

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-alkane-sulfonyldihydroartemisinin 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 antimalarial² 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 instability⁵ and toxicity⁶ 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

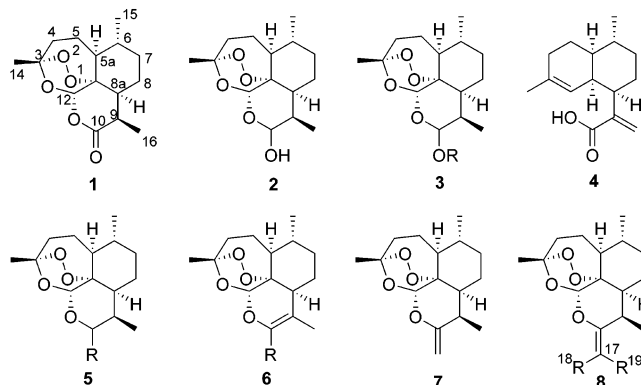


FIGURE 1. Artemisinin and its derivatives.

first synthesized by Jung et al.⁷ and then by Haynes et al.⁸ from artemisinic acid (4) (Figure 1).

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 10 α - 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 antimalarial¹² 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 glycol.¹⁴

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

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(1) Klayman, D. L. *Science* **1985**, *228*, 1049.

(2) (a) Luo, X.-D.; Shen, C.-C. *Med. Res. Rev.* **1987**, *7*, 29. (b) Jung, M. *Curr. Med. Chem.* **1994**, *1*, 35. (c) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73. (d) Vroman, J. A.; Alvim-Gaston, M.; Avery, M. A. *Curr. Pharm. Design* **1999**, *5*, 101.

(3) (a) Beekman, A. C.; Barentsen, A. R. W.; Woerdenbag, H. J.; Uden, W. V.; Pras, N.; Konings, A. W. T.; El-Ferally, F. S.; Galal, A. M.; Wikström, H. V. *J. Nat. Prod.* **1997**, *60*, 325. (b) Jung, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1091. (c) Posner, G. H.; Ploypradith, P.; Parker, M. H.; O'Dowd, H.; Woo, S.-H.; Northrop, J.; Krasavin, M.; Dolan, P.; Kensler, T. W.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 4275. (d) Li, Y.; Shan, F.; Wu, J.-M.; Wu, G.-S.; Ding, J.; Xiao, D.; Yang, W.-Y.; Atassi, G.; Léonce, S.; Caignard, D.-H.; Renard, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 5. (e) Posner, G. H.; Northrop, J.; Paik, I.-H.; Borstnik, K.; Dolan, P.; Kensler, T. W.; Xie, S.; Shapiro, T. A. *Bioorg. Med. Chem.* **2002**, *10*, 227. (f) Jung, M.; Lee, S.; Ham, J.; Lee, K.; Kim, H.; Kim, S. K. *J. Med. Chem.* **2003**, *46*, 987. (g) Posner, G. H.; Paik, I.-H.; Sur, S.; McRiner, A. J.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2003**, *46*, 1060. (h) Oh, S.; Jeong, I. H.; Shin, W.-S.; Lee, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3665.

(4) (a) Li, Y.; Yu, P.-L.; Chen, Y.-X.; Li, L.-Q.; Gai, Y.-Z.; Wang, D.-S.; Zheng, Y.-P. *Kexue Tongbao* **1979**, *24*, 667. (b) Brossi, A.; Venugopalan, B.; Gerpe, L.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645. (c) Lin, A. J.; Klayman, D. L.; Milhous, W. K. *J. Med. Chem.* **1987**, *30*, 2147.

(5) (a) Baker, J. K.; McChesney, J. D.; Chi, H. T. *Pharm. Res.* **1993**, *10*, 662. (b) Jung, M.; Lee, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1003.

(6) (a) Smith, S. L.; Fishwick, J.; McLean, W. G.; Edwards, G.; Ward, S. A. *Biochem. Pharm.* **1997**, *53*, 5. (b) Genovese, R. F.; Newman, D. B.; Brewer, T. G. *Pharmacol. Biochem. Behav.* **2000**, *67*, 37.

