 M in hexanes, 1 ml, 1.5 mmol). The resulting bright yellow solution was stirred for 1 h at the same temperature, and then a solution of **4**[10] (415 mg, 1.5 mmol) in dry THF (10 ml) was added. The mixture was allowed to reach 0 °C, poured into ice-water mixture (15 ml), and extracted with ether (3× 25 ml). The combined organic extracts were washed with brine (25 ml), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) followed by recrystallization from hexanes/ether (9:1) to afford **31** (202 mg, 37%, 1:1 mixture of 2 diastereomers) as a colorless solid. Mp 64–66 °C (hexanes/ether 9:1). ^1H NMR ($CDCl_3$) δ 1.60–2.42 (m, 22H), 3.18 (s, 0.5H), 3.40 (s, 0.5H), 7.28 (d, $J = 3.0$ Hz, 0.5 H), 7.30 (d, $J = 3.0$ Hz, 0.5H), 7.69 (d, $J = 3.3$ Hz, 0.5H), 7.72 (d, $J = 3.0$ Hz, 0.5H). ^{13}C NMR ($CDCl_3$) δ 26.45, 26.46, 26.85, 29.98, 30.09, 34.73, 34.77, 34.79, 34.86, 36.34, 36.40, 36.48, 36.75, 36.77, 72.44, 73.00, 107.91, 107.97, 111.61, 111.84, 119.02, 141.95, 142.16, 177.99, 178.23. Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.78; H, 6.93; N, 3.85. Found: C, 62.94; H, 7.01; N, 3.89.

5.22. Adamantane-2-spiro-3′-8′-hydroxy-8′-(2′-pyridinylmethyl)-1′,2′,4′-trioxaspiro[4.5]decane (32)

To a stirred solution of 2-picoline (279 mg, 3.0 mmol) in dry THF (10 ml) under N_2 at −78 °C was added *n*-BuLi (1.6 M in hexanes, 1.9 ml, 3.0 mmol). The resulting bright yellow solution was stirred at the same temperature for 1 h before a solution of **4**[10] (690 mg, 2.5 mmol) in dry THF (15 ml) was added slowly. The mixture was allowed to reach 0 °C, then poured into ice water (50 ml), and extracted with ether (3× 50 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, and concentrated. The purification of the crude product by flash chromatography (silica gel, 70% EtOAc in hexanes) followed by recrystallization from ethanol afforded **32** (385 mg, 41%) as a colorless solid. Mp 128–130 °C. ^1H NMR ($CDCl_3$) δ 1.41–2.25 (m, 22H), 2.88 (s, 2H), 5.82 (s, 1H), 7.11 (d, $J = 7.7$ Hz, 1H), 7.17 (dd, $J = 7.3$, 4.6 Hz, 1H), 7.63 (ddd, $J = 7.7$, 7.7, 1.9 Hz, 1H), 8.49 (d, $J = 4.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.51, 26.89, 29.93, 34.80, 35.03, 36.43, 36.83, 47.30, 70.09, 109.01, 111.30, 121.53, 124.42, 136.89, 148.40, 159.55. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.31; H, 7.94; N, 3.93.

5.23. (*cis*-Adamantane-2-spiro-3′-1′,2′,4′-trioxaspiro[4.5]decan-8′-yl)methyl sodium sulfate (33)

To a stirred suspension of sulfur trioxide pyridine complex (1.62 g, 10 mmol) in dry pyridine (5 ml) was added **10**[14] (1 g, 3.4 mmol) in portions. Stirring was continued for 24 h at rt. After removal of the pyridine under reduced pressure, a saturated Na_2CO_3 solution (10 ml) was added. The mixture was kept at −20 °C for 4 h, then at 0 °C overnight. The precipitate was filtered, washed with cold water (5 ml), and dried in a vacuum oven to give trioxolane **33** as a colorless solid (0.55 g, 41%). Mp 156–157 °C. ^1H NMR (DMSO-d_6) δ 1.01–1.12 (m, 2H), 1.51–1.95 (m, 21H), 3.52 (d, $J = 6.3$ Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 26.01, 26.41, 26.68, 33.39, 34.44, 34.46, 35.64, 35.96, 36.29, 69.96, 108.80, 110.60. Anal. Calcd for $C_{17}H_{25}NaO_7S$: C, 51.51; H, 6.36. Found: C, 51.47; H, 6.31.

