Artemisinin Tricyclic Analogs Bearing a Methyl Group at C-5a: Preparation and Antimalarial Activity

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Syntheses of the two artemisinin tricyclic analogs **39** and **40** bearing a methyl group at C-5a have been accomplished. The common starting material in both approaches was enantiomerically pure oxo nitrile (*R*)-**10** which was elaborated through the Michael addition of chiral imine **9** to acrylonitrile. Several strategies for converting **10** into targets **39** and **40** were investigated. The strategy which was ultimately adopted employed the addition of [chloro(trimethylsilyl)methyl]lithium (**15**) to **10**. The resulting epoxysilane **16** was converted into vinylsilane **36** by an original route involving first the regioselective opening of the oxirane ring by means of HBr, followed by zinc reduction. Addition of methyllithium to form **36** furnished pivotal derivative **37** which was finally converted into our targets **39** and **40** by ozonization. These trioxanes were thus synthesized by a linear sequence of seven chemical operations, with an overall yield of ca. 9% and 11%, respectively, from 2-methylcyclohexanone (**8**). Both compounds proved to be completely devoid of antimalarial activity on the "H" clone of *Plasmodium falciparum*. In contrast, the two structural analogs **43** and **44** having a hydrogen atom at the C-5a angular position display relatively high antimalarial activities. Thus, the fact that the replacement of the hydrogen atom at C-5a by a methyl group in tricyclic trioxanes **6** was detrimental to biological activity reinforced the hypothesis that tight hemin-trioxane complexes of type **7** are involved in the activation phase of these antimalarial agents.

Introduction

Malaria remains an important health problem in the tropics and subtropics, which affects over 350 million people especially in Africa and Southeast Asia, causing deaths in excess of 2 million each year. Since resistance to currently used antimalarials is spreading rapidly, there is a great need for new effective drugs. Among them, the endoperoxides constitute a promising class of antimalarial agents. Artemisinin (**1**), the prototype, also commonly referred to by its chinese name *Qinghaosu*, is a naturally occurring cadinane sesquiterpene possessing a 1,2,4-trioxane peroxy moiety, isolated from *Artemisia annua (Compositae)*. The remarkable antimalarial activity and low toxicity of artemisinin have made it an important addition to the range of antimalarial drugs, especially for the treatment of multidrug-resistant cases. The parasite responsible for the most life-threatening form of malaria is *Plasmodium falciparum*. Artemisinin is effective against the blood-stage of this protozoan at nanomolar concentrations; the drug also has gametocidal activity.[1]

Much strong evidence indicates that artemisinin reacts first with intraparasite heme, giving rise to free radicals.[2] Computational studies have shown that artemisinin and heme dock in configuration **2**, which allows the heme iron atom to cleave the endoperoxide bridge. Docking studies also revealed that electrostatic and van der Waals forces are the factors which determine the alignment of the peroxide group with the heme iron atom.[3] This activation phase is followed by the homolytic, Fenton-type cleavage of the peroxide which affords primarily the oxyl radicals **3a** and/or **3b**. Rearrangement of **3** then gives centered C radicals (exemplified by **4a** or **4b**), entities responsible for antimalarial activity (Figure 1)[4], a hypothesis recently reinforced by the characterization of a covalent adduct between artemisinin and a heme model.[5] Due to their reactivity, these C-centered radicals ultimately alkylate nearby macromolecules within the *Plasmodium*, causing the parasite clearance. Specific alkylations of proteins[6], DNA[7], and heme[5] have thus been identified.

By correlating the structure and activity of various cyclic trioxanes, is was found that certain rings in artemisinin are redundant. Thus, for example a relatively high antimalarial activity was maintained in most of simplified tricyclic analogs **5**, which mimic parts of the artemisinin skeleton.[8] As

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Figure 1. Heme-artemisinin interaction hypothesis

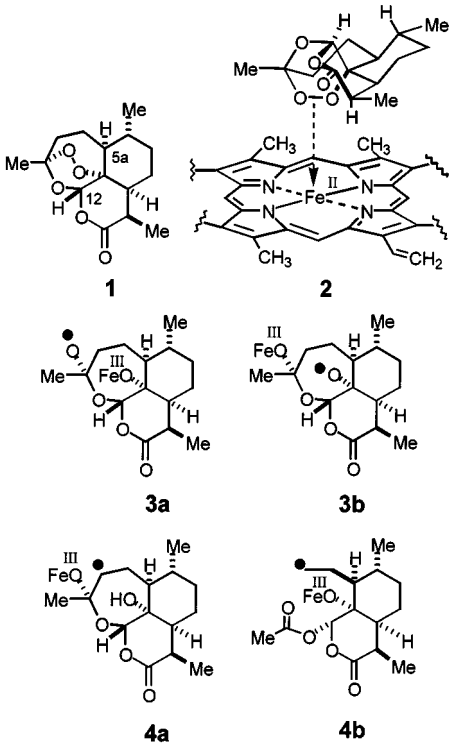
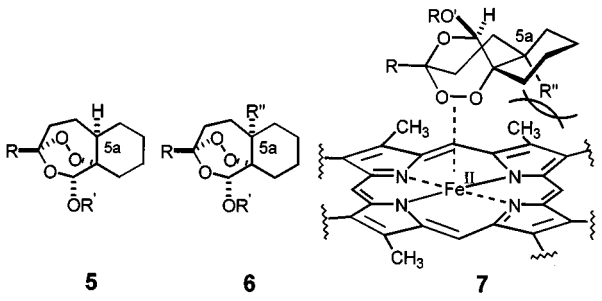


Figure 2. Presumed interaction of C-5a-substituted trioxanes with heme

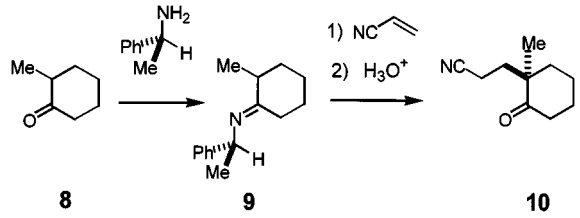


a matter of fact, artemisinin (**1**) and other active artemisinin-like trioxane analogs, such as **5**, generally possess a hydrogen atom at the C-5a angular position. We reasoned that, in the case of trioxanes **6**, in which this hydrogen atom is replaced by an alkyl substituent, formation of a tight heme-trioxane complex such as **7** should be impeded because of the destabilizing steric interaction between the *axial* R″ group of **6** and the heme nucleus (Figure 2). Consequently, an abrupt loss of activity was expected for such molecules, over the nonsubstituted counterparts. With the aim of supporting the above putative mechanism, a series of tricyclic 1,2,4 trioxanes bearing a methyl group at the C-5a angular position (**6**, R″ = Me) were synthesized, and their antimalarial potencies were evaluated.[9]

Results and Discussion

Several strategies have evolved for the elaboration of the 1,2,4-trioxane system. In this paper, two of them were used

Scheme 1. Enantioselective Michael addition of chiral imine **9** to acrylonitrile

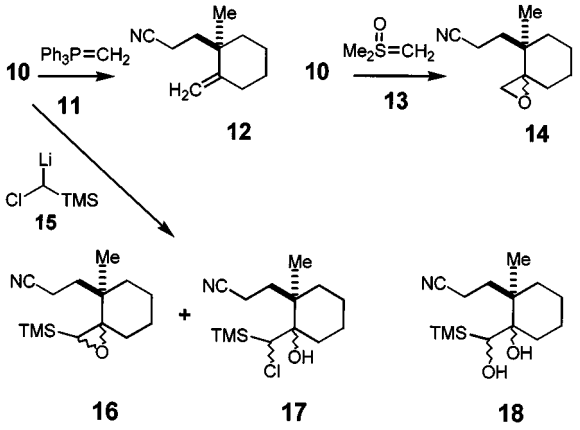


for constructing trioxanes **6**: The photo-oxygenation of enol ethers[10], and the ozonization of vinylsilanes.[11] The common starting material in both approaches was enantiomerically pure oxo nitrile (*R*)-**10**, bearing the crucial quaternary carbon atom (future C-5a center of trioxanes), which was efficiently prepared in two steps from *racemic* 2-methylcyclohexanone (**8**). Condensation of this cyclanone with (*S*)-1-phenylethylamine gave chiral imine **9**, which upon addition to acrylonitrile followed by hydrolytic workup, afforded in a 75% overall yield oxo nitrile (*R*)-**10** with an excellent ee (≥ 95%) (Scheme 1).[12][13]

