Pergamon

Tetrahedron Letters 43 (2002) 2891–2894

TETRAHEDRON LETTERS

A simple synthesis of C-10 substituted deoxoartemisinin and 9-*epi*-deoxoartemisinin with various organozinc reagents†

Seokjoon Lee[a,*] and Sangtae Oh[b]

[a]*Department of Premedical Science, College of Medicine, Kwandong University, Gangnung 210-701, South Korea*
[b]*Department of Chemistry, Yonsei University, Wonju 220-710, South Korea*

Received 4 February 2002; revised 5 March 2002; accepted 7 March 2002

Abstract—A direct substitution reaction of 10α- or 10β-benzenesulfonyl dihydroartemisinin, prepared from dihydroartemisinin with thiophenol in the presence of BF_3Et_2O and consecutive oxidation with H_2O_2/urea complex, with organozinc reagents derived from allyl, benzyl, phenyl, vinyl and *n*-butyl Grignard reagents stereoselectively produced C-10 substituted deoxoartemisinins in good to moderate yields. The same reaction of 10β-benzenesulfonyl-9-*epi*-dihydroartemisinin gave corresponding 9-*epi*-deoxoartemisinin derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

The natural sesquiterpene endoperoxide artemisinin **1**, isolated from *Artemisia annua* L.,[1] has become a leading compound in the development for fast action, low toxicity and high activity against drug resistant malaria[2] and antitumor agents.[3] From the course of the research to discover new generation antimalarial drugs, semi-synthetic acetal-type artemisinin derivatives **3**, ether and ester derivatives of trioxane lactol dihydroartemisinin **2**, are now widely used to treat patients in many parts of the world.[4] Because of the presence of unstable acetal groups at the C-10 position of all acetal derivatives[5] and some toxicity of dihydroartemisinin,[6] Jung[7] and other researchers[8] reported the semi-synthetic methods of nonacetal-type artemisinin derivatives **4**, 10-alkyl or aryl substituted deoxoartemisin, from artemisinic acid as a starting material, other constituent of *A. annua* L. Since Jung and Lee reported that nonacetal-type derivatives are 15–22 times more stable than those acetal-type derivatives in simulated stomach acid, it is very important to economically synthesize nonacetal-type artemisinin analogues.[9] In my opinion, it is the most effective and economic method to form C-10 substituted derivatives **4** that adequate reactive carbanion reagents replace the oxygen of C-10 position in artemisinin or dihydroartemisinin.

The C-10 position of dihydroartemisinin, cyclic hemiacetal, can be regarded as a sugar-anomeric center to give a carbon–carbon glycoside bond. Based on the idea, Posner et al. reported a simple semi-synthetic method for the direct conversion of the dihydroartemisinin to nonacetal analogues via 10β-artemisinyl fluoride, electrophilic glycoside donor, with various aromatic, heteroaromatic and acetylide reagents.[10] Ziffer et al. also reported the reaction of dihydroartemisinin acetate with several enol ethers in the presence of $TiCl_4$ for C-10

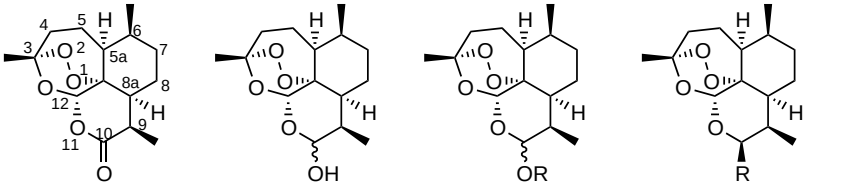


Figure 1.

* Corresponding author. Tel.: +82-33-649-7454; fax: +82-33-641-1074; e-mail: sjlee@mail.kwandong.ac.kr

† Dedicated to professor Byoung Hee Youn on his honorable retirement.

