Antimalarial Peroxide Dyads from Natural Artemisinin and Hydroxyalkylated 1,2,4-Trioxanes

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Three synthetic approaches to highly antimalarial peroxide dyads that are composed of the natural artemisinin part (either as dihydroartemisinin or artesunic acid components) and synthetic 1,2,4-trioxanes linked by ether or ester bridges are described. Photooxygenation is the key step to introduce the trioxane group initially or at the end of the reaction sequence, respectively. Dihydroartemisinin or artesunate coupling to hydroxyethyltrioxanes are the two processes that use intact peroxide units from the beginning, whereas the dihydroartemisinin-coupling to an allylic alcohol is a postphotooxygenation route, where the second trioxane ring is installed in the last step of the procedure.

Introduction

The search for new compounds active against malaria has led to an increasing demand for the synthesis of new cyclic organic peroxides. The naturally occurring sesquiterpene lactone peroxide artemisinin (**1**, quinhaosu) which contains a 1,2,4-trioxane subunit serves as the natural active principle and model compound. More than 1000 synthetic derivatives of **1** have been prepared in the last decades.[1,2] The driving force for these intense efforts is the search for more active derivatives with better oral applicability and the fear of possible resistances[3−5] against artemisinin **1** and the semisynthetic derivatives (Figure 1) arthemether (**2a**, R = Me), artheether (**2b**, R = Et), and artesunic acid and the corresponding salts (**2c**, R = $CO(CH_2)_2$-COOH).[6−8]

In most cases, artemisinin derivatives are prepared by coupling to functional groups via the acetal group C-10 in dihydroartemisinin (DHA[a]).[9,10]

The three major concepts for derivative syntheses are: (a) coupling of the artemisinin skeleton to potential pharmacologically active groups like secondary or tertiary amines, (b) coupling to an antimalarial compound from another pharmacophor family (dual compounds),[11,12] and (c) coupling of two artemisinin derivatives by use of a functionalized linker resulting in highly active dimers.[13−15] Especially, the last two approaches are fruitful tools for the development of new active compounds that additionally show antitumor activities.[16] To the best of our knowledge, however, no efforts have been reported to couple artemisinin to another 1,2,4-trioxane derivative with comparable antimalarial activity. We and others have reported in recent years, that 1,2,4-trioxanes that are spiro-fused to cycloalkanes, especially adamantane, are pronouncedly more active than simple 3,3-dialkylated compounds.[17,18] Thus, a synthetic protocol allowing C-10 linking of natural artemisinin to 1,2,4-trioxanes with concomitant introduction of a spiroadamantane unit to target molecules **3** was desirable.

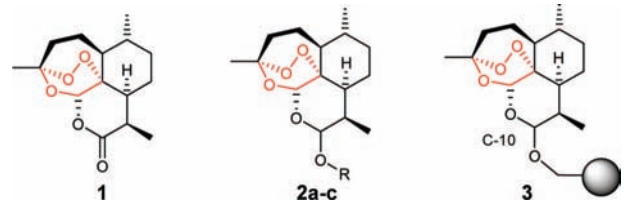
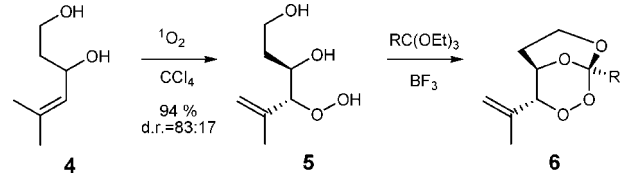


Figure 1. Artemisinin and C-10 ether derivatives.

Scheme 1. The 1,3-Diol Approach to Bicyclic Perorthoesters



Results and Discussion

In a first approach, we used the allylic alcohol **4** as the singlet oxygen acceptor with a bis-homoallylic hydroxyl as a nucleophilic coupling group (Scheme 1). The photooxygenation proceeded with high diastereoselectivity and **5** was previously used as a starting material for perorthoester synthesis (e.g., **6**),[19] however, not for coupling to dihydroartemisinin because of the higher reactivity of the hydroperoxy group. Peroxyacetalization of **5** prior to coupling to dihydroartemisinin was also not successful. A protected derivative of **5** was required, and thus the photooxygenation of the ester **7**[20] investigated. The singlet oxygen photooxygenation of **7** under standard conditions gave the γ-hydroperoxy ester **8** in high yield but with no diastereoselectivity.