First Route: Photo-Oxygenation of Enol Ether 21

Conversion of oxo nitrile **10** into key enol ether **21** required the methoxymethylenation of the oxo group and the subsequent one-carbon elongation of the propionitrile appendage.[8] Direct addition of (methoxymethylene)triphenylphosphorane, generated from the corresponding phosphonium chloride and *n*BuLi, to **10** was first attempted. However, regardless of the experimental conditions, unchanged oxo nitrile **10** was invariably recovered. By contrast, addition of phosphorane **11**, generated with *n*BuLi as base, to **10** afforded the desired methylene derivative **12**, though in low yield (25%). When *n*BuLi was replaced by NaH in DMSO, this addition now proceeded straightforwardly, giving **12** with a 90% yield. Functionalization of **12** through hydroboration of the methylene group was examined next. Unfortunately, this reaction was thwarted by the competitive participation of the nitrile function. An alternative, indirect route for the introduction of a methoxymethylene moiety to **10** would make use of epoxide **14**, obtained as a 2:1 mixture of diastereomers by addition of sulfur ylide **13** to **10**. However, Lewis acid induced rearrangement of this epoxide under various conditions (BF_3-OEt_2, Et_2AlCl, $ZnCl_2$) furnished only minute amounts (10−15%) of the desired aldehyde, along with several unidentified products. In view of the problems encountered in the rearrangement of epoxide **14**, we next decided to prepare the related epoxysilane **16**, since such derivatives are known to undergo a clear-cut acidic rearrangement.[14]. To this end, addition of anion **15**[15], generated from (chloromethyl)trimethylsilane and *s*BuLi, to **10** was attempted. However, this condensation was found to be strongly dependent on the source of the *s*BuLi supply.[16] Furthermore, we established that the order of addition of the reagents

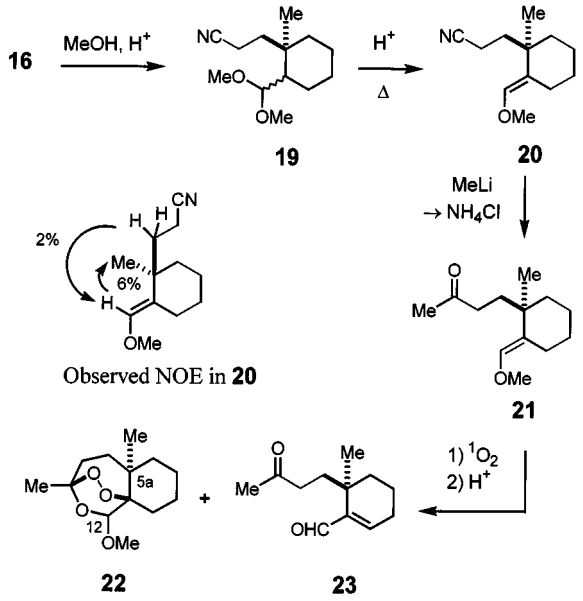
Scheme 2. Attempted homologation of the carbonyl group of oxo nitrile **10** and synthesis of epoxysilane **16**



(i: LiCl; ii: $TMSCH_2Cl$; iii: TMEDA; iv: *s*BuLi; v: **10**) was crucial to gain reproducible results. Under these conditions, epoxysilane **16** (11:8:5:1 mixture of diastereomers) was obtained with a 35% yield, along with chlorohydrin **17** (20% yield) and unreacted starting material **10** (35% yield). The above mixture was separated by flash chromatography on silica gel. During this operation, chlorohydrin **17** was converted into diol **18**, which was next transformed with a 75% yield into the desired epoxysilane **16** by treatment with Ph_3P and DEAD.[17] Taking into account the recovered starting material, oxo nitrile **10** was therefore converted into target epoxysilanes **16** in 75% yield (Scheme 2).

To our delight when epoxysilane **16** was treated with a mixture of *p*-TsOH and $HC(OMe)_3$ in MeOH, the desired acetal **19** was directly obtained with a 90% yield. Simple distillation of **19** in the presence of a catalytic amount of *p*-TsOH gave enol ether **20** (88% yield), of almost pure *E* geometry ($E/Z \geq 20:1$). The *E* configuration in **20** was established by ^{1}H-NMR spectroscopy including NOE experiments. Addition of methyllithium to **20**, followed by aqueous workup afforded methyl ketone **21** with a 70% yield. Photo-oxygenation of the methanolic solution of **21** in the presence of Methylene Blue at −78°C, followed by treatment with Amberlyst[8][10] finally delivered a minute amount (6%) of the desired trioxane **22**, along with 40% of α,β-ethylenic aldehyde **23**, a product arising from the ene reaction of singlet oxygen with **21**.[18] Trioxane **22** proved to be different by ^{1}H NMR and TLC from its isomers **39** and **41** resulting from the ozonization of vinylsilane **37**, and exhibiting both a *syn* relationship between the peroxide bridge and the angular methyl group at C-5a (vide infra); consequently, the peroxide bridge in **22** is necessarily *anti* to this methyl group as depicted. However, because of the very low yield, further spectroscopic investigation of trioxane **22** was not undertaken, and the stereochemical assignment of the methoxy group at C-12 was not determined (Scheme 3). This route was therefore abandoned at this stage, and our next synthetic efforts were focused on the ozonization of vinylsilane **37**.

Scheme 3. Synthesis and photo-oxidation of enol ether **21**

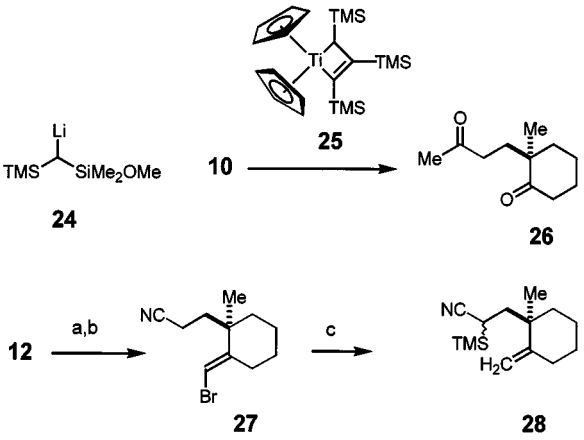


Second Route: Ozonization of Vinylsilane 37

Direct introduction of a vinylsilyl moiety to oxo nitrile **10** was first examined. While the attempted addition of {[(methoxy)dimethylsilyl](trimethylsilyl)methyl}lithium (**24**)[19] to **10** returned only starting material, the condensation of titanacyclobutene **25**[20] to **10** unexpectedly gave diketone **26**, resulting from the addition to the nitrile function, with a 65% yield. The above results clearly indicate that the introduction of a vinylsilyl moiety to **10** is impeded by the steric hindrance of the carbonyl group, due to the presence of the α-quaternary carbon center. An alternative plan was therefore devised, involving metalation of vinylic bromide **27**. This was prepared as a single *E* isomer (stereochemistry established by ^{1}H-NMR spectroscopy including NOE experiments) from olefin **12**, through addition of bromine, followed by dehydrobromination by using KOH in ethanol with a 52% overall yield. Quite surprisingly, treatment of bromide **27** with sodium and trimethylsilyl chloride[21] furnished α-silylated nitrile **28** as a mixture of diastereomers in 55% yield, instead of the expected vinylsilane derivative. Thus, the proton at the α-position to the nitrile group was abstracted by the vinylic anion primarily formed by halogen-metal exchange (Scheme 4).

We therefore decided to apply the same sequence of reactions to an olefinic compound analogous to **12**, but in which the propionitrile appendage was replaced by a "protected" butanone side chain. For this purpose, **12** was first converted into oxo olefin **29** by addition of MeLi with a 85% yield. Since bromination of **29** gave a complex mixture of products, we then envisaged to protect the oxo group by dioxolanation. Unfortunately, all attempts at acetalization of **29** were invariably thwarted by competitive side reactions. To overcome this difficulty, protection of the oxo group of **29** under mild operating conditions was planned. A protected cyanohydrin function was selected for such a purpose. Treatment of **29** with KCN in the presence of sul-

