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Efficient Synthesis of *exo*-Olefinated Deoxoartemisinin Derivatives by Ramberg−Bäcklund Rearrangement

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Abstract: 10-*exo*-Bromoalkylidene- and benzylidenedeoxoartemisinins were synthesized from corresponding 10-alkanesulfonyldihydroartemisinin and 10-phenylmethanesulfonyldihydroartemisinin using a highly efficient, mild, and simple Ramberg−Bäcklund rearrangement.

The natural sesquiterpene endoperoxide artemisinin (**1**), which was isolated from *Artemisia annua L.*,[1] has become a potential lead compound in the development of antimalarial[2] and recently anticancer agents.[3] The semisynthetic acetal-type artemisinin derivatives (**3**), ether and ester derivatives of trioxane lactol dihydroartemisinin (**2**), were developed for their higher antimalarial efficacy and are now widely used to treat malarial patients.[4] However, because of the instability[5] and toxicity[6] of all acetal-type derivatives (**3**), a great deal of interest has been concentrated on the synthesis of nonacetal-type artemisinin derivatives (**5**), which were first synthesized by Jung et al.[7] and then by Haynes et al.[8] from artemisinic acid (**4**) (Figure 1).

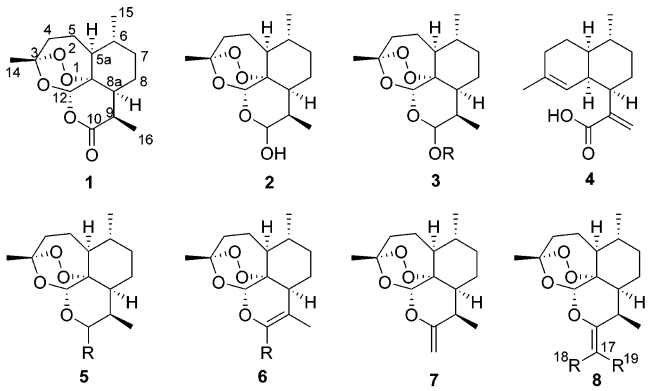

FIGURE 1. Artemisinin and its derivatives.

Posner et al.[9] and Ziffer et al.[10] reported simple semisynthetic methods for the direct conversion of dihydroartemisinin (**2**) to nonacetal analogues (**5**). We have also reported the direct substitution reaction between 10α- or 10*β*-benzenesulfonyldihydroartemisinin and organozinc reagents derived from allyl, benzyl, phenyl, vinyl, and *n*-butyl Grignard reagents for the related 10-substituted deoxoartemisinin derivatives (**5**).[11] In particular, when considering the structural peculiarity and synthetic utility, we were impressed by the report showing that *endo*-olefinated deoxoartemisinin derivatives (**6**) and their dimers synthesized by Posner et al. exhibit a high antimalarial[12] and antitumor activity.[3c]

Therefore, to search for noble types of artemisinin analogues with a high activity and synthetic effectiveness, we decide to synthesize the C-10 *exo*-olefinated deoxoartemisinin derivatives (**8**). In 1994, McChesney et al. reported the synthesis of 10-*exo*-methylene deoxoartemisinin (**7**), but their method was very limited.[13]

In our laboratory, on the basis of the hypothesis that the C-10 position of the dihydroartemisinin (**2**), cyclic hemiacetal, can be regarded as a sugar−anomeric center,[9] we have developed more effective method for target compounds (**8**) by using the Ramberg−Bäcklund rearrangement of *S*-glycoside for 1-*exo*-methylene glycal.[14]

As shown in Scheme 1 and Table 1, the reaction of dihydroartemisinin (**2**) with the corresponding thiol

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SCHEME 1. Synthesis of *exo*-Olefinated Deoxoartemisinin Derivatives by Ramberg−Bäcklund Rearrangement