This low degree of diastereoselectivity for **7** is possibly due to an internal hydrogen bond between the allylic hydroxy group and the ester carbonyl, thus circumventing the stereodirecting hydroxy effect on the singlet oxygen reaction.[21] In case of substrate **4**, where the allylic hydroxy group can serve as H-bond donor as well as acceptor, the hydroxy group effect on the diastereoselectivity of the $^1O_2$ ene reaction is retained.

The peroxacetalization with acetone, cyclohexanone, or adamantanone proceeded under BF_3 catalysis in moderate yields

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[a] Abbreviations: DHA, dihydroartemisinin; DCC, dicyclohexyl carbodiimide; DMAP, 4-dimethylaminopyridine; DBU, 1,8-diazabicylo[5.4.0]undec-7-ene; TPP, *meso*-tetraphenylporphyrin.

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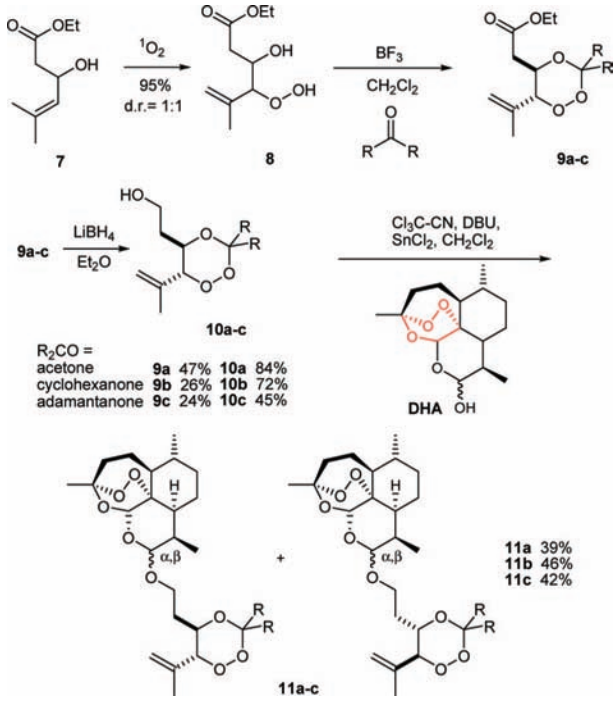
Scheme 2. DHA−Trioxane Coupling Route to Dyads **11a−c**



to give the 3,3-disubstituted and spirofused 1,2,4-trioxanes **9a−c** in 47, 26, and 24% yields (Scheme 2). The *trans*/*cis*-ratio in **9** increased to 9:1, showing that the *threo*-isomer **8** preferentially reacted. Reduction of the ethyl esters in presence of the sensitive peroxide group was achieved with lithium borohydride in high yields.[22]

Trichloroacetamide (Schmidt reaction)[23] coupling of the primary alcohols **10a−c** thus obtained with dihydro-artemisinin (mixture of α,*β*-epimers) resulted in the dyads **11a−c**. An X-ray structure could be obtained for the adamantanone derivative **11c** showing twist boat (right) and chair (left) 1,2,4-trioxane structures in the artemisinin and the synthetic peroxide subunits of **11c**, respectively (Figure 2). All adducts **11** were isolated as 4:1 mixtures of α- and *β*-epimers and as 1:1 diastereoisomeric mixtures with respect to the (racemic) hydroxyalkyltrioxane precursor stereochemistry. The major compound, the *β*-C10-epimer **11c** with trans configuration at the second trioxane ring, crystallized.

A second approach for coupling of hydroxyalkyltrioxanes with the artemisinin skeleton makes use of the readily available artesunic acid **2c** that is applied as the pure α-epimer and can be converted to the corresponding α-artesunates by esterification.