5.24. *cis*-Adamantane-2-spiro-3′-8′-[(4′-carboxyphenoxy)methyl]-1′,2′,4′-trioxaspiro[4.5]decane (34)

A mixture of *cis*-adamantane-2-spiro-3′-8′-[[4′-(ethoxycarbonyl)phenoxy]methyl]-1′,2′,4′-trioxaspiro[4.5]decane[14] (0.30 g, 0.68 mmol), KOH (0.38 g), THF (10 ml), methanol (10 ml), and water (2 ml) was heated at 50 °C for 3 h. The mixture was concentrated to 5 ml, diluted with water (15 ml), and acidified with 1 M aq HCl (1 ml). The resulting solid was collected by filtration to give **34** (0.21 g, 75%) as a colorless solid. Mp 165–168 °C. ^1H NMR (DMSO-d_6) δ 1.15–1.27 (m, 2H), 1.50–2.17 (m, 21H), 3.88 (d, $J = 6.2$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.87 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 25.99, 26.40, 26.53, 33.27, 34.45, 35.35, 35.95, 36.26, 72.09, 108.70, 110.71, 114.41, 123.04, 131.50, 162.47, 167.15. Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.67; H, 7.21.

5.25. *cis*-Adamantane-2-spiro-3′-1′,2′,4′-trioxaspiro[4.5]decane-8′-methyl imidazole-1-carboxylate (35)

To a solution of **10**[14] (0.29 g, 1 mmol) in CH_3CN (10 ml) and THF (3 ml) was added 1,1′-carbonyldiimidazole (0.21 g, 1.3 mmol). The mixture was stirred at rt for 2 h before being quenched with cold water (50 ml). The resulting precipitate was collected by filtration, washed with water, and dried to afford trioxolane **35** (0.34 g, 91%) as a colorless solid. Mp 110–112 °C (water). ^{1}H NMR ($CDCl_3$) δ 1.25–1.50 (m, 2H), 1.51–2.21 (m, 21H), 4.25 (d, $J = 6.3$ Hz, 2H), 7.07 (s, 1H), 7.42 (s, 1H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.61, 27.02, 33.54, 34.86, 34.88, 35.66, 36.57, 36.90, 72.07, 108.17, 111.59, 117.03, 130.76, 137.07, 148.71. Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 65.12; H, 7.12; N, 7.25.

5.26. *cis*-Adamantane-2-spiro-3′-8′-[(4′-pyridinyloxy)methyl]-1′,2′,4′-trioxaspiro[4.5]decane mesylate (36)

A mixture of diisopropyl azodicarboxylate (243 mg, 1.2 mmol) and triphenylphosphine (315 mg, 1.2 mmol) in THF (5 ml) under argon was stirred at 0 °C for 30 min before **10**[14] (294 mg, 1 mmol) and 4-hydroxypyridine (114 mg, 1.2 mmol) were added. The resulting mixture was stirred at rt for 5 h. After concentration, the crude product was purified by flash chromatography (silica gel, 40% ethyl acetate in hexanes, then 2% to 6% MeOH in CH_2Cl_2) to give the crude free base of **36** (eluted first) and pure *cis*-adamantane-2-spiro-3′-8′-[(4′-oxo-1′(4′H)-pyridinyl)methyl]-1′,2′,4′-trioxaspiro[4.5]decane (85 mg, 23%, eluted second) as a colorless solid. Mp 138–140 °C. ^{1}H NMR ($CDCl_3$) δ 1.17–1.35 (m, 2H), 1.59–2.03 (m, 21H), 3.60 (d, $J = 7.3$ Hz, 2H), 6.39 (d, $J = 7.8$ Hz, 2H), 7.22 (d, $J = 7.3$ Hz, 2H). The crude free base of **36** was dissolved in CH_2Cl_2/ether (1:3, 8 ml) and treated with a solution of methanesulfonic acid (77 mg, 0.8 mmol) in ether (2 ml). The precipitate was collected by filtration to afford **36** (172 mg, 37%) as a colorless solid. Mp 153–155 °C. ^{1}H NMR ($CDCl_3$) δ 1.34–1.49 (m, 2H), 1.61–2.09 (m, 21H), 2.88 (s, 3H), 4.08 (d, $J = 6.3$ Hz, 2H), 7.29 (d, $J = 7.3$ Hz, 2H), 8.72 (d, $J = 6.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.41, 26.48, 26.81, 33.46, 34.76, 35.60, 36.36, 36.71, 39.34, 74.77, 108.08, 111.66, 112.64, 143.28, 171.01. Anal. Calcd for $C_{23}H_{33}NO_7S$: C, 59.08; H, 7.11; N, 3.00. Found: C, 58.89; H, 7.15; N, 3.09.