PII: S0040-4039(02)00458-6

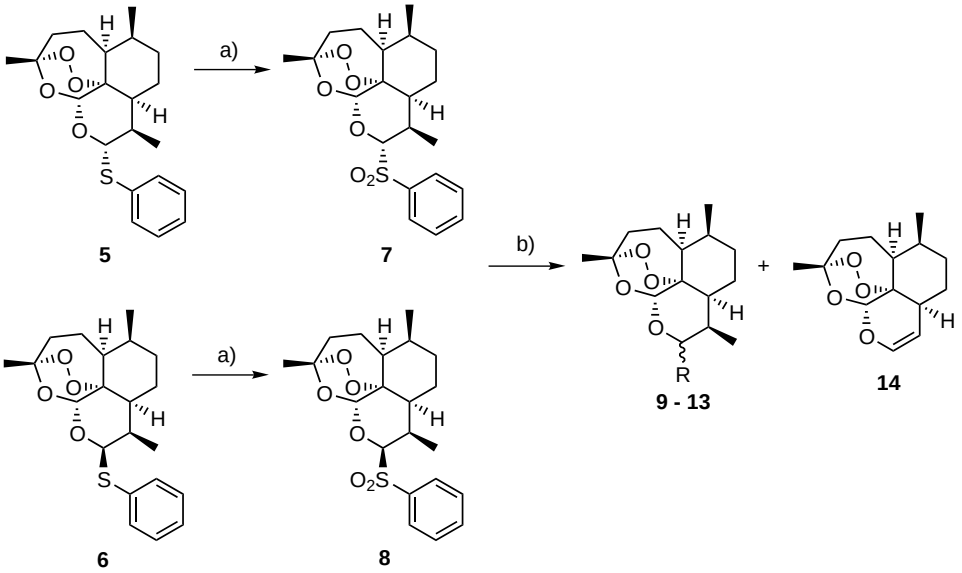
substituted deoxoartemisinin.[11] Unfortunately, those were not general reactions that could be applied to all functional group, for example, allyl, benzyl, phenyl, vinyl and *n*-alkyl groups (Fig. 1).

Therefore, it is very important to transform dihydroartemisinin as a suitable electrophilic glycoside donor with wide application and simplification and to select effective nucleophilic carbanion reagents. We have thought that 10-benzenesulfonyldihydroartemisinins **7** and **8** are the attractive intermediates for the formation of a carbon–carbon bond at the C-10 position of dihydroartemisinin, the benzenesulfonyl group of which functions as a leaving group for direct nucleophilic displacements.

Ley et al. reported the synthesis of benzenesulfonyl pyran from lactol and its analogues with benzenesulfinic acid and the direct substitution of sulfone moiety using a variety of carbon nucleophiles, especially organozinc reagents derived from aryl, vinyl and alkynyl Grignard reagents with $ZnBr_2$ or $ZnCl_2$.[12]

As seen in Scheme 1, direct oxidation of separated diastereomer, 10-phenylthiodihydroartemisinins **5** and **6**, generated from dihydroartemisinin **2** with thiophenol in the presence of BF_3Et_2O as a previously reported method,[13] with H_2O_2/urea complex (UHP), trifluoroacetic anhydride (TFAA) and $NaHCO_3$[14] produced 10α- and 10β-benzenesulfonyldihydroartemisinins **7** and **8**, important intermediates for direct substitution, in good yields.[15]

We have generated in situ the allylzinc chloride reagent from allylmagnesium bromide with $ZnCl_2$ in CH_2Cl_2 at room temperature under a N_2 atmosphere and then added 10α-benzenesulfonyldihydroartemisinin **7** through a double ended needle to produce 10-allyldeoxoartemisinin **9a** and its minor 10α-diastereomer **9b** in 84% yield (2:1 ratio), and anhydrodihydroartemisinin **14** with trace amounts, structures of which were confirmed by comparison with Haynes and Vonwiller's published result.[8] Except in the case of allylic substitution, the other products were synthesized as only β-isomer with each reagent in good to moderate yields, and with the same method we have also concluded the stereochemistry of compounds **10**, **11** and **13**, as listed in Table 1. 10-Vinyldeoxoartemisinin **12**, unreported product, was assigned as a β-stereochemistry with its chemical shift (4.53 ppm) observed for H-10 and small coupling constant (J= 6.03, 3.48 Hz) for H-9 and H-10 which is indicative of a *cis* relationship between these two protons.[7,11]