Coupling of enantiomerically pure **2c** with the racemic trioxane building blocks **10a**,**c** using the dicyclohexyl carbodiimide/4-dimethylamino-pyridine (DCC/DMAP) method gave 1:1 mixtures of diastereoisomers **12a**,**c** (Scheme 3).

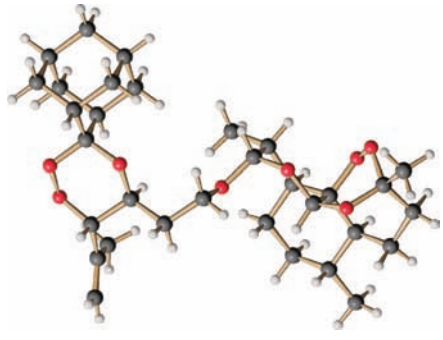
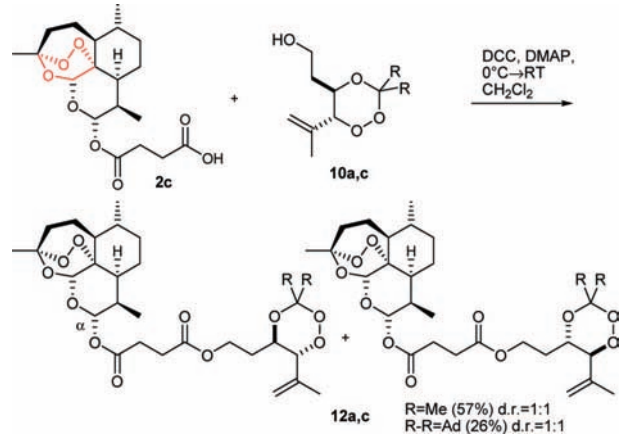
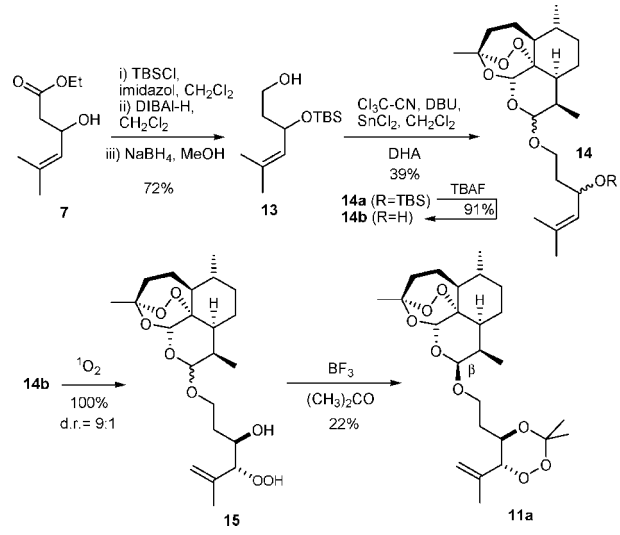


Figure 2. Adamantane derivative **11c** in the crystal.

Scheme 3. Artensunate-Based Synthesis of Dyads **12a** and **12c**



Scheme 4. Coupling/Photooxygenation Route to Dyads **11**



Thus, the first two approaches to couple artemisinine derivatives and synthetic trioxanes were successful but delivered mixtures of diastereoisomers often hard to be separated. Therefore, we envisaged a third approach where the stereoselectivity control during the singlet oxygen ene reaction with the allylic alcohol is influenced already by the sesquiterpene group. As alkene substrate, the aldol **7** was used, protected, and reduced to the bis-homoallylic alcohol **13** (Scheme 4).

Tin-catalyzed trichloroacetamide/DBU coupling with DHA and subsequent desilylation delivered the free allylic alcohol **14b**. The singlet oxygenation, as hoped for, now proceeded in CCl_4 with tetraphenylporphyrin as sensitizer with excellent chemical yields and high diastereoselectivity. Being aware of the sensitivity of ether derivatives of artemisinin in the presence of Lewis acids, the last step was expected to be the critical part of this approach.