5.27. *cis*-Adamantane-2-spiro-3′-8′-[(2′-pyrimidinyloxy)methyl]-1′,2′,4′-trioxaspiro[4.5]decane mesylate (37)

To a suspension of 60% NaH (80 mg, 2 mmol) in DMF (10 ml) under N_2 at 0 °C was added dropwise a solution of **10**[14] (588 mg, 2 mmol) in DMF (20 ml). The mixture was stirred at rt for 1 h and cooled down to 0 °C. After 2-chloropyrimidine (241 mg, 2 mmol) was added, the resulting mixture was stirred at rt overnight. Water (70 ml) was added, and the precipitate was collected by filtration. The crude product was dissolved in ether (20 ml) and added to a solution of methanesulfonic acid (170 mg, 1.77 mmol) in ether/CH_2Cl_2 (1:1, 4 ml). The solid was collected by filtration and dried to afford **37** (530 mg, 57%) as a colorless solid. Mp 133–135 °C. ^{1}H NMR ($CDCl_3$) δ 1.27–1.41 (m, 2H), 1.62–2.04 (m, 21H), 2.93 (s, 3H), 4.42 (d, $J = 7.4$ Hz, 2H), 7.31–7.36 (m, 1H), 8.94 (d, $J = 5.4$ Hz, 2H), 11.28 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.45, 26.51, 26.84, 33.40, 34.77, 35.29, 36.37, 36.75, 39.28, 74.65, 108.31, 111.55, 115.16, 159.43, 160.34. Anal. Calcd for $C_{22}H_{32}N_2O_7S$: C, 56.39; H, 6.88; N, 5.98. Found: C, 56.16; H, 6.72; N, 5.89.

5.28. *cis*-Adamantane-2-spiro-3′-8′-[(methylsulfonyl)methyl]-1′,2′,4′-trioxaspiro[4.5]decane (38)

Step 1. To a solution of sodium thiomethoxide (0.42 g, 6 mmol) in DMF (30 ml) was added dropwise a solution of **11**[14] (1.11 g, 3 mmol) in DMF (10 ml). The mixture was heated at 55 °C for 6 h before removal of the solvent. The residue was dissolved in CH_2Cl_2 (30 ml) and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 90% ethyl acetate in hexanes) to afford *cis*-adamantane-2-spiro-3′-8′-[(methylthio)methyl]- 1′,2′,4′-trioxaspiro[4.5]decane (0.35 g, 36%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.15–1.37 (m, 2H), 1.50–2.02 (m, 21H), 2.10 (s, 3H), 2.40 (d, $J = 7.0$ Hz, 2H).

Step 2. To a solution of the above thioether (350 mg, 1.08 mmol) in CH_2Cl_2 (5 ml) at 0 °C was added dropwise a solution of 3-chloroperoxybenzoic acid (70 % reagent, 790 mg, 3.2 mmol) in $CHCl_3$/CH_2Cl_2 (1:1, 16 ml). After 2 h, the mixture was allowed to warm up to rt and stirred overnight before being quenched with saturated aq $NaHCO_3$ (50 ml). The resulting mixture was concentrated to 50 ml and filtered. The collected precipitate was purified by flash chromatography (silica gel, 25% ethyl acetate in hexanes; then 5% MeOH in CH_2Cl_2) to afford **38** (245 mg, 64%) as a colorless solid. Mp 118–121 °C. ^{1}H NMR ($CDCl_3$) δ 1.33–1.52 (m, 2H), 1.59–2.03 (m, 20H), 2.04–2.25 (m, 1H), 2.92 (s, 3H), 2.94 (d, $J = 6.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.43, 26.81, 30.15, 30.78, 33.66, 34.75, 36.35, 36.73, 42.16, 60.13, 107.72, 111.61. Anal. Calcd for $C_{18}H_{28}O_5S$: C, 60.65; H, 7.92. Found: C, 60.70; H, 7.75.

