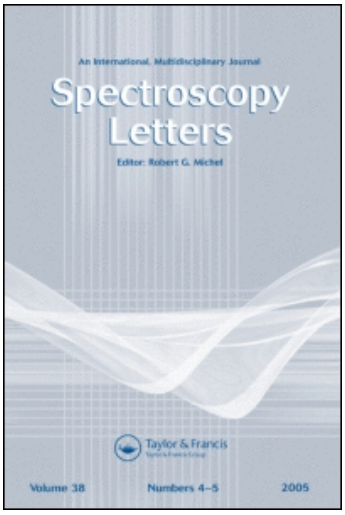


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Antimalarial 1,2,4-Trioxanes Related to Artemisinin: Rules for Assignment of Relative Stereochemistry in Diversely Substituted Analogs

Chang Ho Oh[a]; Dasong Wang[a]; Jared N. Cumming[a]; Gary H. Posner[a]
[a] Department of Chemistry, Zanvyl Krieger School of Arts and Sciences, The Johns Hopkins University, Baltimore, MD

To cite this Article Oh, Chang Ho , Wang, Dasong , Cumming, Jared N. and Posner, Gary H.(1997) 'Antimalarial 1,2,4-Trioxanes Related to Artemisinin: Rules for Assignment of Relative Stereochemistry in Diversely Substituted Analogs', Spectroscopy Letters, 30: 2, 241 — 255
To link to this Article: DOI: 10.1080/00387019708006985
URL: http://dx.doi.org/10.1080/00387019708006985

SPECTROSCOPY LETTERS, 30(2), 241-255 (1997)

ANTIMALARIAL 1,2,4-TRIOXANES RELATED TO ARTEMISININ: RULES FOR ASSIGNMENT OF RELATIVE STEREOCHEMISTRY IN DIVERSELY SUBSTITUTED ANALOGS

Chang Ho Oh,† Dasong Wang,‡ Jared N. Cumming,§ and Gary H. Posner¶

Department of Chemistry, Zanvyl Krieger School of Arts and Sciences,
The Johns Hopkins University, Baltimore, MD 21218

Abstract: A series of rules has been developed, using mainly 1D and 2D NMR spectroscopy, for identification of relative stereochemistry in a variety of substituted antimalarial 1,2,4-trioxanes.

INTRODUCTION

The resurgence of malaria as a worldwide health threat due to the causative parasites' rapidly increasing resistance to traditional alkaloidal drugs has prompted extensive investigation into alternative chemotherapies. An extremely promising prospect from these searches is the sesquiterpene trioxane endoperoxide artemisinin (**1**).[1,2] This natural product and derivatives (**2**–**5**) of the corresponding lactol are used extensively, mostly in Asia, to treat both uncomplicated and severe malaria infections caused by drug-resistant *Plasmodium falciparum* parasites.[3] Syntheses of artemisinin[4] and related analogs[5,6] are complex, however, and large quantities of the natural product are directly

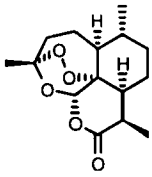
†On leave from: Department of Chemistry, Inje University, Kimhae 621-749, Korea.

‡Current address: Ariad Pharmaceuticals, Inc., 26 Landsdowne St., Cambridge, MA 02139.

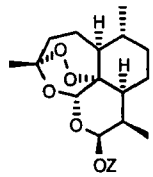
§Recipient of a Graduate Fellowship from the Organic Chemistry Division of the American Chemical Society (1995–1996) sponsored by Abbott Laboratories.

¶Author to whom correspondence should be addressed.

isolated from the plant, while many derivatives are made semi-synthetically.[7-12] Given that the central endoperoxide linkage is believed to be the key to the antimalarial potency of this class of drugs,[13] numerous researchers have designed structurally simplified analogs of artemisinin whose syntheses are much shorter than that of the natural product.[14-18] Some of these analogs are equally or more potent than the natural product and its derivatives.



artemisinin (1)



Z = Me, artemether (2)

Z = Et, arteether (3)

Z = $C(O)CH_2CH_2COONa$, sodium artesunate (4)

Z = CH_2–C$_6$H$_4$–COONa, sodium artelinate (5)