Indeed, the yield of peroxyacetalization was moderate, even if acetone was applied in high excess, indicating that decomposition of the artemisinine skeleton plays a role here. In contrast to the first approach, however, only one diastereoisomer (*β*-epimer)[24] of **11a** was obtained here in enantiomerically pure form (X-ray structure: Figure 3).[25] Lewis acid induced epimerization at C-10 must have been occurred during the last reaction step to result in the pure epimer **11a**.

In vitro activity testing of compounds **11a** and **11b** against *Plasmodium falciparum* isolate NF54[26] in comparison with the

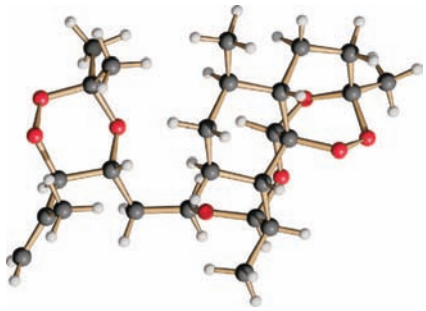


Figure 3. Acetone derivative **11a** in the crystal.

standard compound dihydroartemisinin (DHA) resulted in ratios IC_{50} (DHA) vs IC_{50} (**11a**,**b**) of 0.54 and 0.49,[27] respectively. These data were determined for a *P. falciparum* isolate NF54 after 72 h as described in the Experimental Section.

Summary

The high activity of artemisinin is largely retained in these peroxide dyads. In summary, we have described here three multistep approaches to dyads with α- and β-configuration at C-10 composed of the artemisine skeleton and a synthetic 1,2,4-trioxane either incorporated from the beginning of the synthesis or generated via the singlet oxygen/peroxyacetalization route of an intact artemisinine−allylic alcohol dyad in the final part of the synthesis.

Experimental Section

Chemistry. General Methods. Artemisinin and artemisinin derivatives were purchased from Plant Extracts, Xian, China. Reactions were monitored by thin-layer chromatography on silica-gel precoated sheets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300, DRX-500, or AV-600 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard. Mass spectra and accurate mass determinations were obtained with a Finnigan MAT 900S by electrospray ionization. Infrared spectra were recorded with a Perkin-Elmer FT-IR-S 1600 Fourier transform spectrometer. The elemental analyses were performed with a Elementar Vario EL. From all new compounds, satisfactory elemental analyses and high-resolution mass spectra, respectively, as well as HPLC analyses were obtained, confirming >95% purity. For photooxygenation reactions were used: either a halogen street lamp (150 W) or a high-pressure mercury lamp (150 W) in combination with a 370 nm cutoff filter.

Ethyl-4-hydroperoxy-3-hydroxy-5-methylhexyl-5-enoate (8). Polystryrene (1% divinylbenzene copolymer, 1.5 g) was distributed on a Petri dish and treated with dichloromethane (10 mL). The β-hydroxyester **7** (320 mg, 1.85 mmol) and tetraphenylporphyrin (TPP, 3 mg) in ethyl acetate (10 mL) were subsequently added and the excess solvent was evaporated by leaving the Petri dish in a well ventilated hood. The Petri dish was loosely covered with a glass plate, and the mixture was irradiated with a 150 W sodium street lamp for 20 h. The polymer beads were subsequently rinsed with ethanol (3 × 15 mL) and filtered. After removing the solvent, a diastereoisomeric mixture of the hydroperoxides **8a** and **8b** (dr = 48:52) was obtained as pale-yellow oil. The conversion of the photooxygenation reaction was 100%. **8a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.27 (t, 3H, J = 7.2 Hz, $C\underline{H}_3CH_2$), 1.78 (s, 3H, $C\underline{H}_3$), 2.47 (m, 2H, $C\underline{H}_2$), 4.22 (m, 3H, $CH_3C\underline{H}_2$, C$\underline{H}$OH), 4.33 (d, 1H, J = 7.8 Hz, C$\underline{H}$OOH), 5.09 (d, 2H, $\underline{H}C{=}C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 14.0 ($\underline{C}H_3CH_2$), 18.2 ($\underline{C}H_3C{=}$), 36.9 ($\underline{C}H_2$), 60.9 ($CH_3\underline{C}H_2$), 67.4 ($\underline{C}$HOH), 90.4 ($\underline{C}$HOOH), 115.4 ($H_2\underline{C}{=}C$), 140.7 ($\underline{C}{=}CH_2$), 171.9 ($\underline{C}{=}O$). **8b** (additional significant signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.27 (t, 3H, J = 7.2 Hz, $C\underline{H}_3CH_2$), 1.82 (s, 3H, $C\underline{H}_3$), 2.62 (m, 2H, $C\underline{H}_2$), 4.22 (m, 3H, $CH_3C\underline{H}_2$, C$\underline{H}$OH), 4.41 (d, 1H, J = 5.4 Hz, C$\underline{H}$OOH), 5.11 (d, 2H, $\underline{H}C{=}C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 19.0 ($\underline{C}H_3C{=}$), 38.0 ($\underline{C}H_2$), 67.9 ($\underline{C}$HOH), 91.7 ($\underline{C}$HOOH), 116.6 ($H\underline{C}{=}C$), 141.0 ($\underline{C}{=}CH$), 172.8 ($\underline{C}{=}O$). IR (film): ν (cm^{-1}) = 3414 (s), 2979 (m), 2928 (m), 1715 (s), 1649 (w), 1373 (s), 1174 (s), 1021 (s), 907 (m).