5.29. *cis*-Adamantane-2-spiro-3′-8′-[(phenylsulfonyl)methyl]-1′,2′,4′-trioxa-8′-azaspiro[4.5]decane (39)

A solution of *O*-methyl 2-adamantanone oxime[27] (1.79 g, 10 mmol) and 4-[(phenylsulfonyl)methyl]cyclohexanone[14] (1.20 g, 4.76 mmol) in pentane (50 ml) and CH_2Cl_2 (25 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 33% ether in hexanes) to afford **39** (0.78 g, 39%) as a colorless solid. Mp 120–122 °C (ether/hexanes 1:1). ^{1}H NMR ($CDCl_3$) δ 1.25–1.46 (m, 2H), 1.60–2.21 (m, 21H), 2.99 (d, $J = 6.3$ Hz, 2H), 7.54–7.62 (m, 2H), 7.63–7.70 (m, 1H), 7.88–7.96 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.44, 26.83, 30.11, 31.19, 33.69, 34.75, 34.76, 36.35, 36.75, 61.79, 107.77, 111.53, 127.73, 129.32, 133.63, 140.21. Anal. Calcd for $C_{23}H_{30}O_5S$: C, 66.00; H, 7.22. Found: C, 66.15; H, 7.10.

5.30. *cis*-Adamantane-2-spiro-3′-8′-[(2′-pyrimidinylsulfonyl)methyl]-1′,2′,4′-trioxaspiro[4.5]decane (40)

Step 1. To a mixture of **10**[14] (588 mg, 2 mmol) and triphenylphosphine (628 mg, 2.4 mmol) in benzene (10 ml) at rt under N_2 was added dropwise a solution of DIPAD (486 mg, 2.4 mmol) in benzene (2 ml). After 5 min, 2-pyrimidinethiol (224 mg, 2 mmol) in benzene (5 ml) was added slowly over a period of 20 min. The stirring was continued for 24 h before removal of the solvent. The crude product was purified by flash chromatography (silica gel, 15% ethyl acetate in hexanes) to give *cis*-adamantane-2-spiro-3′-8′-[(2′- pyrimidinylthio)methyl]-1′,2′,4′-trioxaspiro[4.5]decane (420 mg, 54%) as a colorless solid. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$) δ 1.21–1.42 (m, 2H), 1.60–2.11 (m, 21H), 3.09 (d, $J = 6.9$ Hz, 2H), 6.95 (t, $J = 4.8$ Hz, 1H), 8.50 (d, $J = 4.7$ Hz, 2H).

Step 2. To a solution of the above thioether (396 mg, 1.0 mmol) in CH_2Cl_2 (5 ml) at 0 °C was added dropwise a solution of 3-chloroperoxybenzoic acid (70% reagent, 790 mg, 3.2 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 16 ml). After 2 h, the mixture was allowed to warm up to rt and stirred overnight before being quenched with saturated aq $NaHCO_3$ (40 ml). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2× 20 ml). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (silica gel, 20–50% ethyl acetate in hexanes) to afford **40** (315 mg, 73%) as a colorless solid. Mp 152–154 °C. ^{1}H NMR ($CDCl_3$) δ 1.32–1.49 (m, 2H), 1.61–2.07 (m, 20H), 2.12–2.29 (m, 1H), 3.47 (d, $J = 6.8$ Hz, 2H), 7.57 (dd, $J = 4.9$, 4.9 Hz, 1H), 8.96 (d, $J = 4.9$ Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.44, 26.82, 30.04, 30.87, 33.66, 34.76, 36.35, 36.75, 56.34, 107.78, 111.59, 123.71, 158.66, 166.30. Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 60.16; H, 6.78; N, 6.77.

5.31. *cis*-Adamantane-2-spiro-3′-8′-[[(1′-methyl-1′*H*-imidazol-2′-yl)sulfonyl]methyl]-1′,2′,4′-trioxaspiro[4.5]decane (41)

Step 1. To a suspension of 60% NaH (160 mg, 4 mmol) in DMF (5 ml) under N_2 at 0 °C was added dropwise a solution of 2-mercapto-1-methylimidazole (456 mg, 4.0 mmol) in DMF (10 ml). The mixture was stirred for 1 h before a solution of **11**[14] (744 mg, 2 mmol) in DMF (4 ml) was added dropwise. The mixture was stirred at rt overnight and concentrated. The residue was dissolved in CH_2Cl_2 (30 ml), washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 25% ethyl acetate in hexanes) to afford *cis*-adamantane-2-spiro-3′-8′-[[(1′-methyl-1′*H*-imidazol-2′-yl)thio]methyl]-1′,2′,4′-trioxaspiro[4.5]decane (0.24 g, 30%) as a colorless solid. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$) δ 1.20–1.35 (m, 2H), 1.60–2.00 (m, 21H), 3.00 (d, $J = 6.8$ Hz, 2H), 3.60 (s, 3H), 6.90 (s, 1H), 7.03 (s, 1H).