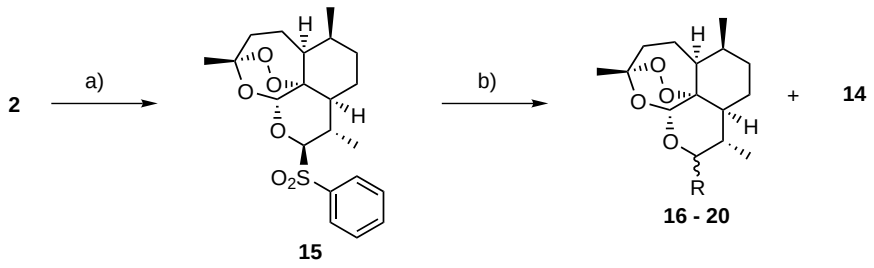


Scheme 1. *Reagents and conditions*: (a) UHP (3 equiv.), TFAA (3 equiv.), $NaHCO_3$ (5 equiv.), CH_3CN, −30°C (95% for **7** and 93% for **8**); (b) RMgBr (2 equiv.), $ZnCl_2$ (1.2 equiv.), CH_2Cl_2, rt.

Table 1. Direct substitution of sulfone intermediates **7** and **8** with various organozinc reagents

Reactant	R (compound no.)	C-10 stereochemistry	Yield (%)[a]	Ref.
7	Allyl (β: **9a**, α: **9b**)	β:α = 2:1	84	8
8	Allyl (β: **9a**, α: **9b**)	β:α = 2:1	78	8
7	Benzyl (**10**)	β	69	7b
7	Phenyl (**11**)	β	91	8
7	Vinyl (**12**)	β	73	
7	*n*-Butyl (**13**)	β	48	7a

[a] Isolated but not optimized.



Scheme 2. *Reagents and conditions*: (a) Benzenesulfinic acid (2 equiv.), BF_3Et_2O (1 equiv.), MC, rt (75%); (b) RMgBr (2 equiv.), $ZnCl_2$ (1.2 equiv.), CH_2Cl_2, rt.

The known dihydroartemisinin **2** with benzenesulfinic acid in the presence of BF_3Et_2O was directly converted to 10β-benzenesulfonyl-9-*epi*-dihydroartemisinin **15**, the intermediate for 9-*epi*-deoxoartemisinin derivatives, in more improved yield (75%), which had been prepared from artemisinin **1** via anhydrodihydroartemisinin **14** in three steps and 31% yield by Posner et al.[16] The stereochemistry of 9-*epi*-intermediate **15** synthesized in this reaction was determined by ^1H and ^{13}C NMR of 9-*epi*-artemisinin series as reported by Bégué et al.[17] and comparison with its diastereomeric sulfone intermediates **7** and **8**. The chemical shift of H-10 and 16-methyl carbon at C-9 in **7** having natural stereochemistry appeared at 4.41 ppm ($J=10.98$ Hz) and 14.0 ppm, while its epimer **15** appeared at 5.13 ppm ($J=10.24$ Hz) and 20.0 ppm, respectively, which signals indicate all *trans* configuration and a diastereomeric relationship between the sulfonyl group and 16-methyl at C-9 in **7** and **15** (Scheme 2).