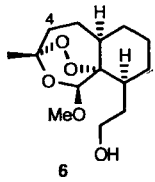
It is important to note that the biosynthesis of artemisinin involves strict enzymatic control over both absolute and relative stereochemistry such that a single enantiomer is produced.[19-21] Although researchers have shown that both enantiomers of a particular analog are equipotent *in vitro*,[22] different diastereomers may have vastly different antimalarial efficacies.[23,24] Identification of relative stereochemistry for a particular compound, therefore, is very important. Herein we report methods, mainly NMR spectroscopy, for stereochemical elucidation of diastereomers within families of simplified 1,2,4-trioxanes which have distinguished themselves (1) as potent *in vitro* and *in vivo* antimalarials and (2) as useful tools to probe the mechanism of action of artemisinin-like antimalarials. These spectroscopic techniques have been applied successfully to establish the relative stereochemistry of several newly synthesized trioxanes that are antimalarially active.

RESULTS AND DISCUSSION

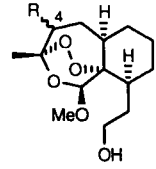
Configuration of Intermediates en route to Trioxane Systems

C_4-Unsubstituted trioxane alcohol **6** and C_4-alkylated trioxane alcohols **7–9** are available in six to eight synthetic operations from commercial cyclohexanone. Several

derivatives of trioxane alcohol **6** are potent *in vitro* antimalarials[18,25] and two such analogs—a benzyl ether and a diphenyl phosphate ester—are comparably active to arteether (**3**) in mice and monkeys.[26] C_4-Alkylated trioxane alcohols **7–9** have demonstrated a dependence of *in vitro* antimalarial efficacy on the nature of a carbon-centered radical formed during their iron(II)-induced degradation.[23]



6

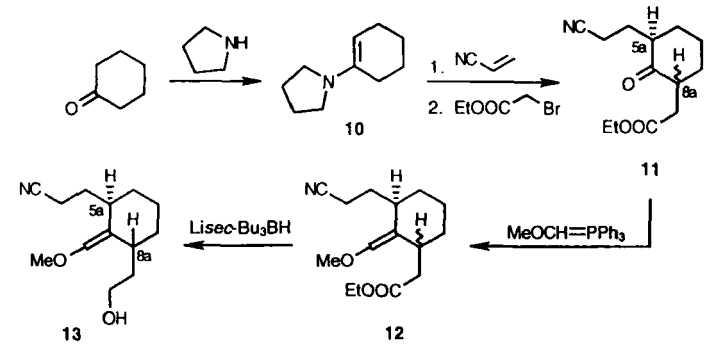


7: R = Me
8: R = $PhCH_2$
9: R = Me_3SiCH_2

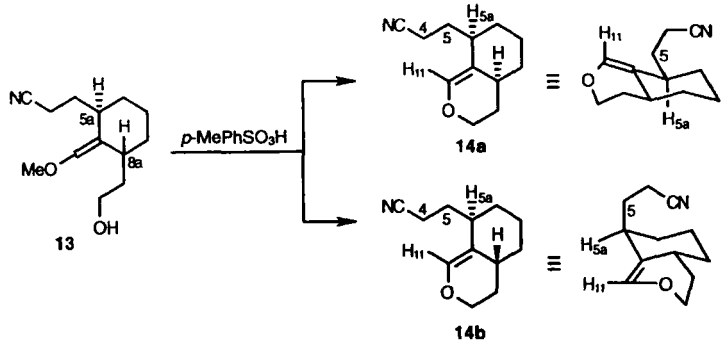
Syntheses of these trioxane alcohols **6–9** (Scheme 1)[18] began with bisalkylation of pyrrolidino-enamine **10** to produce substituted cyclohexanone **11** as an inseparable mixture of two diastereomers—1,3-*cis* and 1,3-*trans* with respect to the side arm attachments at C_{5a} and C_{8a}. Subsequent Wittig olefination of this mixture did not produce an additional pair of diastereomers in the product enol ethers **12**. Distinct vinyl proton resonances at approximately 5.9 δ in the ^1H NMR spectrum of this material, however, showed that the two diastereomers, differing only in their side arm configurations, had been formed in a 4 : 1 ratio. Lithium trialkylborohydride reduction of the ester portion of enol ethers **12** did not affect the side chain configurations and allowed separation of diastereomers of the resulting alcohol to afford the major diastereomer **13**.