Step 2. To a solution of the above thioether (250 mg, 0.6 mmol) in CH_2Cl_2 (5 ml) at 0 °C was added dropwise a solution of 3-chloroperoxybenzoic acid (70% reagent, 400 mg, 1.6 mmol) in $CHCl_3/CH_2Cl_2$ (1:1, 8 ml). After 2 h, the mixture was allowed to warm up to rt, stirred overnight, and concentrated to 3 ml. The residue was diluted with saturated aq $NaHCO_3$ (20 ml) and extracted with CH_2Cl_2 (2× 20 ml). The combined extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 10–50% ethyl acetate in hexanes) to afford **41** (130 mg, 51%) as a colorless solid. Mp 151–152 °C. ^{1}H NMR ($CDCl_3$) δ 1.31–1.51 (m, 2H), 1.59–2.04 (m, 20H), 2.06–2.25 (m, 1H), 3.41 (d, $J = 6.3$ Hz, 2H), 3.99 (s, 3H), 6.98 (s, 1H), 7.12 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 26.44, 26.84, 29.96, 30.89, 33.68, 34.76, 35.08, 36.35, 36.75, 59.99, 107.77, 111.55, 125.39, 128.96, 142.61. Anal. Calcd for $C_{21}H_{30}N_2O_5S$/ C, 59.69; H, 7.16; N, 6.63. Found: C, 59.56; H, 7.10; N, 6.47.

5.32. Adamantane-2-spiro-3′-8′-(4′-fluorophenyl)-1′,2′,4′-trioxaspiro[4.5]decane (46)

A solution of *O*-methyl 2-adamantanone oxime[27] (0.36 g, 2 mmol) and 4-(4-fluorophenyl)cyclohexanone[30] (0.38 g, 2 mmol) in pentane (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford **46** (0.36 g, 50%) as a colorless solid. Mp 103–106 °C (ethanol/H_2O 1:1). ^{1}H NMR ($CDCl_3$) δ 1.58–2.25 (m, 22H), 2.43–2.70 (m, 1H), 6.90–7.02 (m, 2H), 7.11–7.22 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.43, 26.84, 31.57, 34.63, 34.76, 36.36, 36.75, 42.15, 108.24, 111.41, 115.06 (d, $J = 21.4$ Hz), 128.03 (d, $J = 7.4$ Hz), 141.75 (d, $J = 3.0$ Hz), 161.26 (d, $J = 244.1$ Hz). Anal. Calcd for $C_{22}H_{27}FO_3$: C, 73.72; H, 7.59. Found: C, 73.65; H, 7.66.

5.33. *cis*-Adamantane-2-spiro-3′-8′-[(4′-methylsulfonyl)phenyl]-1′,2′,4′-trioxaspiro[4.5]decane (47)

A solution of *O*-methyl 2-adamantanone oxime[27] (0.54 g, 3 mmol) and 4-[4-(methylsulfonyl)phenyl]cyclohexanone (0.75 g, 3 mmol) in pentane (50 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 30% ethyl acetate in hexanes) to afford **47** (0.22 g, 18%) as a colorless solid. Mp 132–135 °C (hexanes/CH_2Cl_2 4:1). ^{1}H NMR ($CDCl_3$) δ 1.62–2.19 (m, 22H), 2.60–2.74 (m, 1H), 3.04 (s, 3H), 7.40 (d, $J = 8.3$ Hz, 2H), 7.86 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.48, 26.88, 31.14, 34.48, 34.80, 36.43, 36.78, 42.94, 44.53, 107.95, 111.64, 127.59, 127.80, 138.45, 152.59. Anal. Calcd for $C_{23}H_{30}O_5S$: C, 66.00; H, 7.22. Found: C, 66.08; H, 7.16.