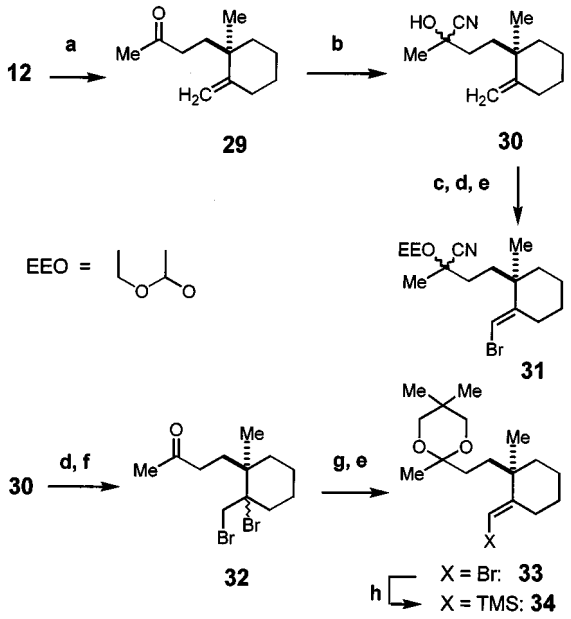
Scheme 4. Attempted olefination of oxo nitrile **10** by a (trimethylsilyl)methylene group and attempted functionalization of the methylene group of **12**; reagents and conditions: (a) Br_2, CH_2Cl_2, 0°C; (b) KOH, EtOH; (c) Na, TMSCl, Et_2O



furic acid gave the expected cyanohydrin **30** with a 89% yield, which was then protected as the acetal form by condensation with ethyl vinyl ether. Addition of bromine followed by treatment with KOH gave vinylic bromide (*E*)-**31**, with an overall yield of 11% from cyanohydrin **30**. Unfortunately, when **31** was sequentially exposed to *t*BuLi and TMSCl, methylene compound **29** was the only isolated product. The vexing formation of **29** from **31**, *in the absence of any hydrolytic workup*, can be tentatively interpreted by invoking an anionic fragmentation of the protected cyanohydrin group. At this stage, it was clear that a protected cyanohydrin function was not resistant to the conditions required for halogen-metal exchange at the vinylic center. We speculated that an acetal function, known to be stable under strongly basic conditions would be a more appropriate protecting group. The specific choice of an acetal derived from 2,2-dimethylpropanediol was guided by the observation made by Avery that this kind of protecting group can be selectively hydrolyzed in the presence of a vinylsilane function.[11] Thus, bromination of **30**, followed by mild basic treatment gave dibromo ketone **32**, which was acetalized by condensation with 2,2-dimethylpropanediol. KOH-promoted dehydrobromination of the resulting acetal led to vinylic bromide (*E*)-**33** with a 50% yield based on **30**. To our delight, sequential exposition of **33** to *t*BuLi and TMSCl now furnished the desired vinylsilane (*E*)-**34** with a 85% yield. Unfortunately, all attempts to hydrolyze the ketal group of **34** proved to be either inefficient (silica gel impregnated with 10% oxalic acid[11]), or not selective (10% AcOH), giving essentially the "desilylated" methylene ketone **29** (Scheme 5).

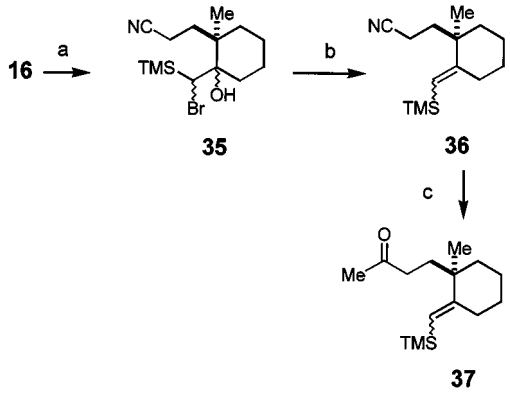
The difficulties encountered to elaborate the vinylsilane moiety prompted us to develop an original route for the preparation of required silyl derivative **37**, based on the two-step deoxygenation of epoxysilane **16**.[22] Treatment of **16** with 48% aqueous HBr[14] afforded regioselectively bromohydrin **35** with a 76% yield, which upon zinc reduction in the presence of aqueous NH_4Cl gave key vinylsilane **36** as a 1.5:1 mixture of geometrical isomers (92%).

Scheme 5. Attempted halogen-metal exchange to vinylic bromide **31** and **33**; reagents and conditions: (a) MeLi, Et_2O; (b) KCN, H_2SO_4, EtOH; (c) ethyl vinyl ether, cat. 12 N HCl; (d) Br_2, CH_2Cl_2; (e) KOH, EtOH; (f) aq. NaOH; (g) 2,2-dimethylpropanediol, TsOH; (h) i: *t*BuLi, Et_2O, −78°C; ii: TMSCl



Addition of MeLi to **36**, followed by mild hydrolytic workup then led to pivotal oxo vinylsilane **37** (stereomers in the ratio 1.5:1) in 65% yield (Scheme 6).

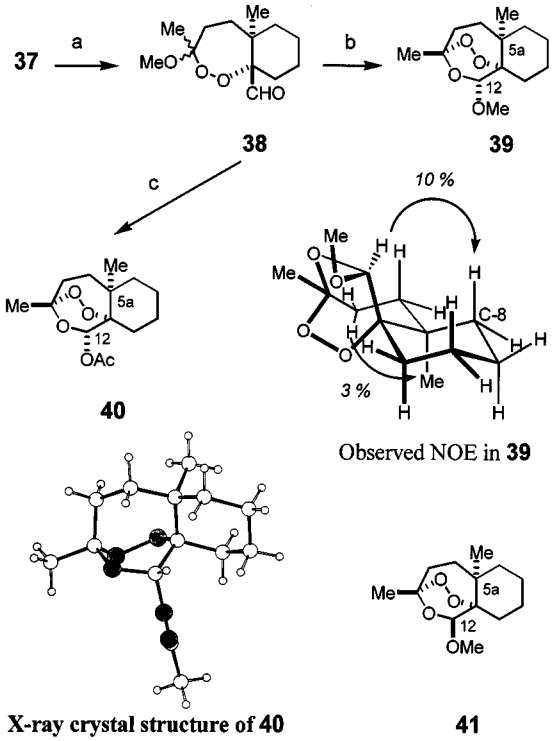
Scheme 6. Synthesis of vinylsilane **37** from epoxysilane **16**; reagents and conditions: (a) HBr 48%, CH_2Cl_2; (b) Zn, THF, aq. NH_4Cl; (c) MeLi, Et_2O



Ozonization of **37**, followed by treatment with BF_3-OEt_2[11] gave sensitive peroxide aldehyde **38** (not fully characterized), which was finally converted into trioxane **39** with $HC(OMe)_3$ in MeOH in the presence of BF_3-OEt_2 in 35% yield based on **37**. The structure of **39** was determined by NMR spectroscopy, including HMQC, HMBC and NOE experiments. Trioxane **40**, the structure of which was unequivocally established by an X-ray crystallographic analysis[23], was obtained in a similar fashion by treating **38** with Ac_2O and BF_3-OEt_2[11] (41% from **37**). Stereochemical assignments in trioxane **39** were definitely proved by converting **40** into **39**. Incidentally, an interesting observation was made during this operation: When trioxane **40**

was exposed to methanol in the presence of a catalytic amount of BF_3-OEt_2, the two trioxanes **39** and **41**, epimers at C-12, were simultaneously formed at the beginning of the reaction. However, due to the concomitant isomerization of the β-methoxy derivative **41** into the thermodynamically more stable α-methoxy isomer **39**, the former epimer progressively vanished. Another important stereochemical aspect of trioxanes **39** and **40** is that both exhibit the same relative configuration as that found in artemisinin (**1**), namely, a *syn* relationship between the substituent at C-5a and the peroxide bridge, and an α orientation of the acyloxy (alkoxy) group at C-12. Furthermore, since the common material in the synthesis of trioxanes **39** and **40** was enantiomerically pure oxo nitrile (*R*)-**10**, these goals were in turn obtained in their (5a*R*) enantiomerically pure form, mimicking the absolute configuration of natural artemisinin (**1**) (Scheme 7).

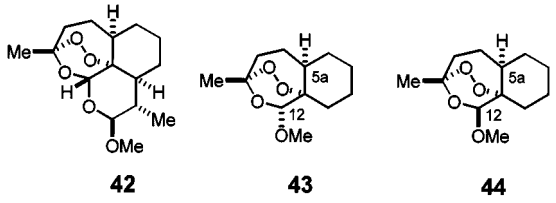
Scheme 7. Synthesis of trioxanes **39** and **40**; reagents and conditions: (a) i: O_3, CH_2Cl_2, −78°C, ii: BF_3-OEt_2, 20°C; (b) BF_3-OEt_2, MeOH, $HC(OMe)_3$, 20°C; (c) BF_3-OEt_2, Ac_2O, 20°C



Antimalarial Activity

Samples of **39** and **40**, together with appropriate reference compounds, were tested in vitro against the "H" clone of *Plasmodium falciparum*[24] by the method developed by Desjardins and co-workers involving the uptake of tritiated hypoxanthine.[25] Both synthetic trioxanes proved to be completely devoid of biological activity in the range of 20−500 nM. In comparison, on the same strain of *Plasmodium*, artemisinin (**1**) and artemether (**42**) exhibited IC_{50} values of 19 nM and 11 nM, respectively. It is worth noting that in sharp contrast, racemic tricyclic trioxanes **43** and **44**, structural analogs to **39** and **40** lacking the methyl group at C-5a, display relatively high antimalarial activities [IC_{50} values of 40 nM and 8 nM, respectively on the Indochina (W2) clone of *Plasmodium falciparum*] (Figure 3)[8b]. Thus, in line with our original assumption, the presence of a methyl substituent at C-5a in tricyclic trioxanes **39** and **40** completely abolished their antiprotozoal potency.