Several chemical and ^1H NMR experiments were conducted to determine the relative stereochemistry of the two side arms and of the enol ether of alcohol **13**. The configuration of the side arms at C_{5a} and C_{8a} was determined using COSY and 1D NOE experiments on a more structurally constrained derivative. Thus, cyclization of alcohol **13** by treatment with *p*-toluenesulfonic acid in refluxing toluene afforded a cyclic enol ether[27] without changing the stereochemistry of attachment of the ring substituents (Scheme 2). This bicycle could be either 1,3-*cis* enol ether **14a** or 1,3-*trans* enol ether **14b**.

The spatial relationship of vinyl proton H_{11} with ring junction proton H_{5a} and side arm protons $H_{5,5'}$ are very different in enol ethers **14**, with the 1,3-*cis* configuration **14a**



Scheme 1.

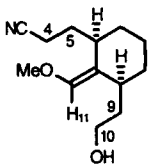


Scheme 2.

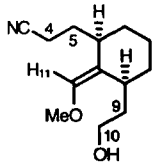
having H_{11} closer to $H_{5,5'}$ than to H_{5a} and the reverse relationship with the 1,3-*trans* configuration **14b**. A COSY experiment allowed identification of the resonances for H_{5a} and $H_{5,5'}$ by correlation beginning with the α-nitrile protons $H_{4,4'}$. Given that such protons resonate at 2–3 δ, a multiplet at 2.43 δ, the only resonance in the appropriate region, was identified on first principles as corresponding to $H_{4,4'}$. These protons are coupled to $H_{5,5'}$, which the COSY spectrum indicated resonate at 1.94 δ and 1.57 δ, which are in turn coupled to H_{5a}, which were found on the contour plot to resonate at 1.82 δ. The NOE difference spectrum with presaturation of H_{11} at 6.11 δ showed a significant

NOE between H_{11} and $H_{5,5'}$ but virtually none between H_{11} and H_{5a}. This implied spatial relationship—H_{11} being closer to $H_{5,5'}$ than H_{5a}—is consistent with 1,3-*cis* alcohol **14a**, indicating that the parent alcohol **13** must also have a 1,3-*cis* relationship.

The stereochemistry of the enol ether portion of alcohol **13** was then determined with similar COSY and 1D NOE experiments directly on that compound, which had to be either (*E*)-enol ether **15a** or (*Z*)-enol ether **15b**. Again, the spatial relationship of the vinyl proton H_{11} with protons $H_{4,4'}$ and $H_{5,5'}$ and with protons $H_{9,9'}$ and $H_{10,10'}$ is distinct in the two possible configurations. (*E*)-Enol ether **15a** has H_{11} closer to $H_{9,9'}$ and $H_{10,10'}$ whereas (*Z*)-enol ether **15b** has H_{11} to $H_{4,4'}$ and $H_{5,5'}$.



15a

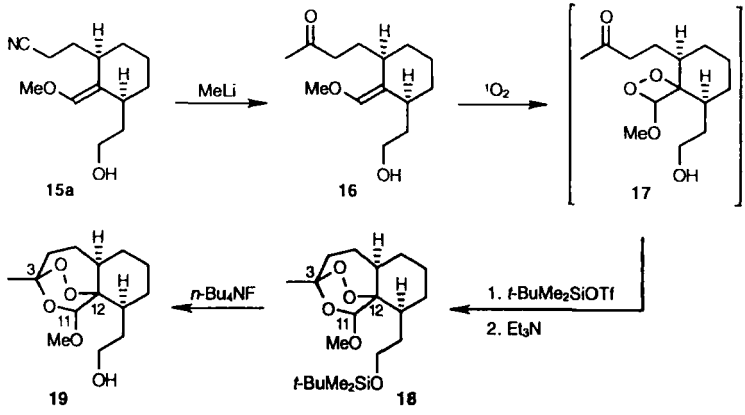


15b

Another COSY experiment permitted identification of resonances of protons $H_{9,9'}$ by correlation beginning with the α-hydroxy protons $H_{10,10'}$, generally found at 3–4 δ. A multiplet at 3.64 δ was assigned to these protons since this signal was expected to be complex. $H_{10,10'}$ are coupled to $H_{9,9'}$, which the COSY spectrum indicated resonate at 1.66 δ. Similarly, identification of the resonances corresponding to protons $H_{5,5'}$ began with the α-nitrile protons $H_{4,4'}$, which typically resonate at 2–3 δ. The triplet at 2.33 δ was identified as corresponding to $H_{4,4'}$. The contour plot showed that $H_{5,5'}$, coupled to $H_{4,4'}$, resonate at 1.88 δ and 1.76 δ. The NOE difference spectrum with presaturation of H_{11} at 5.90 δ indicated a greater NOE between H_{11} and $H_{9,9'}$ than between H_{11} and $H_{5,5'}$. This implied spatial relationship—H_{11} being closer to $H_{9,9'}$ than $H_{5,5'}$—is consistent with (*E*)-enol ether **15a**, which shows the completely assigned structure of the common intermediate.