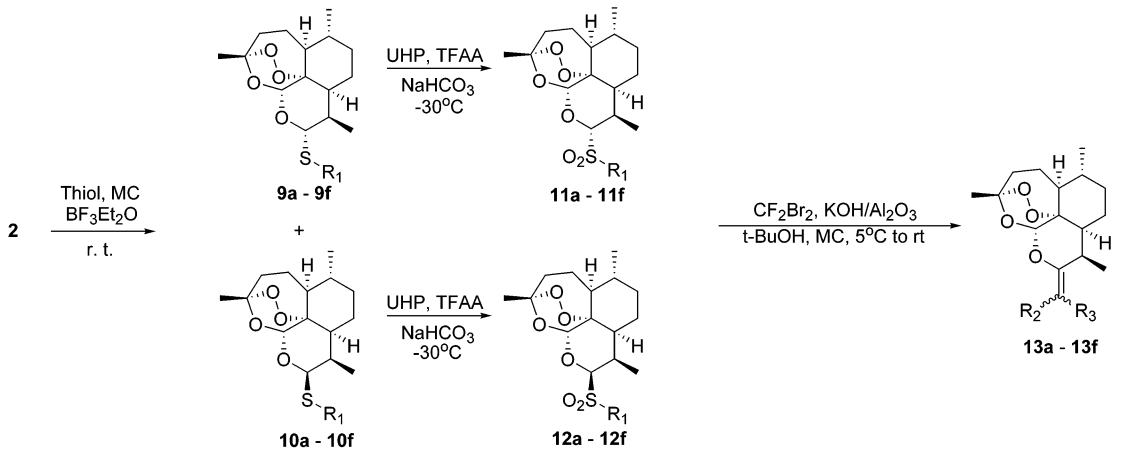

TABLE 1. Synthesis of Thioacetal Artemisinin Derivatives from Dihydroartemisinin

		yields[a] (%)			
	R_1	**9**	**10**	**11**	**12**
a	methyl	41	32	78	70
b	ethyl	86	6	84	86
c	*n*-butyl	74	10	95	91
d	isopropyl	80	5	83	80
e	benzyl	82	8	82	80
f	allyl	70	11	96	97

[a] Isolated yield.

TABLE 2. *exo*-Olefination of C-10-Substituted Sulfonyl Dihydroartemisinin by Modified Ramberg−Bäcklund Rearrangement

reactants	products	*E*/*Z* ratio[a]	yield[b] (%)
11a	**13a** (R_2, H; R_3, Br)	50:50	74
11b	**13b** (R_2, CH_3; R_3, Br)	84:16	76
12b	**13b** (R_2, CH_3; R_3, Br)	80:20	19
11c	**13c** (R_2, *n*-propyl; R_3, Br)	92:8	84
12c	**13c** (R_2, *n*-propyl; R_3, Br)	93:7	15
11d	**13d** (R_2, R_3, CH_3)	*c*	26
11e	**13e** (R_2, H; R_3, phenyl)	70:30	78
11f	**13f** (R_2, vinyl; R_3, Br)	*d*	*d*

[a] Isolated ratio. [b] Isolated yield. [c] Stereochemistry not determined. [d] Product not obtained.

reactants[15] in the presence of $BF_3{\cdot}Et_2O$ gave a separable mixture of major thioacetal dihydroartemisinin (**9a**−**f**) with a C-10α stereochemistry and minor C-10*β* diastereomers (**10a**−**f**), respectively.[11,16] The C-10 stereochemistry of all those products was confirmed by a coupling constants between H-9 and H-10 in their ^1H NMR spectra.[17] In addition, continuous oxidation reaction of each purified thioacetal compounds (**9a**−**f** and **10a**−**f**) with H_2O_2/urea (UHP), trifluoroacetic anhydride (TFAA), and $NaHCO_3$ produced 10α-substituted sulfonyl dihydroartemisinin (**11a**−**f**) and 10*β* derivatives (**12a**−**f**), respectively,[18] which will be important precursors for the synthesis of *exo*-olefinated deoxoartemisinin derivatives (**8**) by modified Ramberg−Bäcklund rearrangement conditions.[19]