5.34. *cis*-Adamantane-2-spiro-3′-8′-(4′-carboxyphenyl)-1′,2′,4′-trioxaspiro[4.5]decane (48)

Step 1. A solution of *O*-methyl 2-adamantanone oxime[27] (1.10 g, 6.2 mmol) and 4-[4-(ethoxycarbonyl)phenyl]cyclohexanone[31] (1.70 g, 6.2 mmol) in pentane (100 ml) and CH_2Cl_2 (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford *cis*-adamantane-2-spiro-3′-8′-[4′-(ethoxycarbonyl)phenyl]-1′,2′,4′-trioxaspiro[4.5]decane (1.60 g, 63%) as a colorless solid. Mp 129–132 °C (hexanes/ether 9:1). ^{1}H NMR ($CDCl_3$) δ 1.38 (t, $J = 7.2$ Hz, 3H), 1.63–2.22 (m, 22H), 2.56–2.71 (m, 1H), 4.36 (q, $J = 7.2$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 7.96 (d, $J = 8.0$ Hz, 2H).

Step 2. A mixture of *cis*-adamantane-2-spiro-3′-8′-[4′-(ethoxycarbonyl)phenyl]-1′,2′,4′-trioxaspiro[4.5]decane (1.38 g, 3.35 mmol), KOH (1.13 g), THF (30 ml), methanol (30 ml), and water (6 ml) was heated at 50 °C for 2 h. The mixture was concentrated to 10 ml, diluted with water (50 ml), and extracted with ethyl acetate. The aqueous layer was acidified with 1 M aq HCl to pH 2, and the resulting solid was collected by filtration to give **48** (1.08 g, 84%) as a colorless solid. Mp 157 °C dec. ^{1}H NMR (CDCl$_3$) δ 1.63–2.22 (m, 22H), 2.57–2.72 (m, 1H), 7.31 (d, $J = 8.3$ Hz, 2H), 8.03 (d, $J = 8.1$ Hz, 2H). ^{13}C NMR (CDCl$_3$) δ 26.49, 26.90, 31.14, 34.58, 34.81, 36.43, 36.80, 43.10, 108.14, 111.54, 126.99, 127.23, 130.46, 152.54, 171.45. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.68; H, 7.33.

5.35. *cis*-Adamantane-2-spiro-3′-8′-[4′-(4′,5′-dihydro-4′,4′-dimethyl-2′-oxazolyl)phenyl]-1′,2′,4′-trioxaspiro[4.5]decane hydrochloride (49)

Step 1. A solution of *O*-methyl 2-adamantanone oxime[27] (1.32 g, 7.4 mmol) and 4-[4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]cyclohexanone[31,32] (2.00 g, 7.4 mmol) in pentane (100 ml) and CH$_2$Cl$_2$ (50 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10–30% ether in hexanes) to afford *cis*-adamantane-2-spiro-3′-8′-[4′-(4′,5′-dihydro-4′,4′-dimethyl-2′-oxazolyl)phenyl]-1′,2′,4′-trioxaspiro[4.5]decane (0.80 g, 25%) as a colorless solid. Mp 138–140 °C (ethanol). ^{1}H NMR (CDCl$_3$) δ 1.37 (s, 6H), 1.59–2.16 (m, 22H), 2.51–2.68 (m, 1H), 4.08 (s, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 2H).

Step 2. To a solution of *cis*-adamantane-2-spiro-3′-8′-[4′-(4′, 5′-dihydro-4′,4′-dimethyl-2′- oxazolyl)phenyl]-1′,2′,4′-trioxaspiro[4.5]decane (0.21 g, 0.48 mmol) in ether (9 ml) and CH$_2$Cl$_2$ (1 ml) was added 1 M ethereal HCl (0.5 ml). The resulting precipitate was collected by filtration to afford **49** (0.20 g, 88%) as a colorless solid. Mp 143–145 °C. ^{1}H NMR (CDCl$_3$) δ 1.58–2.25 (m, 28H), 2.58–2.80 (m, 1H), 4.69 (br s, 2H), 7.44 (br s, 2H), 8.40 (br s, 2H). ^{13}C NMR (CDCl$_3$) δ 26.44, 26.84, 27.19, 30.87, 34.37, 34.76, 36.39, 36.74, 43.21, 63.92, 83.36, 107.83, 111.59, 117.60, 128.16, 131.38, 156.27, 168.98. Anal. Calcd for $C_{27}H_{36}ClNO_4$: C, 68.41; H, 7.65; N, 2.95. Found: C, 68.26; H, 7.80; N, 2.90.