Figure 3. Antimalarial reference compounds



Conclusion

A concise, direct approach for the enantioselective synthesis of tricyclic trioxanes **39** and **40**, simplified analogs to artemisinin but bearing a methyl group at the C-5a angular position, has been developed. The key tactical element was a new route for the preparation of vinylsilanes **36**, based on the two-step deoxygenation of epoxysilane **16**, via bromohydrin **35**. Thus, according to the strategy that was ultimately adopted, trioxanes **39** and **40** have been synthesized by a linear sequence of seven chemical operations, with an overall yield of ca. 9 and 11% respectively, from 2-methylcyclohexanone (**8**). Both synthetic trioxanes **39** and **40** proved to be completely devoid of antimalarial activity. Thus, the fact that the replacement of the hydrogen atom at C-5a by a methyl group in trioxanes **6** was detrimental to activity reinforces the hypothesis that tight hemin-trioxane complexes of type **7** are involved in the activation phase of these antimalarial agents.

Experimental Section

General: Melting points were recorded with a Büchi capillary-tube melting-point apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer 841 spectrometer from neat films between NaCl plates or KBr pellets. Only significant absorptions are listed. The ^1H- and ^{13}C-NMR spectra were recorded with Bruker AC 200 P (200 MHz and 50 MHz, for ^1H and ^{13}C, respectively) or Bruker ARX 400 (400 MHz and 100 MHz, for ^1H and ^{13}C, respectively) spectrometers. Recognition of methyl, methylene, methine, and quaternary carbon nuclei in ^{13}C-NMR spectra rests on the *J*-modulated spin-echo sequence. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter in a 1-dm cell. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ precoated glass plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230−400 mesh ASTM). Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Methanol was dried with magnesium and distilled. Benzene, toluene, DMF, HMPA and CH_2Cl_2 were distilled from calcium hydride, under nitrogen. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-

dried under a positive pressure of nitrogen. Organic layers were dried with anhydrous $MgSO_4$. The boiling points refer to oil-bath temperatures. Chemicals obtained from commercial suppliers were used without further purification. Mass specra were recorded by electron impact at 70 eV with a JEOL-JMS-AX500 spectrometer. All elemental analyses were performed by the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin Elmer 2400 analyzer.

(−)-(R)-3-(1-Methyl-2-oxo-cyclohexyl)propanenitrile (**10**): (*S*)-(−)-1-Phenylethylamine (59.4 g, 0.49 mol, $[\alpha]_D^{22} = -39.1$ (neat), ee 96%) was added to a solution of 2-methylcyclohexanone (50.0 g, 0.446 mol) and *p*-toluenesulfonic acid (0.2 g, 1.2 mmol) in toluene (500 ml). The reaction mixture was refluxed for 15 h with azeotropic removal of water. The reaction mixture was cooled and concentrated under reduced pressure and distilled to give imine **9** (b.p. 95°C/0.1 Torr) as a colorless oil (88 g, 92%). To a solution of the imine **9** (20 g, 92 mmol) in THF (10 ml), acrylonitrile (42.2 g, 800 mmol) and hydroquinone (0.2 g) were then added and the mixture was stirred at 20°C. After 3 d, 20% aqueous acetic acid (200 ml) and THF (500 ml) were added, and the mixture was stirred for 3 h. The solvents were removed under reduced pressure and 1 N HCl (200 ml) was added to the residual oil. The mixture was extracted with ether and the collected organic phases were washed with brine, dried and concentrated in vacuo. Chromatographic separation on silica gel (hexane/ethyl acetate, 4:1) and distillation afforded 12.2 g of oxo nitrile **10** (80%), colorless oil, b.p. 100−110°C/0.1 Torr. − $[\alpha]_D^{22} = -7$ (EtOH, $c = 26$). − IR (neat): $\tilde{\nu} = 2238$ cm^{-1} (CN), 1703 (C=O). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.12 (s, 3 H, CH_3), 1.60−2.00 (m, 8 H), 2.20−2.50 (m, 4 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 11.4 (CH_2, *C*H_2CN), 20.0 (CH_2), 21.3 (CH_3), 26.4 (CH_2), 32.7 (CH_2), 37.4 (CH_2), 37.6 (CH_2), 46.8 (C, C-1), 119.3 (CN), 213 (C=O). − MS (70 eV); *m/z* (%): 165 (2) [M$^+$], 121 (100), 112 (46), 94 (28), 81 (60), 69 (20), 55 (72). − $C_{10}H_{15}NO$ (165.2): calcd. C 72.70, H 9.15, N 8.47; found C 72.60, H 9.09, N 8.38.

(R)-3-(1-Methyl-2-methylenecyclohexyl)propanenitrile (**12**): Sodium hydride (75% in mineral oil, 1.8 g, 75 mmol) was placed in a nitrogen-flushed flask. Hexane (20 ml) was added and the dispersion was stirred for 2 min. The NaH was allowed to settle and the supernatant liquid was removed with a syringe. The washing operation was repeated and dry DMSO (75 ml) was then added to the reaction flask. (Methyl)triphenylphosphonium iodide (24 g, 60 mmol) was added in portions and stirring was continued until H_2 evolution had ceased. Oxo nitrile **10** (5.0 g, 30.3 mmol) in DMSO (5 ml) was then added dropwise and the resulting mixture was stirred at 20°C for 40 min. The reaction mixture was poured into ice-cooled 1 N aqueous HCl and extracted with ether. The combined organic phases were washed with brine, dried and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 20:1) and distillation afforded 4.5 g (91%) of nitrile **12**, colorless oil, b.p. 70°C/0.1 Torr. − $[\alpha]_D^{22} = +80$, period1 (EtOH, $c = 18$). − IR (neat): $\tilde{\nu} = 2238$ cm^{-1} (CN), 1640 (C=C). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.03 (s, 3 H, CH_3), 1.26−1.72 (m, 7 H), 1.97−2.23 (m, 5 H), 4.63 (t, $J = 1.2$ Hz, 1 H, *H*C=C), 4.81 (t, $J = 1.6$ Hz, 1 H, *H*C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.0 (CH_2, *C*H_2CN), 21.7 (CH_2), 24.8 (CH_3), 28.0 (CH_2), 32.7 (CH_2), 32.8 (CH_2), 38.9 (C, C-1), 40.1 (CH_2, C-6), 108.7 (CH_2, H_2C=C), 120.3 (C, H_2C=*C*), 152.1 (CN). − $C_{11}H_{17}N$ (163.3): calcd. C 80.92, H 10.50, N 8.57; found C 80.75, H 10.55, N 8.43.

3-[(1R-trans)- and (1R-cis)-2-Epoxymethylene-1-methylcyclohexyl)propanenitrile (**14**): In a nitrogen-flushed flask was placed sodium hydride (60% in mineral oil, 80 mg, 3 mmol). Hexane (20 ml) was added and the dispersion was stirred for 2 min. The NaH was allowed to settle and the supernatant liquid was removed with a syringe. The washing operation was repeated and dry DMSO (15 ml) was then added to the reaction flask. Trimethylsulfoxonium iodide (250 mg, 1.1 mmol) was added in portions and stirring was continued until H_2 evolution had ceased. Oxo nitrile **10** (150 mg, 0.9 mmol) in DMSO (2 ml) was then added dropwise, and the resulting mixture was stirred at 60°C for 2 h. The cooled mixture was poured into 1 N aqueous HCl, and extracted with ether. The combined organic phases were washed with brine, dried and concentrated under reduced pressure. Chromatographic separation on silica gel (hexane/ethyl acetate, 70:30) afforded 100 mg (62%) of epoxides **14** as a 2:1 mixture of diastereomers. Less polar isomer, $R_f = 0.30$, colorless crystals, m.p. 45−48°C. − $[\alpha]_D^{22} = +34$ (EtOH, $c = 0.2$). − IR (neat): $\tilde{\nu} = 2238$ cm^{-1} (CN), 1452, 1388. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.83 (s, 3 H, CH_3), 1.10−1.70 (m, 9 H), 1.93 (m, 1 H), 2.10−2.30 (m, 3 H), 2.73 (dd, $J = 4.4$, 1.5 Hz, 1 H, H_2CO). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 11.7 (CH_2, *C*H_2CN), 20.7 (CH_2), 20.8 (CH_3), 24.9 (CH_2), 30.9 (CH_2), 31.8 (CH_2), 35.6 (C, C-4), 37.3 (CH_2), 49.0 (CH_2, H_2C-O), 62.1 (C, *C*O), 120.2 (CN). − $C_{11}H_{17}NO$ (179.3): calcd. C 73.74, H 9.49, N 7.82; found C 73.84, H 9.59, N 7.86. − More polar isomer, $R_f = 0.23$, colorless oil. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.71 (s, 3 H, CH_3), 1.44−2.25 (m, 10 H), 2.25 (t, $J = 7.5$ Hz, 2 H, H_2CCN), 2.36 (d, $J = 4.2$ Hz, 1 H, H_2CO), 2.80 (d, $J = 4.2$ Hz, 1 H, H_2CO). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 11.9 (CH_2, *C*H_2CN), 19.0 (CH_3), 21.1 (CH_2), 24.0 (CH_2), 30.8 (CH_2), 32.7 (CH_2), 33.5 (C, C-4), 36.4 (CH_2, C-5), 50.7 (CH_2, H_2*C*O), 63.0 (C, *C*O), 120.2 (CN).