Stereochemistry of Centers Introduced During Trioxane Formation

The syntheses of the C_4-unsubstituted trioxane alcohol **6** and C_4-alkylated trioxane alcohol **7–9** diverge from alcohol **15a**. Toward the former (Scheme 3),[18] addition of

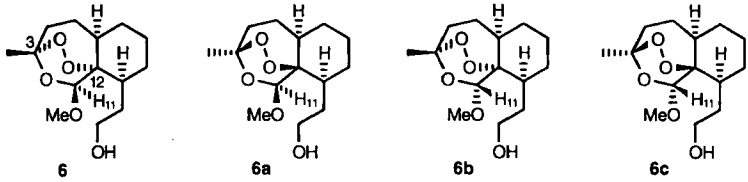


Scheme 3.

methyllithium to the nitrile moiety of the common intermediate produced ketone **16** without affecting the stereochemistry at any centers. Formation of dioxetane **17** followed by Lewis acid (trialkylsilyl triflate)-induced rearrangement to trioxane silyl ether **18** resulted in the formation of three new stereogenic centers at C_3, C_{11}, and C_{12}. This trioxane **18** was immediately desilylated to give the target trioxane alcohol as a single diastereomer **19** whose relative stereochemistry at C_3, C_{11}, and C_{12} remained to be determined.

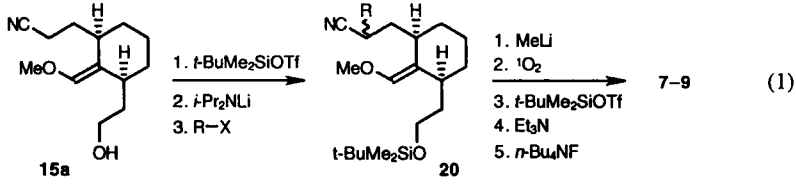
Topological constraints ensure that the carbon–oxygen bonds at C_3 and C_{12} have a *syn* relationship. The relative stereochemistry of this endoperoxide bridge to the new stereocenter at the acetal C_{11} as well as to the pre-existing centers at C_{5a} and C_{8a} was predicted by examination of ^1H NMR coupling patterns and then unambiguously determined by X-ray crystallography. The acetal proton H_{11} of the target trioxane alcohol appeared at 5.19 δ as a doublet (J = 1.6 Hz). With no *geminal* or *vicinal* proton, this splitting must arise through long-range coupling[28]. In fact, consideration of several relative configurations reveals that only a $C_{11\alpha}$-oriented proton would be able to W-couple[29] with H_{5a}, implying that the relative configuration of the desired trioxane alcohol

must be that of **6** or **6a**. X-ray crystallographic analysis of the trioxane alcohol revealed the relative relationship of C_{11} to C_3 and C_{12} to be that of trioxane alcohol **6**.



Stereochemistry at C_4 in C_4-Alkylated Trioxanes

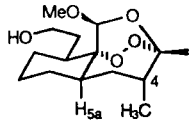
C_4-alkylated trioxane alcohols **7–9** have an additional stereocenter introduced by substitution on the seven-membered ring. Diverging from the synthesis of C_4-unsubstituted trioxane alcohol **6**, silylation of intermediate alcohol **15a** followed by deprotonation α to the nitrile and treatment with the appropriate alkyl halide produced alkylated nitriles **20** as roughly 1 : 1 mixtures of diastereomers (Eq. 1).[23,24] These mixtures were carried forward synthetically as with the synthesis of C_4-unsubstituted system—addition of methyllithium to the nitrile, dioxetane formation by photooxygenation of the enol ether, Lewis acid-induced rearrangement to the trioxane skeleton, finishing with desilylation to produce trioxane alcohols **7–9** still as 1 : 1 mixtures of diastereomers.