5.36. *cis*-Adamantane-2-spiro-3′-8′-(1′*H*-imidazol-2′-yl)-1′,2′,4′-trioxaspiro[4.5]decane (50)

To a solution of *cis*-adamantane-2-spiro-3′-8′-formyl-1′,2′, 4′-trioxaspiro[4.5]decane[14] (292 mg, 1 mmol) and 40% glyoxal (145 mg, 1 mmol) in methanol (12 ml) at 0 °C was added ammonia (0.45 ml, 7 N in methanol). The resulting mixture was stirred at rt overnight and concentrated. The crude product was crystallized from hexanes/CH$_2$Cl$_2$ (3:2) to afford trioxolane **50** (240 mg, 73%) as a colorless solid. Mp 138–140 °C (hexanes/CH$_2$Cl$_2$, 3:2). ^{1}H NMR (CDCl$_3$) δ 1.58–2.23 (m, 22H), 2.75–2.98 (m, 1H), 6.96 (s, 2H). ^{13}C NMR (CDCl$_3$) δ 26.54, 26.94, 29.11, 33.92, 34.82, 34.86, 36.23, 36.47, 36.84, 108.00, 111.54, 121.10 (br s), 151.00. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 69.04; H, 7.93; N, 8.60.

5.37. Adamantane-2-spiro-3′-5′,5′-bis(4′-fluorophenyl)-1′,2′,4′-trioxolane (51)

A solution of *O*-methyl 2-adamantanone oxime[27] (0.90 g, 5 mmol) and 4,4′-difluorobenzophenone (1.09 g, 5 mmol) in pentane (90 ml) and CH$_2$Cl$_2$ (10 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 2% ether in petroleum ether) to afford **51** (0.87 g, 45%) as a colorless solid. mp 86–89 °C (ethanol/H$_2$O 1:1). ^{1}H NMR (CDCl$_3$) δ 1.60–2.05 (m, 12H), 2.06–2.40 (m, 2H), 6.90–7.20 (m, 4H), 7.35–7.65 (m, 4H). ^{13}C NMR (CDCl$_3$) δ 26.41, 26.84, 34.77, 34.96, 36.17, 36.71, 108.95, 114.21, 115.06 (d, $J = 21.3$ Hz), 128.96 (d, $J = 8.4$ Hz), 135.56, 162.95 (d, $J = 248.0$ Hz). Anal. Calcd for $C_{23}H_{22}F_2O_3$/ C, 71.86; H, 5.77. Found: C, 71.78; H, 5.87.

5.38. Adamantane-2-spiro-3′-5′,5′-bis(4′-carboxyphenyl)-1′,2′,4′-trioxolane (52)

Step 1. A solution of *O*-methyl 2-adamantanone oxime[27] (1.79 g, 10 mmol) and 4,4′-bis(ethoxycarbonyl)benzophenone (3.26 g, 10 mmol) in pentane (60 ml) and CH$_2$Cl$_2$ (40 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 10% ether in hexanes) to afford adamantane-2-spiro-3′-5′,5′-bis[4′-(ethoxycarbonyl)phenyl]-1′,2′,4′-trioxolane (1.77 g, 36%) as a colorless solid. Mp 143–145 °C (ether). ^{1}H NMR (CDCl$_3$) δ 1.38 (t, $J = 7.1$ Hz, 6H), 1.60–2.07 (m, 12H), 2.20 (app d, $J = 12.2$ Hz, 2H), 4.37 (q, $J = 7.2$ Hz, 4H), 7.58 (d, $J = 8.3$ Hz, 4H), 8.03 (d, $J = 8.3$ Hz, 4H).

Step 2. A mixture of adamantane-2-spiro-3′-5′,5′-bis[4′-(ethoxycarbonyl)phenyl]-1′,2′,4′-trioxolane (0.44 g, 0.89 mmol), THF (7 ml), and 40% aq KOH (4.5 ml) was heated at 50 °C for 5 days. The reaction mixture was cooled to rt and extracted with ether (5× 20 ml). The aqueous layer was acidified to pH 3 with concd HCl. The resulting precipitate was filtered and recrystallized from ethanol/water (2:1) to afford **52** (0.35 g, 90%) as a colorless solid. Mp 170 °C (EtOAc) dec. ^{1}H NMR (DMSO-*d*$_6$) δ 1.60–2.05 (m, 12H), 2.13 (app d, $J = 11.7$ Hz, 2H), 7.60 (d, $J = 8.8$ Hz, 4H), 7.98 (d, $J = 8.8$ Hz, 4H). ^{13}C NMR (DMSO-*d*$_6$) δ 25.79, 26.19, 34.25, 34.42, 35.56, 35.99, 108.40, 113.95, 126.42, 129.46, 131.47, 143.44, 166.69. Anal. Calcd for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 68.64; H, 5.34.