4-(Ethyl-2-acetyl)-3-(prop-1en-2yl)-spiro[1,2,4-trioxa-cyclohexane-3,2′-adamantane] (9c). A stirred solution of hydroperoxide **8** (377 mg, 1.85 mmol) and adamantanone (278 mg, 1.85 mmol) in dichloromethane was treated with a catalytic amount of $BF_3{\cdot}Et_2O$. After stirring for 12 h at rt, the reaction was quenched by a saturated solution of $NaHCO_3$. The two-phase mixture was separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with brine and were dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was submitted to flash column chromatography with hexane/diethyl ether (4:1, R_f = 0.71), affording a diastereoisomeric mixture (dr = 91:8) of trioxanes **9c** and **9c′** (148 mg, 0.44 mmol, 24%) as a colorless oil. **9c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.25 (t, 3H, J = 7.2 Hz, $C\underline{H}_3CH_2$), 1.54 −1.80 (m, 12 H, $C\underline{H}_2$, C$\underline{H}$), 1.77 (s. 3H, $C\underline{H}_3$), 2.41 (m, 2H, $C\underline{H}_2$), 2.94 (br s, 1H, C$\underline{H}$), 4.15 (q, 2H, J = 7.2 Hz, $CH_3C\underline{H}_2$), 4.32 (d, 1H, J = 9.9 Hz, $\underline{H}CO$), 4.48 (m, 1H, C$\underline{H}$OO), 5.10 (s, 2H, $C{=}C\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 14.2 ($\underline{C}H_3CH_2$), 19.4 ($\underline{C}H_3$), 27.1 (2 × $\underline{C}$H), 29.9 ($\underline{C}$H), 32.7 ($\underline{C}H_2$), 33.3 (2 × $\underline{C}H_2$), 33.4 ($\underline{C}H_2$), 36.4 ($\underline{C}$H), 37.1 ($\underline{C}H_2C{=}O$), 60.7 ($CH_3\underline{C}H_2$), 65.9 ($\underline{C}$HO), 86.7 ($\underline{C}$HOO), 105.2 (O$\underline{C}$OO), 118.5 ($C{=}\underline{C}H_2$), 138.7 ($\underline{C}{=}CH_2$), 170.6 ($\underline{C}{=}O$). **9c′** (additional significant signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.27 (t, 3H, J = 7.2 Hz, $C\underline{H}_3CH_2$), 2.83 (br s, 1H, C$\underline{H}$), 4.15 (q, 2H, J = 7.2 Hz, $CH_3C\underline{H}_2$), 4.74 (m, 1H, C$\underline{H}$OO), 5.00 (s, 2H, $C{=}CH_2$). IR (film): ν (cm^{-1}) = 2913 (s), 2855 (m), 1738 (s), 1648 (w), 1450 (m), 1379 (w), 1262 (m), 1173 (s), 1109 (s), 1023 (m), 926 (m). HRMS (ESI) calcd: 359.183 g/mol; found: 359.183 ± 0.0015.