(7) (a) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Synlett* **1990**, 743. (b) Jung, M.; Lee, S. *Heterocycles* **1997**, *45*, 1055.

(8) Haynes, R. K.; Vonwiller, S. C. *Synlett* **1992**, 481.

(9) (a) Woo, S. H.; Parker, M. H.; Ploypradith, P.; Northrop, J.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 1533. (b) Posner, G. H.; Parker, M. H.; Northrop, J.; Elias, J. S.; Ploypradith, P.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 300.

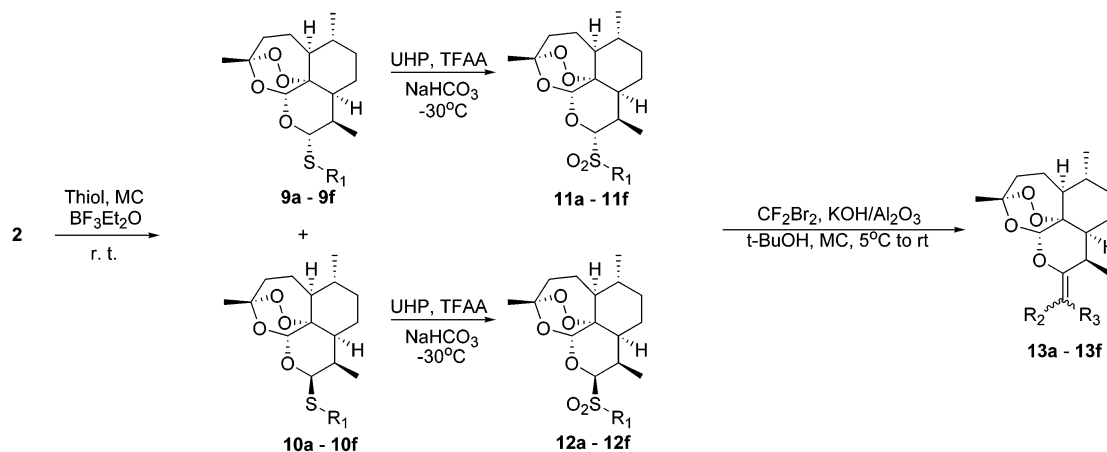
(10) (a) Pu, Y. M.; Ziffer, H. *J. Med. Chem.* **1995**, *38*, 613. (b) Ma, J.; Katz, E.; Ziffer, H. *Tetrahedron Lett.* **1999**, *40*, 8543.

(11) Lee, S.; Oh, S. *Tetrahedron Lett.* **2002**, *43*, 2891.

(12) O'Dowd, H.; Ploypradith, P.; Xie, S.; Shapiro, T. A.; Posner, G. H. *Tetrahedron* **1999**, *55*, 3625.

(13) Srivastava, R. P.; Sindelar, R. D.; McChesney, J. D. *Nat. Prod. Lett.* **1994**, *4*, 279.

(14) Lough, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.8, p 861.

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

TABLE 1. Synthesis of Thioacetal Artemisinin Derivatives from Dihydroartemisinin

	R ₁	yields ^a (%)			
		9	10	11	12
a	methyl	41	32	78	70
b	ethyl	86	6	84	86
c	<i>n</i> -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.

reactants¹⁵ in the presence of BF₃·Et₂O gave a separable mixture of major thioacetal dihydroartemisinin (**9a–f**) with a C-10 α 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 H₂O₂/urea (UHP), trifluoroacetic anhydride (TFAA), and NaHCO₃ produced 10 α -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 10 α -methanesulfonyl dihydroartemisinin (**11a**) and CF₂Br₂, and KOH/Al₂O₃ 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 10 α -

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

reactants	products	<i>E/Z</i> 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 , <i>n</i> -propyl; R ₃ , Br)	92:8	84
12c	13c (R ₂ , <i>n</i> -propyl; R ₃ , Br)	93:7	15
11d	13d (R ₂ , R ₃ , CH ₃)	<i>c</i>	26
11e	13e (R ₂ , H; R ₃ , phenyl)	70:30	78
11f	13f (R ₂ , vinyl; R ₃ , Br)	<i>d</i>	<i>d</i>

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

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 10 α -isomers (**11b** and **11c**) as previously reported.^{18b}

The stereoselectivity 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 10 α -*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 bromo-alkenylidene analogues (**13a**, **13b**, and **13c**) were expected to have potential synthetic utilities and might be

(15) Methanthiol was not useful as thiol reactant for **9a** and **10a**, so methyl disulfide was used.; Li, P.; Sun, L.; Landry, D. W.; Zhao, K. *Carbohydr. Res.* **1995**, *275*, 179.