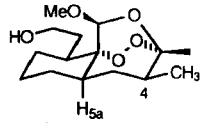
(1)

Since the transformations leading to trioxane alcohols **7–9** mirror those leading to C_4-unsubstituted trioxane alcohol **6**, the configurations at all analogous stereocenters—C_3, C_{11}, and C_{12}—were presumed to be identical. For each C_4-substituted trioxane alcohol, the two diastereomers at C_4 were separated by HPLC. It was originally hoped that an NOE experiment looking at the spatial relationship of the C_4-methyl group with H_{5a} would help in the stereochemistry determination. Looking at the two possible configurations **7a** and **7b**, it is clear that a $C_{4\alpha}$-methyl group **can** be spatially close to H_{5a} whereas a $C_{4\beta}$-methyl

cannot. Unfortunately, no significant NOE was seen in either diastereomer, possibly due to the conformational freedom of the seven-membered ring.

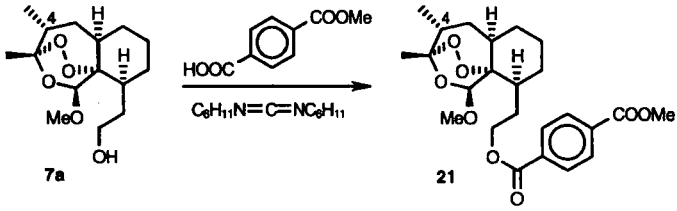


7a



7b

The assignment of stereochemistry at this center was finally made on the C_4-methyl trioxane alcohols **7** by X-ray crystallography and then made with the other two pairs of alcohols **8** and **9** by analogy using primarily relative ^1H NMR chemical shifts of the acetal protons, with secondary consideration of relative chromatographic polarities. One diastereomer of C_4-methyl trioxane alcohols **7** was derivatized as its monomethyl terephthalate ester (Eq. 2)[27] and X-ray crystallography revealed this system to be the $C_{4\alpha}$-methyl trioxane derivative **21**, implying the starting alcohol had been $C_{4\alpha}$-methyl trioxane alcohol **7a**.



(2)

In its ^1H NMR spectrum, the acetal proton H_{11} of this parent alcohol **7a** was further upfield than that of the $C_{4\beta}$-methyl trioxane alcohol (Table 1). In addition, it was the less polar diastereomer of C_4-methyl trioxane alcohols **7**. Using the unambiguously assigned stereochemistry of the C_4-methyl trioxane alcohols, separated pairs of diastereomers of C_4-benzyl **8** and C_4-(trimethylsilyl)methyl **9** trioxane alcohols were assigned by analogy using primarily the relative shifts of their acetal protons and looking to their relative polarities for further confirmation.

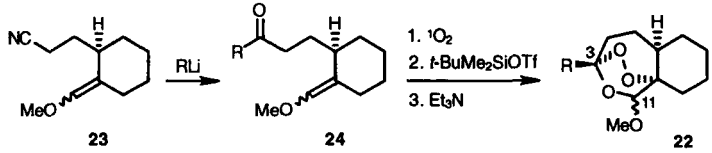
Acetal Configuration in Simplified 1,2,4-Trioxanes

Trioxanes **22**, with varied substitution at C_3, but lacking a hydroxyethyl moiety at C_{8a}, have also been valuable both as active antimalarials[14] and as mechanistic probes.[23,30]

Table 1. ^1H NMR Spectral Data and Relative Polarity Information Used in Assignment of C_4 Stereochemistry of C_4-Substituted Trioxane Alcohols **7–9**.

trioxane	R^4	H_{11}, δ	polarity	assignment
7a	Me	5.17	less	$C_{4\alpha}$ (X-ray)
7b	Me	5.21	more	$C_{4\beta}$
8a	$PhCH_2$	5.20	less	$C_{4\alpha}$
8b	$PhCH_2$	5.24	more	$C_{4\beta}$
9a	Me_3SiCH_2	5.16	less	$C_{4\alpha}$
9b	Me_3SiCH_2	5.19	more	$C_{4\beta}$

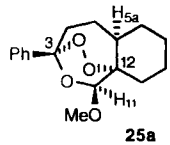
These compounds share as a common precursor known enol ethers **23**,[17] diastereomers which are formed by Wittig olefination of commercially-available 2-(2'-cyanoethyl)cyclohexanone. The syntheses of trioxanes **22** (Eq. 3)[14] proceeded by addition of the desired organometallic reagent to the nitrile moiety of enol ethers **23** to produce the corresponding ketones **24**. As described earlier, dioxetane formation followed by trialkylsilyl triflate-induced cyclization produced the skeleton of these C_3-substituted trioxanes **22** with the same relative stereochemistry assigned to C_3 and C_{12} as in the analogous photooxygenation/ rearrangement of trioxane alcohols **6–9**.