4-(Hydroxethyl)-3-(prop-1-en-2yl)-spiro[1,2,4-trioxa-cyclohexane-3,2′-adamantane] (10c). $LiBH_4$ (20 mg, 92 mmol, 2.1 equiv) was added to stirred solution of trioxane **9c** (148 mg, 0.44 mmol) in THF (4 mL) at ambient temperature. The mixture was stirred until TLC showed complete disappearance of the starting material. The reaction was cooled to 0 °C and was quenched with a saturated solution of NH_4Cl. The two-phase mixture was separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phases were washed with brine and were dried with Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography with hexane/diethyl ether (1:1, R_f = 0.41) providing a diastereoisomeric mixture (dr = 85: 15) of the trioxanes **10c** and **10c′** (58 mg, 0.20 mmol, 45%) as a colorless oil. **10c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 1.55 −2.01 (m, 15H, 5 × CH_2, 3 × CH, $C\underline{H}_2CH_2OH$), 1.76 (s. 3H, CH_3), 2.28 (br s, 1H, OH), 2.95 (br s, 1H, CH), 3.81 (m, 2H, $C\underline{H}_2OH$), 4.20 (dt, 1H, J = 3.6 Hz, 9.6 Hz, HCO), 4.36 (d, 1H, J = 9.6 Hz, CHOO), 5.09 (d, 2H, J = 1.2 Hz, $C{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 19.8 (CH3), 27.1 (CH), 29.8 (CH), 33.1 ($\underline{C}H_2CH_2OH$), 33.2 (CH_2), 33.3 (CH_2), 33.4 (CH), 33.5 (CH_2), 33.9 (CH_2), 36.5 (CH), 37.1 (CH_2), 60.4 (CH_2OH), 68.6 (CHO), 87.1 (CHOO), 105.2 (OCOO), 118.4 ($C{=}CH_2$), 138.9 ($C{=}CH_2$). **10c′** (additional significant signals): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.89 (br s, 1H, CH), 4.49 (m, 1H, HCO), 5.03 (s, 2H, $C{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 22.2 (CH_3), 30.9 (CH), 36.0 (CH), 60.8 (CH_2OH), 66.9 (CHO), 84.9 (CHOO), 118.5 ($C{=}CH_2$), 141.6 ($C{=}CH_2$). IR (film): ν (cm^{-1}) = 3370 (s), 2904 (s), 2853 (s), 1647 (w), 1448 (m), 1378 (m), 1221 (m), 1107 (s), 1080 (s), 1022 (s), 923 (m). MS (ESI) m/z (%): 317.16 (M^+ + Na).

10β-(2-(3-(Prop-1-en-2yl)-spiro[1,2,4-trioxacyclohexane-3,2′-adamantane]-4-ethyloxy))dihydroartemisinin (11c). A solution of DHA (71 mg, 0.25 mmol), trichloroacetonitrile (1.9 mg, 0.28 mmol, 1.1 equiv), and DBU (2.2 mg, 0.013 mmol, 0.05 equiv) in dichloromethane (3 mL) was stirred at ambient temperature for 18.5 h. This was then added to a solution of trioxane **10c** (220 mg, 0.75 mmol, 3 equiv) and $SnCl_2$ (2.4 mg, 0.013 mmol, 0.05 equiv) in dichloromethane (1 mL). After another 2 h, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ and the organic layer was dried with $MgSO_4$. After removing the solvent under reduced pressure, the residue was purified by fash column chromatography