Reaction of [Chloro(trimethylsilyl)methyl]lithium (**15**) *with Oxo Nitrile* **10**: To a suspension of LiCl (0.52 g, 12.5 mmol) in THF (8 ml) was successively added chloro(trimethylsilyl)methane (0.80 g, 6.25 mmol) and TMEDA (1 ml). The reaction mixture was cooled to −78°C, and a solution of *s*BuLi (1.6 M in hexane, 4.6 ml, 7.3 mmol, the use of freshly supplied reagent is essential) was added dropwise. The reaction mixture was stirred for 1 h at −78°C. During this time the yellow color gradually faded. A solution of oxo nitrile **10** (0.66 g, 4 mmol) in THF (1 ml) was then added, and the resulting mixture was stirred at −60°C for an additional 3 h. An NH_4Cl aqueous solution was added and the mixture was extracted with ether. The combined organic phases were washed with brine, dried and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 80:20) afforded 335 mg of *3-{1-methyl-2-[(trimethylsilyl)epoxymethylene]cyclohexyl}propanenitrile* (**16**) (35%), $R_f = 0.50$, colorless oil. − IR (neat): $\tilde{\nu} = 2238$ cm^{-1} (CN), 1454, 1427, 1251. − ^{1}H NMR ($CDCl_3$, 200 MHz), the presence of 4 stereomers in an 11:8:5:1 ratio complicates the spectrum: δ = 0.095 and 0.18 [2 s, 9 H, (CH_3)$_3$Si], 0.72, 0.75, 0.83 and 0.87 (4 s, 3 H, CH_3C-4), 1.20−2.10 (m, 10 H), 2.10−2.40 (m, 3 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = −1.70 and −0.30 [3 CH_3, (CH_3)$_3$Si], 11.8, 11.9 and 12.1 (CH_2, *C*H_2CN), 19.0, 21.5 and 22.3 (CH_3, *C*H_3C-4), 21.0 and 21.4 (CH_2), 24.0−37.0 (4 CH_2 and C-4), 51.9, 53.0, 58.3 and 59.4 (CH, Si*C*HO), 65.1, 66.5, 68.0, and 68.5 (C, *C*O), 120.0, 120.2 and 120.4 (CN). − MS (70 eV); *m/z* (%): 251 (1) [M$^+$], 236 (10), 197 (65), 107 (12), 73 (100). − $C_{14}H_{25}NOSi$ (251.4): calcd. C 66.89, H 10.20, N 5.56; found C 66.89, H 10.10, N 5.51. − Further elution gave 215 mg of *3-{2-hydroxy-1-methyl-2-[hydroxy(trimethylsilyl)methyl]cyclohexyl}propanenitrile* (**18**) (20%) as a colorless oil, $R_f = 0.40$. − IR (neat): $\tilde{\nu} = 3546$ cm^{-1} (OH), 2945, 2242 (CN). − ^{1}H NMR ($CDCl_3$, 200 MHz), the presence of 4 stereomers in a 40:35:25:10 ratio complicates the spectrum: δ = 0.15, 0.17, 0.20 and 0.25 [4 s, 9 H, (CH_3)$_3$Si], 0.90, 1.05,

1.10 and 1.19 (4 s, 3 H, CH_3), 1.20−1.70 (m, 10 H), 1.70−2.50 (m, 4 H), 3.60, 3.65, 3.70 and 3.75 (4 s, 1 H, OC*H*Si). − Further elution afforded 230 mg of unchanged oxo nitrile **10** (35%), R_f = 0.30.

Conversion of Diol **18** *into Epoxysilane* **16** *by Mitsunobu Reaction:* To a mixture of diol **18** (65 mg, 0.24 mmol) and triphenyphosphane (130 mg, 0.5 mmol) in toluene (3 ml) was added diethyl azodicarboxylate (81 mg, 0.47 mmol). The mixture was stirred for 30 min at 20°C, and for an additional 2 h at 60°C. The reaction mixture was concentrated under reduced pressure. Chromatographic separation on silica gel (hexane/ethyl acetate, 80:/20) gave 46 mg (75%) of epoxysilane **16**.

3-[(1R-trans)- and (1R-cis)-2-(Dimethoxymethyl)-1-methylcyclohexyl]propanenitrile (**19**): To a solution of epoxysilane **16** (1.0 g, 3.98 mmol) in anhydrous methanol (50 ml) were added methyl orthoformate (10 ml, 91.2 mmol) and *p*-toluenesulfonic acid (50 mg). The mixture was refluxed for 2 h. Triethylamine (0.2 ml) was added and the solution was concentrated under reduced pressure to leave 750 mg (90%) of acetal **19** as a pale yellow oil, which was used in the next step without further purification. − IR (neat): $\tilde{\nu}$ = 2238 cm^{-1} (CN), 1451, 1078, 1050. − ^{1}H NMR ($CDCl_3$, 200 MHz), the spectrum reveals the presence of a 1.5:1 mixture of stereomers: δ = 0.91 and 0.95 (2 s, 3 H, CH_3), 1.00−2.50 (m, 13 H), 3.29, 3.32 and 3.34 (3 s, 6 H, CH_3O), 4.12 and 4.20 [2 d, *J* = 6.4 Hz and *J* = 3.5 Hz, 1 H, *H*C(OMe)$_2$]. − ^{13}C NMR ($CDCl_3$, 50 MHz), only the major isomer is described: δ = 11.7 (CH_2,CH_2CN), 21.4 (CH_2), 21.7 (CH_2), 27.1 (CH_3), 29.0 (CH_2), 34.4 (C, C-1), 36.9 (CH_2, C-6), 49.6 (CH, C-2), 54.4 (CH_3, OCH_3), 54.9 (CH_3, OCH_3), 106.1 (CH, O*C*HO), 120.8 (CN).

3-[(1R,2E)-2-(Methoxymethylene)-1-methylcyclohexyl]propanenitrile (**20**): Acetal **19** (320 mg, 1.42 mmol) and *p*-toluenesulfonic acid (20 mg) were placed in a cold-finger distillation apparatus. The mixture was heated at 70°C at 0.1 Torr for 15 min. Then the temperature was gradually raised to 110°C until all the liquid had distilled. 240 mg of enol ether **20** were obtained (88%), colorless oil, b.p. 100°C/0.1 Torr. − IR (neat): $\tilde{\nu}$ = 2238 cm^{-1} (CN), 1638 (C=C), 1451. − ^{1}H NMR ([D_6] benzene, 400 MHz): δ = 0.59 (s, 3 H, CH_3), 0.80 (ddd, *J* = 16.2, 9.8, 6.6 Hz, 1 H, H_2CCH$_2$CN), 1.00−1.30 (m, 6 H), 1.37 (dddd, *J* = 15.0, 14.6, 4.1, 1.5 Hz, 1 H, 3-H_{ax}), 1.47 (m, 2 H, H_2CCN), 1.69 (ddd, *J* = 16.2, 9.4, 6.6 Hz, 1 H, H_2CCH$_2$CN), 2.77 (dddd, *J* = 14.6, 3.8, 3.8, 1.1 Hz, 1 H, 3-H_{eq}), 3.14 (s, 3 H, OCH_3), 5.41 (d, *J* = 1.1 Hz, 1 H, *H*C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 12.1 (CH_2,CH_2CN), 21.3 (CH_2), 21.5 (CH_2), 24.5 (CH_3), 26.6 (CH_2), 32.4 (CH_2), 36.2 (C, C-1), 40.6 (CH_2, C-6), 59.3 (CH_3, OCH_3), 120.7 (CN), 129.7 (C, C-2), 141.0 (CH, CH_3OCH=C).