5.39. Adamantane-2-spiro-3′-5′,5′-bis[4′-(aminomethyl)phenyl]-1′,2′,4′-trioxolane dimesylate (53)

Step 1. To a solution of adamantane-2-spiro-3′-5′,5′-bis[4′- (ethoxycarbonyl)phenyl]-1′,2′,4′- trioxolane[14]

(1.0 g, 2.00 mmol) in ether (5 ml) and THF (2 ml) was added dropwise 2 M lithium borohydride in THF (2.00 ml, 4 mmol) followed by 1 M lithium triethylborohydride in THF (0.4 ml, 0.4 mmol). The resulting mixture was stirred at rt for 24 h and then diluted with ether (30 ml). The mixture was washed with 1 M aqueous NaOH (2× 5 ml), water (2× 5 ml), and brine (5 ml), dried over $MgSO_4$, filtered, and concentrated to afford the diol (0.80 g, 96%) as a colorless solid.

Step 2. Diisopropyl azodicarboxylate (0.70 ml, 3.53 mmol) was added dropwise to a mixture of the diol (0.80 g, 1.96 mmol), phthalimide (0.57 g, 3.87 mmol), and triphenylphosphine (1.31 g, 5 mmol) in THF (20 ml) at 0 °C under N_2. The resulting mixture was stirred at rt for 24 h and then quenched with 5% aqueous $NaHCO_3$ (20 ml). The solid was collected by filtration and washed with water, THF, and ether to afford the bisphthalimide (1.06 g, 81%) as a white solid.

Step 3. A mixture of the bisphthalimide (0.73 g, 1.10 mmol) and hydrazine monohydrate (1 ml) in chloroform (30 ml) and methanol (4 ml) was heated at 50 °C for 24 h. The reaction mixture was cooled to rt, filtered to remove the solid by-product, and concentrated. The residue was dissolved in $CHCl_3$, washed with brine, dried over $MgSO_4$, filtered, and treated with a solution of methanesulfonic acid (0.21 g) in $CHCl_3$ (10 ml). After removal of the solvent, the crude product was purified by crystallization from EtOH/$CHCl_3$ (1:4) to afford **53** (0.20 g, 37%) as a colorless solid. Mp 147–148 °C. ^{1}H NMR (CD_3OD) δ 1.62–1.94 (m, 12H), 2.18–2.25 (m, 2H), 2.68 (s, 6H), 4.13 (s, 4H), 7.47 (d, $J = 8.3$ Hz, 4H), 7.57 (d, $J = 8.3$ Hz, 4H). ^{13}C NMR (CD_3OD) δ 27.85, 28.28, 35.70, 35.94, 37.59, 37.64, 39.48, 43.88, 110.22, 115.35, 128.61, 129.94, 135.26, 142.17. Anal. Calcd for $C_{27}H_{38}N_2O_9S_2$: C, 54.16; H, 6.40; N, 4.68. Found: C, 53.96; H, 6.29; N, 4.80.

5.40. Adamantane-2-spiro-3′-5′,5′-bis(2′-pyridyl)-1′,2′,4′-trioxolane (54)

A solution of *O*-methyl 2-adamantanone oxime[27] (716 g, 4.0 mmol) and di-2-pyridyl ketone (777 mg, 4.2 mmol) in pentane (70 ml) and CH_2Cl_2 (30 ml) was treated with ozone according to the general procedure. The crude product was purified by flash chromatography (silica gel, 4% ethanol in ether) to afford **54** (620 mg, 44%) as a colorless solid. Mp 135–136 °C (ether). ^{1}H NMR ($CDCl_3$) δ 1.60–2.10 (m, 12H), 2.27 (app d, $J = 12$ Hz, 2H), 7.21 (ddd, $J = 8.5$, 5.0, 1.0 Hz, 2H), 7.76 (ddd, $J = 8.0$, 8.0, 2.0 Hz, 2H), 7.95 (d, $J = 8.0$ Hz, 2H), 8.55 (dd, $J = 4.5$, 1.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 26.50, 26.86, 34.81, 34.88, 35.93, 36.74, 107.92, 114.58, 121.16, 123.16, 136.38, 149.12, 158.20. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.94; H, 6.30; N, 7.91.

5.41. Antimalarial screens

In vitro and in vivo antimalarial data were obtained as previously described.[33,34]

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