Next, when the same substitution reactions with 9-*epi*-sulfone **15** with typical method depicted in Scheme 1 were carried out, similar results were obtained and are given in Table 2. Thus, the reaction with allyl reagent afforded a diastereomeric mixture in 71% yield as an 8:1 ratio of 10β-allyl-9-*epi*-deoxoartemisinin **16a** and 10α-diastereomer **16b**, while other reagents gave only 10β isomers **17**–**20**. The stereochemistry of all compounds listed in Table 2 has been confirmed by comparison of each related compounds **9**–**13** in Table 1. For example, the chemical shifts, 4.88 ppm ($J=10.70$ Hz) for H-10 and 20.2 ppm for C-16, of 10β-benzyl-9-*epi*-deoxoartemisinin **17**[18] in contrast with the 5.70 ppm ($J=6.78$ Hz) and 12.7 ppm of 10β-benzyldeoxoartemisinin **10**,[7b] respectively, signified that the benzyl group was β position and C-9 methyl was α, so those groups were in a *trans* relationship.

Based on the results in Tables 1 and 2, the direction of carbon nucleophile entering to form C–C bond at C-10 position nearly depended on the steric hinderance of *endo* peroxide bridge, not stereochemistry of C-9 methyl in related derivatives, which caused by S_N1 mechanism.

In conclusion, the simple and versatile method for forming C-10 substituted deoxoartemisinin was developed by the direct nucleophilic substitution of 10α-, 10β-benzenesulfonyldihydroartemisinin **7**, **8** and 9-*epi*-sulfone **15** with various organozinc reagents. Especially, this is a useful method beyond comparison with early reported methods by the fact that the direct synthesis method has been applied to benzyl, phenyl, vinyl and *n*-butyl as well as allyl group. Syntheses of the new kinds of the derivatives of deoxoartemisinin and biological activity due to stereochemistry are currently under investigation.

Table 2. Direct substitution of sulfone intermediate **15** with various organozinc reagents

Reactant	R (compound no.)	C-10 stereochemistry	Yield (%)[a]
15	Allyl (β: **16a**, α: **16b**)	β:α=8:1	71
15	Benzyl (**17**)	β	65
15	Phenyl (**18**)	β	88
15	Vinyl (**19**)	β	75
15	*n*-Butyl (**20**)	β	42

[a] Isolated but not optimized.

Acknowledgements

We are grateful for financial support from Korea Research Foundation Grant (KRF-99-003-D00141) and Professor Young-Soo Kyoung in Kangnung National University for instrumental support.

References

1. Klayman, D. L. *Science* **1985**, *228*, 1049–1055.
2. (a) Luo, X.-D.; Shen, C.-C. *Med. Res. Rev*. **1987**, *7*, 29–52; (b) Jung, M. *Curr. Med. Chem*. **1994**, *1*, 35–49; (c) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res*. **1997**, *30*, 73–79; (d) Vroman, J. A.; Alvim-Gaston, M.; Avery, M. A. *Curr. Pharm. Design* **1999**, *5*, 101–138.
3. (a) Beekman, A. C.; Barentsen, A. R. W.; Woerdenbag, H. J.; Uden, W. V.; Pras, N.; Konings, A. W. T.; El-Feraly, F. S.; Galal, A. M.; Wikström, H. V. *J. Nat. Prod*. **1997**, *60*, 325–330; (b) Jung, M. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 1091–1094; (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*, 4275–4280; (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*, 5–8; (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*, 227–232.