4-[(1R,2E)-2-(Methoxymethylene)-1-methylcyclohexyl]butan-2-one (**21**): To a solution of enol ether **20** (400 mg, 2 mmol) in ether (10 ml), cooled at −78°C, was added a solution of MeLi (2 M in ether, 2 ml, 4 mmol). The reaction mixture was warmed to 20°C and stirred for 12 h, after which the reaction mixture was cooled to 0°C, an aqueous solution of NH_4Cl (2 ml) was added, and the resulting mixture stirred for 15 min. The organic phase was separated and the aqueous layer extracted with ether. The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 80:20) gave 300 mg (70%) of ketone **21**, colorless oil. − IR (neat): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1638 (C=C), 1451. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.92 (s, 3 H, CH_3C-1), 1.15−1.75 (m, 8 H), 1.95−2.40 (m, 3 H), 2.13 (s, 3 H, CH_3C=O), 2.58 (dt, *J* = 13.4, 3.2 Hz, 1 H, 3-H_{ax}), 3.56 (s, 3 H, OCH_3), 5.68 (s, 1 H, *H*C=C). − ^{13}C NMR ([D_6] benzene, 50 MHz): δ = 21.9 (CH_2), 22.1 (CH_2), 25.2 (CH_3, *C*H_3C-1), 27.3 (CH_2), 29.4 (CH_3, *C*H_3C=O), 30.8 (CH_2), 36.0 (C, C-1), 36.7 (CH_2), 41.3 (CH_2, C-5), 58.9 (CH_3, OCH_3), 122.7 (C, C-2), 140.7 (CH, CH_3O*C*H=C), 206.5 (C=O).

Photo-Oxidation of Enol Ether **21**: 298 mg of enol ether **21** (1.42 mmol) was placed into a photochemical well. A solution of Methylene Blue (13 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (30 ml) was added and the reaction mixture was cooled to −78°C. Oxygen was bubbled into the solution while irradiated with a 400-W tungsten lamp set at 10 cm distance. After 1.5 h, Amberlyst-15 (300 mg) was added and the reaction mixture was warmed to room temperature. After stirring for 16 h, the reaction mixture was filtered through Celite, and the filtrate concentrated. The residue was purified by chromatography on silica gel (hexane then hexane/ethyl acetate, 90:10) to give a first fraction containing 20 mg (6%) of trioxane **22**. − ^{1}H NMR ([D_6] benzene, 400 MHz): δ = 0.91 (s, 3 H, CH_3C-5a), 0.90−1.8 (m, 12 H), 1.32 (s, 3 H, CH_3C-3), 3.20 (s, 3 H, OCH_3), 4.94 (s, 1 H, 10-H). − Further elution gave 102 mg (38%) of aldehyde **23**, colorless oil. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.05 (s, 3 H, CH_3C-1), 1.01−1.80 (m, 6 H), 2.10 (s, 3 H, CH_3C=O), 2.00−2.40 (m, 4 H), 6.70 (t, *J* = 5.5 Hz, 1 H, C=C*H*), 9.25 (s, 1 H, C*H*O).

3-[(1R,2E)-2-(Bromomethylene)-1-methylcyclohexyl]propanenitrile (**27**): Bromine (985 mg, 6.15 mmol) was added dropwise to an ice-cooled mixture of olefin **12** (1.0 g, 6.10 mmol) and pyridine (0.25 g, 3.00 mmol) in CH_2Cl_2 (15 ml). The red mixture was then treated with an aqueous solution of sodium thiosulfate. The organic layer was separated, and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried and concentrated under reduced pressure. The residue (1.65 g) was taken up into absolute ethanol (5 ml) and added dropwise to a solution of anhydrous KOH (11.5 g, 0.2 mol) in 95% ethanol (100 ml). A stream of nitrogen was bubbled through the solution for 10 min, and the reaction mixture was stirred at 25°C for 18 h. The reaction was quenched by addition of 3 N HCl (50 ml) and the mixture was concentrated in vacuo. The residue was taken up in ether, sequentially washed with water and brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/ethyl acetate, 80:20) gave 785 mg (52% overall yield) of bromoolefin **27** as a pale yellow oil. − $[\alpha]_D^{22}$ = +70.5 (EtOH, *c* = 1.1). − IR (neat): $\tilde{\nu}$ = 3108 cm^{-1} (C−H), 2238 (CN), 1613 (C=C). − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (s, 3 H, CH_3), 1.25−1.40 (m, 2 H, 4-H_{ax} and 6-H_{ax}), 1.45−1.66 (m, 4 H, NCCH$_2$C*H*, 5-H_{ax}, 5-H_{eq} and 6-H_{eq}), 1.77−1.85 (m, 1 H, 4-H_{eq}), 1.87 (dddd, *J* = 14.0, 12.4, 4.7, 1.7, 1 H, 3-H_{ax}), 1.95−2.10 (m, 1 H, NCC*H*), 2.12−2.26 (m, 2 H, NCCH$_2$C*H* and NCC*H*), 2.85 (dt, *J* = 14.0, 4.0 Hz, 1 H, 3-H_{eq}), 5.91 (s, 1 H, *H*BrC=). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.3 (CH_2, *C*H_2CN), 21.5 (CH_2, C-5), 24.8 (CH_3), 26.5 (CH_2, C-4), 28.1 (CH_2, C-3), 32.9 (CH_2, *C*H_2CH$_2$CN), 40.2 (CH_2, C-6), 41.2 (C, C-1), 101.4 (CH, HBr*C*=C), 120.0 (C, CN), 147.7 (C, BrHC=*C*). − $C_{11}H_{16}BrN$ (242.2): calcd. C 54.56, H 6.65, N 5.78; found C 54.82, H 6.87, N 5.87.

4-[(1R)-1-Methyl-2-methylenecyclohexyl]butan-2-one (**29**): To a solution of olefin **12** (2.0 g, 12.2 mmol) in ether (40 ml) cooled at −78°C, was added dropwise a solution of MeLi (1.6 M in ether, 25 ml, 40 mmol). The reaction mixture was warmed to 20°C and stirred for 10 min. Aqueous NH_4Cl (15 ml) was then added at 0°C, and the resulting mixture was stirred for 15 min. The organic phase was separated and the aqueous layer extracted with ether. The combined organic phases were dried and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 90:10) gave 1.85 g (85%) of ketone **29**, colorless oil. − $[\alpha]_D^{22}$ = +18.5 (EtOH, *c* = 11). − IR (neat): $\tilde{\nu}$ = 3091, 1720 cm^{-1} (C=O), 1637 (C=C), 1450, 1372. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.97 (s,

3 H, CH_3C-1), 1.28−1.80 (m, 8 H), 2.11 (s, 3 H, COCH_3), 1.80−2.33 (m, 4 H, H_2CCO, 3-H_{ax} and 3-H_{eq}), 4.57 (d, J = 1.6 Hz, 1 H, H_2C=C), 4.70 (s, 1 H, H_2C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.4 (CH_2), 25.0 (CH_3, H_3*C*C-1), 27.9 (CH_2), 29.4 (CH_3, H_3*C*C=O), 30.0 (CH_2), 32.6 (CH_2), 39.8 (C, C-1), 40.2 (CH_2, C-6), 41.4 (CH_2, C-5), 107.0 (CH_2, H_2*C*=C), 153.5 (C, H_2C=*C*), 208.2 (C=O). − $C_{12}H_{20}O$ (180.3): calcd. C 79.94, H 11.18; found C 79.62, H 10.90.

2-Hydroxy-2-methyl-4-[(1R)-1-methyl-2-methylenecyclohexyl]-butanenitrile (**30**): A solution of potassium cyanide (4.0 g, 60 mmol) in water (20 ml) was added to a solution of ketone **27** (900 mg, 5 mmol) in ethanol (50 ml). The reaction mixture was cooled to 0°C, and 12 M sulfuric acid (18 ml, 216 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h, after which water (50 ml) was added. The reaction mixture was extracted with CH_2Cl_2. The organic phases were dried and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/ethyl acetate, 90:10) to give 920 mg (89%) of cyanohydrin **30**, pale yellow oil. − IR (neat): $\tilde{\nu}$ = 3442 cm^{-1} (OH), 3092, 2233 (CN), 1638 (C=C), 1453, 1376. − ^{1}H NMR ($CDCl_3$, 200 MHz), presence of 2 stereomers in a 1:1 ratio complicates the spectrum: δ = 1.05 (s, 3 H, C-1-CH_3), 1.20−1.80 (m, 8 H), 1.60 [s, 3 H, CH_3C(OH)CN], 1.90−2.25 (m, 4 H), 2.35 (1 H, OH), 4.50 (s, 1 H, H_2C=C), 4.75 (s, 1 H, H_2C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 21.7 (CH_2), 25.2 (CH_3, *C*H_3C-1), 27.5 [CH_3, *C*H_3C(CN)(OH)], 28.2 (CH_2), 30.9 (CH_2), 32.8 (CH_2), 36.2 (CH_2), 38.6 and 38.8 (C, C-1), 40.5 (CH_2, C-6), 68.4 (C, HO*C*CN), 107.4 (CH_2, H_2*C*=C), 122.0 (C, CN), 153.7 (C, H_2C=*C*).