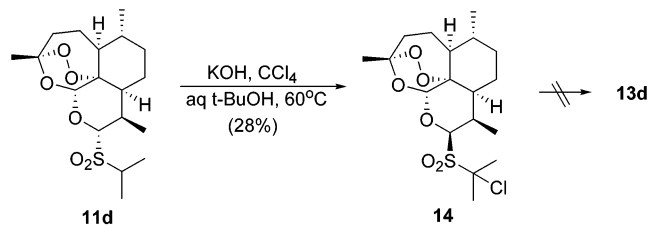
(16) Venugopalan, B.; Karnik, P. J.; Bapat, C. P.; Chatterjee, D. K.; Iyer, N.; Lepcha, D. *Eur. J. Med. Chem.* **1995**, *30*, 697.

(17) Pu, Y. M.; Ziffer, H. *J. Med. Chem.* **1995**, *38*, 613.

(18) (a) Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189. (b) Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299.

(19) Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C. D. *Chem. Commun.* **1994**, 1771.

(20) (a) Murphy, P. V.; McDonnell, C.; Hämig, L.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron: Asymmetry* **2003**, *14*, 79. (b) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8179. (c) Alcaraz, M.-L.; Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183.

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


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

Second, in the case of the secondary alkane-substituted sulfonyl dihydroartemisinin (**11d**), 10-isopropylidene deoxyartemisinin (**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 10 α -phenylmethanesulfonyldihydroartemisinin (**11e**) with an aromatic sulfonyl group gave separable *E*- and *Z*-isomers of the 10-benzylidenedeoxyartemisinin (**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 deoxyartemisinin (**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*-bromoalkylidenedeoxyartemisinin (**13a–d**) and the *exo*-benzylidenedeoxyartemisinin (**13e**) can be synthesized from the corresponding 10-alkane (**11a–d**) and phenylmethanesulfonyldihydroartemisinin (**11e**) by a modified Ramberg–Bäcklund rearrangement. From the

preliminary 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.

Experimental Section

Typical Procedure for *exo*-Olefination by Ramberg–Bäcklund Rearrangement. 10 α -Ethanesulfonyldihydroartemisinin (**11b**, 220 mg, 0.61 mmol) was added to a stirred suspension of alumina-supported potassium hydroxide (KOH/Al₂O₃, 3.80 g)¹⁹ in CH₂Cl₂ (45 mL) and *tert*-butyl alcohol (9 mL) at 5 °C under nitrogen atmosphere. Dibromodifluoromethane (CF₂Br₂, 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/Al₂O₃) 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)-deoxyartemisinin (**13b**) as 76% yield.

E-13b: white crystal; mp 104–105 °C; [α]_D²⁰ –88.2 (*c* = 0.034, CHCl₃); IR (KBr pellet) ν_{max} 2949, 2924, 2872, 1634, 1453, 1382, 1096, 1022, 990 cm⁻¹; ¹H NMR (300 MHz; CDCl₃) δ 5.57 (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; ¹³C NMR (75 MHz; CDCl₃) δ 150.0, 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 C₁₇H₂₅BrO₄: C, 54.70; H, 6.75. Found: C, 54.71; H, 6.70.

Z-13b: white crystal; mp 120–121 °C; [α]_D²⁰ –63.5 (*c* = 0.126, CHCl₃); IR (KBr pellet) ν_{max} 2949, 2924, 2874, 1661, 1451, 1382, 1100, 1026, 986 cm⁻¹; ¹H NMR (300 MHz; CDCl₃) δ 5.57 (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-4 α), 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; ¹³C NMR (75 MHz; CDCl₃) δ 149.2, 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 C₁₇H₂₅BrO₄: 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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(21) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.