with hexane/diethyl ether (4:1, $R_f = 0.32$), affording a diastereoisomeric mixture of the dyads **11c** and **11c′** (59 mg, 0.11 mmol, 42%) as colorless crystals. **11c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 0.90 (m, 1H, C$\underline{H}_2$, H7), 0.91 (d, 3H, $J = 7.2$ Hz, CH_3, H9-Me), 0.95 (d, 3H, $J = 6.3$ Hz, CH_3, H6-Me), 1.25 (m, 1H, C$\underline{H}$, H5a) 1.31 (m, 1H, CH, H6), 1.43 (s, 3H, CH_3, H3-Me), 1.78 (s, 3H, C$\underline{H}_3$), 1.47 − 2.04 (m, 21H, H5, H7, H8a, H8, 3 × CH-Ada, 5 × CH_2-Ada, CH_2CH_2O), 2.09 (m, 1H, C$\underline{H}_2$, H4), 2.37 (dt, 1H, $J = 1.2$ Hz, 6.9 Hz, C$\underline{H}_2$, H4), 2.64 (m, 1H, C$\underline{H}$, H9), 2.90 (s, H, CH-Ada), 3.58 (dt, 1H, $J = 5.1$ Hz, 1.9 Hz, OC$\underline{H}_2$), 3.94 (m, 1H, OC$\underline{H}_2$), 4.17 (t, 1H, $J = 4.9$ Hz, OC$\underline{H}$), 4.29 (d, 1H, $J = 4.9$ Hz, OOC$\underline{H}$), 4.83 (d, 1H, $J = 1.7$ Hz, H10), 5.10 (s, 2H, C═C$\underline{H}_2$), 5.37 (s, 1H, C$\underline{H}$, H12). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 13.1 (t, C9-Me), 19.5 (t, $\underline{C}H_3$), 20.3 (t, C6-Me), 24.5 (d, C5), 24.7 (d, C8), 26.2 (t, C3-Me), 27.2 (s, 2 × CH-Ada), 29.8 (s, CH-Ada), 31.0 (s, C9), 31.6 (d, CH_2-Ada), 33.2 (d, $OCH_2\underline{C}H_2$), 33.2 (d, CH_2-Ada), 33.3 (d, CH_2-Ada), 33.6 (d, CH_2-Ada), 34.6 (d, C7), 36.4 (d, C4), 36.6 (d, CH_2-Ada), 37.1 (s, CH-Ada), 37.5 (s, C6), 44.4 (s, C8a), 52.5 (s, C5a), 63.9 (d, $O\underline{C}H_2CH_2$), 65.0 (s, $O\underline{C}HCH_2$), 81.0 (q, C12a), 87.5 (s, OO$\underline{C}$H), 87.9 (s, C12), 102.2 (s, C10), 104.1 (q, C3), 105.0 (q, O$\underline{C}$OO), 118.4 (q, CH_2═$\underline{C}$), 139.1 (d, $\underline{C}H_2$═C). IR (film): ν (cm^{-1}) = 2912 (s), 2854 (m), 1647 (s), 1449 (m), 1374 (m), 1106 (s), 1023 (s), 875(m). HRMS (ESI) calcd: 583.3247 g/mol; found: 583.323 ± 0.0015.

Biological Testing. *P. falciparum* isolate NF54 was maintained in continuous culture with gentamycin (40 μg/mL) in Petri dishes (5 cm) diameter at 37 °C with a gaseous phase of 90% N_2, 5% O_2, and 5% CO_2, according to a literature protocol.[28,29] Parasites were cultured in human erythrocytes (blood group A+) in RPMI 1640 medium (Sigma) supplemented with 25 mM HEPES, 20 mM sodium bicarbonate, and 10% heat inactivated human A+ plasma at 10% (v/v) hematocrit. The parasitemia of the infected erythrocytes was determined by light microscopy and estimated by Giemsa-stained smears. Parasitemias were scored visually with a 100-fold oil-immersion objective, counting at least 1000 erythrocytes to determine the percentage of infected erythorcytes. The culture was adjusted to 1.5%. Aliquots (200 μL) were suspended in 2 mL of RPMI-medium, dispensed into 12-well microculture trays and incubated at 37 °C. Therefore, growth medium was changed once a day and substances were added to the media as indicated. Parasitemia was estimated in quadruplicates.

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Supporting Information Available: An experimental section including details of the synthesis and chemical and spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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