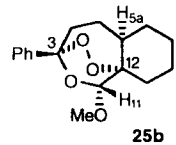
23 **24** **22** (3)

Since ketones **24** were diastereomeric at the enol ether moiety, trioxanes **22** were formed as two C_{11} acetal diastereomers, with ratios varying depending on the substrates. The ^1H NMR spectra of C_3-phenyl trioxanes **25a** and **25b**,[14,17] showed that one diastereomer's acetal proton H_{11} at 5.14 δ was a doublet (J = 1.6 Hz) while the other diastereomer showed H_{11} at 5.20 δ as a singlet. This difference in splitting allowed easy

identification of the acetal stereochemistries since only the α-face acetal proton H_{11} of trioxane **25a**, with its $C_{11}\beta$-methoxy group, can W-couple[28,29] with H_{5a} to give a doublet.



25a



25b

The same pattern was true for C_3-benzyl trioxanes **26**.[14] For C_3-methyl trioxanes **27**,[14,17] however, both diastereomers presented acetal protons as singlets in the ^1H NMR. The X-ray structures of these two diastereomers have been solved, though, and the configurations of each are thus known.[17] Upon examination of the ^{13}C NMR data for these three pairs of trioxane diastereomers **25–27** for which the acetal configuration is confirmed, a pattern emerges (Table 2). For the $C_{11}\beta$-methoxy configuration, the resonances of C_3 and C_{11} are separated by 3 ppm or less and both signals fall above roughly 104 ppm. In contrast, for the $C_{11}\alpha$-methoxy configuration, the resonances of C_3 and C_{11} are separated by approximately 8 ppm and the C_{11} signal falls at or below about 100 ppm.

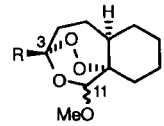
Such distinct, characteristic ^{13}C NMR resonances were easily used to assign acetal stereochemistry in C_3-substituted, C_{8a}-unsubstituted trioxanes **28–32** (Table 2).[14,30,31] In some cases, such as C_3-phenylpropyl trioxane **28**, the acetal proton appeared as a doublet, indicating the $C_{11}\beta$-methoxy configuration, and the C_3 and C_{11} resonances of 106.0 δ and 104.7 δ further confirmed the pattern established with trioxanes **25–27**. However, for trioxanes **29–32**, with diverse substituents at C_3, the acetal protons appeared as singlets, and their C_3 and C_{11} resonances served to confirm that all five new trioxanes possessed the $C_{11}\beta$-methoxy configuration.

Use of Established Correlations for New Trioxanes

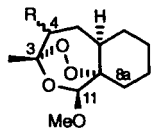
These ^{13}C NMR correlations for determination of C_{11} acetal configuration were combined with the methods for identification of C_4 stereochemistry to assign the

Table 2. ^{13}C and ^{1}H NMR Spectral Data Used in Assignment of C_{11} Stereochemistry of C_3-Substituted C_{8a}-Unsubstituted Trioxanes **25–32**.

		$C_{11\beta}$-OMe			$C_{11\alpha}$-OMe		
trioxane	R^3	C_3, δ	C_{11}, δ	H_{11}, δ	C_3, δ	C_{11}, δ	H_{11}, δ
25	Ph	108.2	105.1	5.14 (d)	104.0	96.1	5.20 (s)
26	$PhCH_2$	105.7	104.7	4.89 (d)	108.7	100.6	4.88 (s)
27	Me	104.9	104.7	4.93 (s)	103.6	95.4	4.95 (s)
28	$Ph(CH_2)_3$	106.0	104.7	4.90 (d)			
29	*i*-$Pr(CH_2)_2$	106.2	104.7	4.91 (s)			
30	CH_2=CH	104.9	103.6	5.01 (s)			
31	CH_3CH_2	106.2	104.8	4.92 (s)			
32	*p*-$PhPhCH_2$	105.6	104.6	4.98 (s)			



stereochemistry of novel, antimalarial C_4-substituted, C_{8a}-unsubstituted, C_3-methyl trioxanes **33–36**.[27,32]