(1R,2E)-2-(Bromomethylene)-1-methyl-1-{3-[(5,5-dimethyl-1,3-dioxan-2-yl)]}butylcyclohexane (**33**): To an ice-cooled solution of cyanohydrin **30** (4.0 g, 19.2 mmol) in CH_2Cl_2 (30 ml), containing a drop of pyridine, was added dropwise a solution of bromine (3.2 g, 20 mmol) in CH_2Cl_2 (20 ml). After stirring for 5 min the reaction was quenched with an aqueous solution of sodium thiosulfate. The reaction mixture was extracted with CH_2Cl_2. The organic phase was dried and concentrated to leave a yellow oil which was taken up in CH_2Cl_2 (50 ml). 2 N NaOH (50 ml) was added, and the two-phase mixture was stirred at 20°C for 15 min. The reaction mixture was extracted with CH_2Cl_2 and the combined organic phases were washed with brine and dried with $MgSO_4$. Chromatographic separation on silica gel (hexane/ethyl acetate, 9:1) afforded 2.0 g of dibromoketone **32**, yellow oil. − IR (neat): $\tilde{\nu}$ = 2942 cm^{-1}, 1718 (C=O), 1450. − To a solution of this material in benzene (40 ml) were added 2,2-dimethyl-1,3-propanediol (2.00 g, 11.7 mmol) and *p*-toluenesulfonic acid (0.02 g, 0.1 mmol). The reaction mixture was refluxed for 2 h with azeotropic removal of water. The mixture was cooled to 20°C and diluted with ether. The organic layer was washed with aqueous sodium bicarbonate, dried and concentrated in vacuo to give 1.9 g of crude ketal which was used directly in the next step. Anhydrous KOH (3.8 g, 60 mmol) was dissolved in 95% ethanol (15 ml), after which a solution of the above dibromoketal in ethanol (2 ml) was added dropwise. A stream of nitrogen was passed through the solution for 10 min, and the reaction mixture was stirred at 25°C for 1 h. The mixture was concentrated in vacuo. The residue was taken up in water and extracted with ether. The organic phases were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/ethyl acetate/Et_3N, 90:10:0.5) gave 0.76 g (11% overall yield from **30**) of bromo olefin **33** as a pale yellow oil. − IR (neat): $\tilde{\nu}$ = 3109 cm^{-1}, 2930, 1613 (C=C), 1471, 1373. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.89 (s, 3 H, CH_3C-1), 1.00 [s, 3 H, (CH_3)$_2$C], 1.03 [s, 3 H, (CH_3)$_2$C], 1.20−1.95 (m, 11 H), 1.30 [s, 3 H, CH_3C(OCH_2)$_2$], 2.76 (dt, J = 10.2, 3.6 Hz, 1 H, 6-H_{ax}), 3.40−3.50 [m, 4 H, CH_3C(OCH_2)$_2$], 5.88 (s, 1 H, *H*C=C). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 20.3 [CH_3, (*C*H_3)$_2$C], 21.5 (CH_2), 22.4 [CH_3, (*C*H_3)$_2$C], 22.7 [CH_3, *C*H_3C(OCH_2)$_2$], 25.2 (CH_3, *C*H_3C-1), 26.7 (CH_2), 27.9 (CH_2), 29.7 [C, (CH_3)$_2$*C*], 30.3 (CH_2), 32.0 (CH_2), 40.5 (CH_2, C-3), 41.0 (C, C-2), 70.1 [2 CH_2, CH_3C(O*C*H_2)$_2$], 98.7 (C, O*C*O), 99.8 (CH, BrH*C*=C), 149.5 (C, BrHC=*C*).

(1R,2E)-1-{3-[(5,5-Dimethyl-1,3-dioxan-2-yl)]}butyl-1-methyl-2-[(trimethylsilyl)methylene]cyclohexane (**34**): To a solution of bromoketal **33** (180 mg, 0.5 mmol) in THF (10 ml) cooled to −78°C was added dropwise a solution of *t*BuLi (1.5 M in pentane) (0.86 ml, 1.3 mmol) and the reaction mixture was stirred for 15 min. Chlorotrimethylsilane (1 ml, 7.8 mmol) was the added and the mixture was stirred for a further 5-min period. The reaction was quenched with aqueous sodium bicarbonate, and warmed to room temperature. The mixture was extracted with ether and the combined organic phases were dried and concentrated under reduced pressure. Chromatographic purification on silica gel (pentane/ether/Et_3N, 92:8:0.5) provided 150 mg (85%) of silane **34** as a colorless oil. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.05 [s, 9 H, (CH_3)$_3$Si], 0.90−0.95 [3 s, 9 H, CH_3C-1 and (CH_3)$_2$C], 0.90−2.15 (m, 11 H), 1.32 [s, 3 H, CH_3C(OCH_2)$_2$], 2.35 (dt, J = 14.0, 3.1 Hz, 1 H, 6-H_{ax}), 3.35−3.55 [m, 4 H, CH_3C(OCH_2)$_2$], 5.15 (s, 1 H, Si*H*C=C).

3-{2-Hydroxy-1-methyl-2-[bromo(trimethylsilyl)methyl]-cyclohexyl}propanenitrile (**35**): A 48% aqueous solution of HBr (5.2 ml, 30 mmol) was added to an ice-cooled solution of epoxysilane **16** (520 mg, 2 mmol) in CH_2Cl_2 (6 ml). After being stirred for 5 min, the reaction mixture was poured into aqueous sodium bicarbonate (20 ml), and extracted with CH_2Cl_2. The organic phases were dried with $MgSO_4$ and concentrated under reduced pressure to give 525 mg of crude bromohydrin **35** (76%) which was used in the next step without further purification. − IR (neat): $\tilde{\nu}$ = 3532 cm^{-1} (OH), 2869, 2239 (CN), 1470, 1452. − ^{1}H NMR ($CDCl_3$, 200 MHz), the presence of 4 stereomers complicates the spectrum: δ = 0.14, 0.16, 0.17, and 0.19 [4 s, 9 H, (CH_3)$_3$Si], 0.84, 0.95, 1.00, and 1.06 (4 s, 3 H, CH_3C-1), 1.13−1.65 (m, 11 H), 1.80−2.28 (m, 2 H, H_2CCN), 3.57, 3.63, 3.65, and 3.71 (4 s, 1 H, SiC*H*Br).

3-{(1R,2E)- and (1R,2Z)-1-Methyl-2-[(trimethylsilyl)methylene]-cyclohexyl}propanenitrile (**36**): Bromohydrin **35** (200 mg, 0.6 mmol) and an aqueous solution of NH_4Cl (1 ml) were successively added to a slurry of 750 mg (11.4 mmol) of zinc powder in absolute ethanol (6 ml). After stirring for 10 min, the reaction mixture was filtered through alumina. The filtrate was concentrated in vacuo, and the residue was taken up in water. The mixture was extracted with ether, the organic phase was dried and concentrated under reduced pressure. Chromatographic separation on silica gel (hexane/ethyl acetate, 9:1) gave 110 mg (92%) of vinylsilanes **36**, colorless oil. − IR (neat): $\tilde{\nu}$ = 2943 cm^{-1}, 2238 (CN), 1604 (C=C), 1453. − ^{1}H NMR ($CDCl_3$, 200 MHz), the presence of 2 stereomers in a 55:45 ratio complicates the spectrum; major isomer: δ = 0.08 [s, 9 H, (CH_3)$_3$Si], 0.98 (s, 3 H, CH_3C-1), 1.20−1.80 (m, 9 H), 1.90−2.25 (m, 2 H, H_2CCN), 2.39 (dt, J = 13.3, 4.5 Hz, 1 H, 3-H_{ax}), 5.13 (s, 1 H, Si*H*C=); minor isomer: δ = 0.13 [s, 9 H, (CH_3)$_3$Si], 1.12 (s, 3 H, CH_3C-1), 1.20−1.80 (m, 10 H), 1.90−2.40 (m, 2 H, H_2CCN), 5.16 (s, 1 H, Si*H*C=). − ^{13}C NMR ($CDCl_3$, 50 MHz), only the major isomer is described: δ = 0.2 [3 CH_3, (*C*H_3)$_3$Si], 12.2 (CH_2, H_2*C*CN), 21.6 (CH_3, *C*H_3C-1), 25.3 (CH_2), 28.1 (CH_2), 31.4 (CH_2), 32.9 (CH_2), 39.9 (C, C-1), 40.6 (CH_2), 120.5 (C, CN), 121.9 (CH, SiH*C*=C), 161.2 (C, SiHC=*C*). − $C_{14}H_{25}NSi$ (235.4): calcd. C 71.42, H 10.69, N 5.94; found C 71.35, H 10.67, N 5.79.