First, as shown in Scheme 1 and Table 2, the reaction between 10α-methanesulfonyl dihydroartemisinin (**11a**) and CF_2Br_2, and KOH/Al_2O_3 in *t*-BuOH and methylene chloride (2:1) at room temperature gave an inseparable *E* and *Z* mixture of 10-bromomethylenedeoxoartemisinin (**13a**) in the same ratio,[20] which is the first example of the deoxoartemisinin with an *exo*-methylene moiety formed by intramolecular rearrangement in artemisinin chemistry. Under the same reaction conditions, the 10α-ethanesulfonyl dihydroartemisinin (**11b**) stereoselectively produced a separable *E* and *Z* mixture of 10-(1-bromoethylidene) deoxoartemisinin (**13b**) (76% yield, *E*/*Z* = 84:16). Though there was no difference in the chemical shift of the H-18 in *E*- and *Z*-**13b**, the NOE experiment between H-18 and H-9 showed that the major product possessed an *E*-olefin configuration. However, a similar reaction of the 10*β*-isomers (**12b** and **12c**) produced the corresponding products (**13b** and **13c**) in a very low yield (19% for **13b** and 15% for **13c**) because they react at a lower rate than the 10α-isomers (**11b** and **11c**) as previously reported.[18b]

The streoselectivity of *exo*-olefination was greatly improved when longer alkyl chains were used. 10-(1-Bromobutylidene)deoxoartemisinin (**13c**) with a high stereoselectivity (*E*/*Z* = 92:8) and yield (84%) was formed from 10α-*n*-butanesulfonyl dihydroartemisinin (**11c**) with a relatively longer carbon chain than **11a** and **11b**.

Except for the *exo*-bromomethylene glycols from the methanesulfonyl glycosides,[20a] it is a very rare case that as in artemisinin chemistry, the bromo-olefinated products could be synthesized from alkanesulfonyl reactants by a Ramberg−Bäcklund rearrangement. The bromoalkenylidene analogues (**13a**, **13b**, and **13c**) were expected to have potential synthetic utilities and might be

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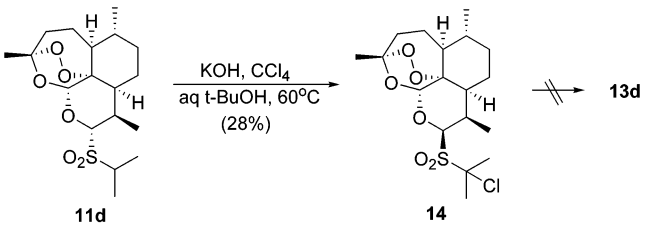
SCHEME 2. Synthesis of 10-Isopropylidene Deoxoartemisinin Using Meyers' Condition



used to synthesize new multisubstituted deoxoartemisinin derivatives derived from the metalation and successive addition reaction.

Second, in the case of the secondary alkane-substituted sulfonyl dihydroartemisinin (**11d**), 10-isopropylidene deoxoartemisinin (**13d**) was obtained in a very low yield (26%) due to steric hindrance of the isopropyl group. To improve the effectiveness, an alternative method, the Meyers' condition was used, as shown in Scheme 2.[21] However, this method only gave a synthetic intermediate **14** in a 28% yield and was not useful as a secondary alkanesulfone precursor.

Finally, unlike the alkanesulfonyl reactants (**11a**−**d**), the 10α-phenylmethanesulfonyldihydroartemisinin (**11e**) with an aromatic sulfonyl group gave separable *E*- and *Z*-isomers of the 10-benzylidenedeoxoartemisinin (**13e**) with no bromide in a 78% yield (*E*/*Z* = 70:30). The stereochemistry of *E*-**13e** and *Z*-**13e** was determined by comparing each chemical shift of H-17 (6.43 ppm for *E* and 5.45 ppm for *Z*) and H-9 (3.45 ppm for *E* and 3.33 ppm for *Z*) of the two isomers.

As for other derivatives, although the allyl precursor **11f** was totally consumed, the desired 10-allylidene deoxoartemisinin (**13f**) could not be obtained. The formation of **13f** by other reaction conditions deserves further study.