33: R = $HOCH_2$
34: R = $PhCH_2$
35: R = *p*-$(HOCH_2)PhCH_2$
36: R = Ph

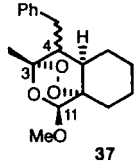
In all four cases, both separated diastereomers had C_3 and C_{11} ^{13}C NMR signals within the range indicative of $C_{11}\beta$-methoxy (Table 3), and their C_4 stereochemistry was assigned based on the relative shift of their acetals protons H_{11} by ^{1}H NMR spectra. For trioxanes **33–35** their relative acetal shifts were consistent with their relative polarities, as established with the C_4-alkylated trioxane alcohols **7–9**. For trioxane **36**, whose structure was confirmed by X-ray crystallography of the $C_{4\alpha}$ isomer, the pattern was reversed, emphasizing the importance of the ^{1}H NMR data in assignment of stereochemistry at C_4.

Interestingly, these methods were useful even for ring-contracted trioxanes **37**.[27,32] The ^{13}C NMR resonances for C_3 and C_{11} of both diastereomers (105.4/102.3 δ

Table 3. ^{13}C and ^{1}H NMR Spectral Data Used in Assignment of Stereochemistry at C_4 and C_{11} in Novel, Antimalarial C_4-Substituted C_{8a}-Unsubstituted C_3-Methyl Trioxanes **33–36**.

trioxane	R^4	C_3	C_{11}	H_{11}	polarity	assignment
33a	$HOCH_2$	105.5	103.7	4.91 (d)	less	$C_{4\alpha}$
33b	$HOCH_2$	106.0	104.5	4.95 (d)	more	$C_{4\beta}$
34a	$PhCH_2$	106.1	104.0	4.95 (s)	less	$C_{4\alpha}$
34b	$PhCH_2$	107.2	104.6	4.97 (s)	more	$C_{4\beta}$
35a	(p-$HOCH_2$) $PhCH_2$	106.1	104.0	4.84 (d)	less	$C_{4\alpha}$
35b	(p-$HOCH_2$) $PhCH_2$	106.9	104.3	4.97 (s)	more	$C_{4\beta}$
36a	Ph	105.6	103.9	4.99 (d)	*more*	$C_{4\alpha}$ (X-ray)
36b	Ph	107.2	104.5	5.03 (d)	*less*	$C_{4\beta}$

and 105.6/102.9 δ) fell into the range indicative of $C_{11\beta}$-methoxy, and this assignment was verified by their acetal protons H_{11}, which appeared as doublets in their ^{1}H NMR, W-coupling with H_{5a}. The stereochemistry at C_4 was assigned based on relative shift of their acetal protons (5.15 δ and 5.04 δ) and was consistent with their relative polarities. These structural assignments were unambiguously confirmed by X-ray crystallographic analysis of the $C_{4\beta}$ isomer of trioxanes **37**.



37

CONCLUSIONS

A series of 1D and 2D NMR experiments has been used to identify the relative stereochemistry of a number of simplified, antimalarial 1,2,4-trioxane analogs of the

natural product artemisinin **1**. Based on these data, rules have been developed for use primarily of NMR spectroscopy to assign configurations in new, diversely-substituted trioxanes. The relative shift of the acetal protons H_{11} in the ^1H NMR spectra can be used to identify the stereochemistry of pairs of diastereomers at the mechanistically important C_4 center. These assignments can, in most cases, be confirmed by correlation with the relative chromatographic polarity of the C_4-substituted trioxanes. The position and spacing of ketal and acetal carbons C_3 and C_{11}, respectively, in ^{13}C NMR spectra can be used to identify the configuration of the acetal C_{11}. Such rules for assignment of stereochemistry are crucial to ensure correct identification of new analogs to probe and to further research toward better chemotherapies against the spreading deadly infectious disease, malaria.

ACKNOWLEDGMENTS

We thank the NIH (AI-34885) and the Non-Directed Research Fund (04D0209), Korea Research Foundation for financial support.

REFERENCES

1. Klayman, D. L. *Science* **1985**, *228*, 1049–1055.

2. Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301–315.