4-{(1R,2E)- and (1R,2Z)-1-Methyl-2-[(trimethylsilyl)-methylene]-1-cyclohexyl}-2-butanone (**37**): To a solution of vinylsil-

ane **36** (400 mg, 1.7 mmol) in ether (8 ml), cooled at −78°C, was added a solution of MeLi (2 M in ether, 4 ml, 6.4 mmol). The reaction mixture was warmed to 20°C and stirred for 15 min. The mixture was then cooled to 0°C, an aqueous solution of NH_4Cl was added, and the resulting mixture stirred for 15 min. The organic phase was separated and the aqueous layer extracted with ether. The combined organic phases were dried and concentrated in vacuo. Chromatography on silica gel (hexane/ethyl acetate, 95:5) gave 280 mg (65%) of ketone **37**, colorless oil. − IR (neat): $\tilde{\nu}$ = 2933, 1722 cm^{-1} (C=O), 1605 (C=C). − ^1H NMR ($CDCl_3$, 200 MHz), the presence of 2 stereomers in a 1.5:1 ratio complicates the spectrum; major isomer: δ = 0.01 [s, 9 H, $(CH_3)_3Si$], 0.87 (s, 3 H, CH_3C-1), 1.17−1.70 (m, 8 H), 1.90−2.30 (m, 4 H), 2.04 (s, 3 H, CH_3CO), 5.05 (s, 1 H, SiHC=); minor isomer: δ = 0.07 [s, 9 H, $(CH_3)_3Si$], 1.02 (s, 3 H, CH_3C-1), 1.17−1.70 (m, 8 H), 1.90−2.30 (m, 4 H), 2.04 (s, 3 H, CH_3CO), 5.25 (s, 1 H, SiHC=). − ^{13}C NMR ($CDCl_3$, 50 MHz), only the major isomer is described: δ = 0.22 [3 CH_3, $(CH_3)_3Si$], 21.6 (CH_2), 25.6 (CH_3, CH_3C-1), 28.3 (CH_2), 30.5 (CH_3, CH_3CO), 31.3 (2 CH_2), 38.6 (CH_2), 40.0 (C, C-1), 40.8 (CH_2, C-6), 119.9 (CH, SiHC=C), 163.2 (C, SiHC=C), 209.0 (C=O). − $C_{15}H_{28}NOSi$ (252.5): calcd. C 71.36, H 11.18; found C 71.14, H 11.24.

[5aR-(3β,5aα,9aβ)]- and [5aR-(3α,5aα,9aβ)]-4,5,5a,6,7,8,9,9a-Octahydro-3-methoxy-3,5a-dimethyl-3aH-1,2-benzodioxepin-9a-carboxaldehyde (**38**): A solution of vinylsilane **37** (270 mg, 1.07 mmol) in CH_2Cl_2 (15 ml) and anhydrous MeOH (5 ml) was cooled at −78°C and treated with a stream of ozone until the characteristic blue color appeared. Oxygen was bubbled through the solution until the color faded, and boron trifluoride etherate complex (115 mg, 0.8 mmol) was added. The temperature was raised to 20°C, and the mixture was stirred for 2 h. A solution of aqueous sodium bicarbonate was added, the mixture was extracted with ether, the etheral layer was dried and concentrated to leave 201 mg of crude peroxy-aldehyde **38** (78%) which was used directly in the next step, pale yellow oil. − IR (neat): $\tilde{\nu}$ = 2945 cm^{-1} , 2717 (H−CO), 1707 (C=O), 1453. − ^1H NMR ($CDCl_3$, 200 MHz), the presence of 2 stereomers in a 3:1 ratio complicates the spectrum: δ = 0.98 and 1.11 (s, 3 H, CH_3C-5a), 1.33−2.30 (m, 12 H), 1.41 and 1.42 (s, 3 H, CH_3C-3), 3.23 and 3.44 (s, 3 H, OCH_3), 9.37 and 9.89 (s, 1 H, -CHO).

[3R-(3α,5aβ,9aα,10R)]-3,4,5,5a,6,7,8,9-Octahydro-10-methoxy-3,5a-dimethyl-9aH-3,9a-(epoxymethano)-1,2-benzodioxepin* (**39**): A solution of crude peroxyaldehyde **38** (200 mg, 0.82 mmol) in anhydrous methanol (4 ml) was cooled at −78°C. Boron trifluoride−diethyl ether (460 mg, 3.2 mmol) and methyl orthoformate (200 mg, 1.9 mmol) were added. The reaction mixture was stirred for 10 min and warmed up to 20°C. After being stirred at 20°C for 1 h, aqueous sodium bicarbonate was added. The mixture was extracted with CH_2Cl_2, the organic phase was dried and concentrated in vacuo. Chromatographic purification on silica gel (hexane/ethyl acetate, 20:1) afforded 90.5 mg (35% overall yield from **37**) of trioxane **39**, colorless needles, m.p. 42−48°C (hexane). − $[\alpha]_D$ = +16.2 (EtOH, *c* = 1.5). − IR (KBr): $\tilde{\nu}$ = 2936 cm^{-1}, 1470, 1376, 1205, 1103. − ^1H NMR ([D_6] benzene, 400 MHz): δ = 0.99 (s, 3 H, CH_3C-5a), 1.05−1.23 (m, 4 H, 6-H_{ax}, 3-H, 5-H_{ax}), 1.29 (s, 3 H, CH_3C-3), 1.20−1.35 (m, 2 H, 8-H), 1.35−1.41 (m, 2 H, 9-H_{ax}, 6-H_{eq}), 1.60−1.68 (m, 2 H, 4-H_{eq}, 5-H_{eq}), 2.26 (ddd, *J* = 17.6, 14.2, 2.6 Hz, 1 H, 4-H_{ax}), 2.38−2.46 (m, 1 H, 9-H_{eq}), 3.36 (s, 3 H, OCH_3), 4.95 (s, 1 H, 10-H). − ^{13}C NMR ([D_6] benzene, 50 MHz): δ = 20.9 (CH_3, CH_3C-3), 21.2 (CH_2, C-7), 23.2 (CH_2, C-8), 26.4 (CH_3, CH_3C-5a), 29.5 (CH_2, C-9), 35.5 (CH_2, C-5), 36.4 (CH_2, C-4), 39.6 (CH_2, C-6), 40.7 (C, C-5a), 54.9 (CH_3, CH_3C-10), 83.8 (C, C-9a), 95.8 (CH, C-10), 102.6 (C, C-3). − MS (CI, NH_3); *m/z* (%): 260 (19) [M^+ + NH_4], 243 (2), 228 (11), 211 (20), 210 (67), 183 (19), 165 (17), 147 (27), 139 (100).

[3R-(3α,5aβ,9aα,10R)]-3,4,5,5a,6,7,8,9-Octahydro-3,5a-dimethyl-9aH-3,9a-(epoxymethano)-1,2-benzodioxepin-10-yl Acetate* (**40**): To an ice-cooled solution of peroxyaldehyde **38** (100 mg, 0.41 mmol) in CH_2Cl_2 (2 ml) were added acetic anhydride (2.21 g, 21.7 mmol) and boron trifluoride−diethyl etherate (115 mg, 0.8 mmol). The reaction mixture was warmed to 20°C and stirred for 18 h, and sodium bicarbonate (100 mg) was then added. The mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 90:10) to give 46 mg (41%) of trioxane **40**, colorless crystals, m.p. 88−90°C (hexane). − $[\alpha]_D$ = +26.6 (EtOH, *c* = 1.2). − IR (KBr): $\tilde{\nu}$ = 2941 cm^{-1}, 1748 (CO), 1454, 1379. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.07 (s, 3 H, CH_3C-5a), 1.21−1.32 (m, 3 H) 1.38 (s, 3 H, CH_3C-3), 1.45−1.99 (m, 8 H), 2.18 (s, 3 H, CH_3OCO), 2.44 (td, *J* = 14.7, 1.9 Hz, 1 H, 9-H_{ax}), 6.55 (s, 1 H, 10H). − $C_{14}H_{22}O_5$ (270.3): calcd. C 62.20, H 8.20; found C 62.02, H 8.27.

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[23] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication with deposition number CCDC-101058. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336033; E-mail: deposit@ccdc.cam.ac.uk].
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