4. 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*, 645–650.
5. Baker, J. K.; McChesney, J. D.; Chi, H. T. *Pharm. Res.* **1993**, *10*, 662–668.
6. Smith, S. L.; Fishwick, J.; McLean, W. G.; Edwards, G.; Ward, S. A. *Biochem. Pharmacol.* **1997**, *53*, 5–10.
7. (a) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Synlett* **1990**, 743–744; (b) Jung, M.; Lee, S. *Heterocycles* **1997**, *45*, 1055–1058.
8. Haynes, R. K.; Vonwiller, S. C. *Synlett* **1992**, 481–483.
9. Jung, M.; Lee, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1003–1006.
10. (a) Woo, S. H.; Parker, M. H.; Ploypradith, P.; Northrop, J.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 1533–1536; (b) Posner, G. H.; Parker, M. H.; Northrop, J.; Elias, J. S.; Ploypradith, P.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 300–304.
11. (a) Pu, Y. M.; Ziffer, H. *J. Med. Chem.* **1995**, *38*, 613–616; (b) Ma, J.; Katz, E.; Ziffer, H. *Tetrahedron Lett.* **1999**, *40*, 8543–8545.
12. Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293–4308.
13. Venugopalan, B.; Karnik, P. J.; Bapat, C. P.; Chatterjee, D. K.; Iyer, N.; Lepcha, D. *Eur. J. Med. Chem.* **1995**, *30*, 697–706.
14. (a) Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189–191; (b) Caron, S.; Do, N. M.; Sieser, J. E. *Tetrahedron Lett.* **2000**, *41*, 2299–2302.
15. Spectral data for **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (2H, d, $J=7.89$ Hz, Ph), 7.63 (1H, t, $J=7.14$ Hz, Ph), 7.50 (2H, t, $J=7.89$ Hz, Ph), 5.26 (1H, s, H-12), 4.42 (1H, d, $J=10.98$ Hz, H-10), 2.42 (1H, m), 2.26 (1H, td, $J=14.46$, 4.02 Hz), 1.35 (3H, s, 3-CH_3), 1.12 (3H, d, $J=6.96$ Hz, 9-CH_3), 0.90 (3H, d, $J=6.03$ Hz, 6-CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 133.8, 130.0, 128.4, 104.3, 91.9, 90.7, 79.6, 51.2, 46.5, 37.3, 35.9, 33.9, 28.3, 25.6, 24.6, 21.3, 20.0, 14.0 ppm. For **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (2H, d, $J=6.87$ Hz, Ph), 7.60 (1H, t, $J=7.23$ Hz, Ph), 7.52 (2H, t, $J=7.50$ Hz, Ph), 5.98 (1H, s, H-12), 5.01 (1H, d, $J=6.27$ Hz, H-10), 3.17 (1H, m), 2.28 (1H, td, $J=14.37$, 3.87 Hz), 1.35 (3H, d, $J=7.68$ Hz, 9-CH_3), 1.18 (3H, s, 3-CH_3), 0.94 (3H, d, $J=4.50$ Hz, 6-CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 129.1, 128.8, 128.7, 103.8, 92.0, 90.3, 80.9, 52.1, 43.8, 37.0, 36.1, 34.1, 31.6, 25.5, 24.5, 23.4, 20.1, 13.2 ppm.
16. Posner, G. H.; Maxwell, J. P.; O'Dowd, H.; Krasavin, M.; Xie, S.; Shapiro, T. A. *Bioorg. Med. Chem.* **2000**, *8*, 1361–1370.
17. (a) Chorki, F.; Crousse, B.; Bonnet-Deipon, D.; Bégué, J. P.; Brigaud, T.; Portella, C. *Tetrahedron Lett.* **2001**, *42*, 1487–1489; (b) Chorki, F.; Grellepois, F.; Crousse, B.; Ourévitch, M.; Bonnet-Deipon, D.; Bégué, J. P. *J. Org. Chem.* **2001**, *66*, 7858–7863.
18. Spectral data for **17**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.14 (5H, m, Ph), 5.40 (1H, s, H-12), 4.49 (1H, td, $J=10.70$, 2.49 Hz, H-10), 3.02 (1H, dd, $J=15.12$, 2.42 Hz, benzyl), 2.68 (1H, dd, $J=15.15$, 8.60 Hz, benzyl), 1.32 (3H, s, 3-CH_3), 1.08 (3H, d, $J=6.87$ Hz, 9-CH_3), 0.93 (3H, d, $J=5.68$ Hz, 6-CH_3) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 139.8, 129.5, 128.3, 126.2, 102.3, 91.0, 82.5, 75.3, 51.9, 47.8, 41.0, 40.4, 37.7, 36.9, 34.6, 32.3, 26.0, 25.2, 20.5, 20.3 ppm.