3. Hien, T. T.; White, N. J. *Lancet* **1993**, *341*, 603–608.

4. Zhou, W. S.; Xu, X. X. *Acc. Chem. Res.* **1994**, *27*, 211–216.

5. Avery, M. A.; Fan, P.; Karle, J. M.; Bonk, J. D.; Miller, R.; Goins, D. K. *J. Med. Chem.* **1996**, *39*, 1885–1897.

6. Avery, M. A.; Gao, F.; Chong, W. K. M.; Mehrotra, S.; Milhous, W. K. *J. Med. Chem.* **1993**, *36*, 4264–4275.

7. Torok, D. S.; Ziffer, H.; Meshnick, S. R.; Pan, X. Q. *J. Med. Chem.* **1995**, *38*, 5045–5050.

8. Ramu, K.; Baker, J. K. *J. Med. Chem.* **1995**, *38*, 1911–1921.

9. Haynes, R. K.; Vonwiller, S. C.; Wang, H. J. *Tetrahedron Lett.* **1995**, *36*, 4641–4642.

10. Brossi, A.; Venugopalan, B.; Gerpe, L. D.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645–650.

11. Lin, A. J.; Klayman, D. L.; Milhous, W. K. *J. Med. Chem.* **1987**, *30*, 2147–2150.

12. China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials *J. Trad. Chin. Med.* **1982**, *2*, 17–24.

13. Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1996**, *37*, 253–297.

14. Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *Heteroatom Chem.* **1995**, *6*, 105–116.

15. Singh, C.; Misra, D.; Saxena, G.; Chandra, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1913–1916.

16. Peters, W.; Robinson, B. L.; Tovey, G.; Rossier, J. C.; Jefford, C. W. *Ann. Trop. Med. Parasitol.* **1993**, *87*, 111–123.

17. Jefford, C. W.; Velarde, J. A.; Bernardinelli, G.; Bray, D. H.; Warhurst, D. C.; Milhous, W. K. *Helv. Chim. Acta* **1993**, *76*, 2775–2788.

18. Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459–2467.

19. Misra, L. N.; Thakur, R. S. *J. Nat. Prod.* **1993**, *56*, 215–219.

20. Akhila, A.; Thakur, R. S.; Popli, S. P. *Phytochem.* **1987**, *26*, 1927–1930.

21. El-Feraly, F. S.; Al-Meshal, I. A.; Al-Yahya, M. A.; Hifnawy, M. S. *Phytochem.* **1986**, *25*, 2777–2778.

22. Jefford, C. W.; Kohmoto, S.; Jaggi, D.; Timári, G.; Rossier, G. C.; Rudaz, M.; Barbuzzi, O.; Gérard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G.; Manzanares, I.; Canfield, C. J.; Fleck, S. L.; Robinson, B. L.; Peters, W. *Helv. Chim. Acta* **1995**, *78*, 647–662.

23. Posner, G. H.; Wang, D.; Cumming, J. N.; Oh, C. H.; French, A. N.; Bodley, A. L.; Shapiro, T. A. *J. Med. Chem.* **1995**, *38*, 2273–2275.

24. Posner, G. H.; Oh, C. H.; Wang, D.; Gerena, L.; Milhous, W. K.; Meshnick, S. R.; Asawamahasakda, W. *J. Med. Chem.* **1994**, *37*, 1256–1258.

25. Posner, G. H.; McGarvey, D. J.; Oh, C. H.; Kumar, N.; Meshnick, S. R.; Asawamahasakda, W. *J. Med. Chem.* **1995**, *38*, 607–612.

26. Posner, G. H.; Oh, C. H.; Webster, K.; Ager, A. L., Jr.; Rossan, R. N. *Am. J. Trop. Med. Hyg.* **1994**, *50*, 522–526.

27. All new compounds were characterized spectroscopically and by high-resolution mass spectrometry.

28. Günther, H. *NMR Spectroscopy*; 2nd ed.; John Wiley: Chichester, England, 1995; Chapter 4, section 2.

29. Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*; John Wiley: Chichester, England, 1990; Chapter 3, section 5.

30. Posner, G. H.; Park, S. B.; González, L.; Wang, D.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A.; Bachi, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 3537–3538.

31. Posner, G. H.; Cumming, J. N.; Ploypradith, P.; Oh, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 5885–5886.

32. *In vitro* antimalarial data for new compounds will be reported in a future publication.

Received: July 15, 1996
Accepted: August 23, 1996