In conclusion, for the first time, we have shown that the *exo*-bromoalkylidenedeoxoartemisinin (**13a**−**d**) and the *exo*-benzylidenedeoxoartemisinin (**13e**) can be synthesized from the corresponding 10-alkane (**11a**−**d**) and phenylmethanesulfonyldihydroartemisinin (**11e**) by a modified Ramberg−Bäcklund rearrangement. From the preliminarly antimalarial and antitumoral study as well as other synthetic applications of the *exo*-olefinated derivatives, we have obtained interesting results which will be reported elsewhere.

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Experimental Section

Typical Procedure for *exo*-Olefination by Ramberg−Bäcklund Rearrangment. 10α-Ethanesulfonyldihydroartemisinin (**11b**, 220 mg, 0.61 mmol) was added to a stirred suspension of alumina-supported potassium hydroxide (KOH/Al_2O_3, 3.80 g)[19] in CH_2Cl_2 (45 mL) and *tert*-butyl alcohol (9 mL) at 5 °C under nitrogen atmosphere. Dibromodifluoromethane (CF_2Br_2, 0.73 mL, 7.7 mmol) was then added dropwise through a syringe for 5 min with additional stirring for 1 h at room temperature. After the reaction was complete, the excess solid reagent (KOH/Al_2O_3) was removed by suction filtration through a pad of Celite. The filter residue was washed thoroughly with dichloromethane, and the combined filtrates were concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give 10-(1-bromoethylidene)-deoxoartemisinin (**13b**) as 76% yield.

***E*-13b:** white crystal; mp 104−105 °C; $[\alpha]^{20}_D$ −88.2 (*c* = 0.034, $CHCl_3$); IR (KBr pellet) ν_{max} 2949, 2924, 2872, 1634, 1453, 1382, 1096, 1022, 990 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ5.57 (1H, s, H-12), 3.33 (1H, m, *J* = 7.7 Hz, H-9), 2.29 (3H, s, H-18), 1.36 (3H, s, H-14), 1.13 (3H, d, *J* = 7.3 Hz, H-16), 0.97 (3H, d, *J* = 6.0 Hz, H-15) ppm; ^{13}C NMR (75 MHz; $CDCl_3$) δ150.0, 106.5, 102.9, 93.1, 81.2, 50.4, 42.8, 37.6, 36.1, 34.2, 25.5, 25.0, 24.2, 21.7, 19.8, 14.5 ppm; GC/MSD (*m*/*z*) retention time 20.69 (min) 374 (M^+ + 1), 345, 328, 301, 265, 247 (100). Anal. Calcd for $C_{17}H_{25}BrO_4$: C, 54.70; H, 6.75. Found: C, 54.71; H, 6.70.

***Z*-13b:** white crystal; mp 120−121 °C; $[\alpha]^{20}_D$ −63.5 (*c* = 0.126, $CHCl_3$); IR (KBr pellet) ν_{max} 2949, 2924, 2874, 1661, 1451, 1382, 1100, 1026, 986 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ5.57 (1H, s, H-12), 3.25 (1H, m, *J* = 7.5 Hz, H-9), 2.32 (1H, td, *J* = 13.9, 3.8 Hz, H-4α), 2.28 (3H, s, H-18), 1.45 (3H, s, H-14), 1.09 (3H, d, *J* = 7.5 Hz, H-16), 0.97 (3H, d, *J* = 6.0 Hz, H-15) ppm; ^{13}C NMR (75 MHz; $CDCl_3$) δ149.2, 103.4, 102.2, 92.8, 81.2, 50.5, 43.5, 37.5, 36.2, 34.1, 31.0, 25.4, 25.0, 23.8, 22.5, 19.9, 15.8 ppm; GC/MSD (*m*/*z*) retention time 21.72 (min) 374 (M^+ + 1), 345, 328, 301, 265, 247 (100). Anal. Calcd for $C_{17}H_{25}BrO_4$: C, 54.70; H, 6.75. Found: C, 54.86; H, 6.84.

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Supporting Information Available: Typical procedure for sulfonation of thioacetal dihydroartemisinin, *exo*-olefination by Ramberg−Bäcklund rearrangement, and characterization data for **11a**−**f**, **12a**−**f**, **13a**−**e**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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