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A one-pot conversion of artemisinin to its ether derivatives†

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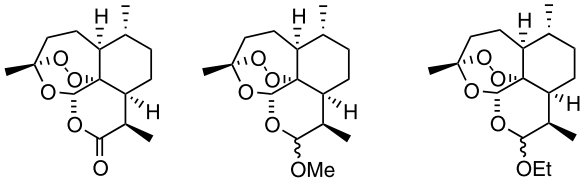
Abstract—A one-pot preparation of artemether, arteether and related antimalarial compounds from artemisinin, using $NaBH_4$/Amberlyst-15, is reported.

Artemisinin **1** is the active principle of the Chinese traditional antimalarial drug *Artemisia annua*.[1] Its semi synthetic derivatives, such as artemether **3** and arteether **4** are effective against both chloroquine sensitive and chloroquine resistant *P. falciparum* and are clinically used for the treatment of cerebral malaria.[2]

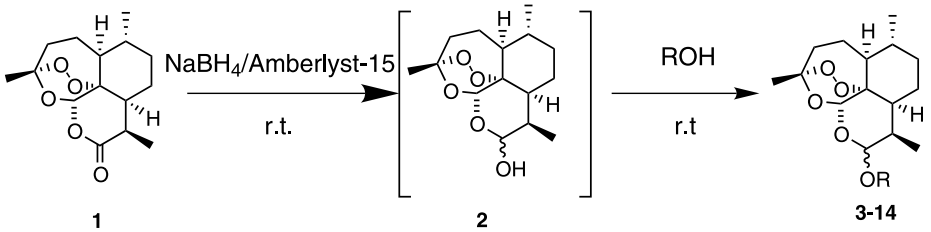


1 **3** **4**

Compounds **3**, **4** and related ether derivatives are currently prepared in two steps. In the first step artemisinin is reduced with $NaBH_4$ in MeOH to furnish dihydroartemisinin **2**.[3] This step suffers from two major drawbacks: (i) the reaction conditions are highly basic which leads to rapid degradation of artemisinin and dihydroartemisinin, if stringent low temperature conditions (~0°C) are not maintained, and (ii) $NaBH_4$ reacts exothermically with MeOH, therefore, great care has to be exercised during the addition of $NaBH_4$. Further, this step requires extensive drying of dihydroartemisinin as only moisture free dihydroartemisinin can be used in the next step.

In the second step, dihydroartemisinin is reacted with an appropriate alcohol in the presence of an acid catalyst such as $BF_3{\cdot}Et_2O$, HCl, Me_3SiCl or PTSA.[4–7] This step again requires aqueous work-up. Thus, the conversion of artemisinin to its ether derivatives requires two independent steps, both of which require aqueous work-up.

Herein, we report an improved one-pot conversion of artemisinin to its ether derivatives, which does not suffer from the above drawbacks. The process consists of reduction of artemisinin with the $NaBH_4$/Amberlyst-15 combination to dihydroartemisinin and its in situ conversion to the desired ether derivative by the addition of an appropriate alcohol. The product is isolated by removal of the resin by filtration, concentration of the filtrate and column chromatography of the crude product. As the process does not require any aqueous work-up and is conducted in a single pot, it is well suited for the industrial synthesis of the ether derivatives of artemisinin.



1 **2** **3-14**

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Table 1.

Compd	R	Reaction solvent[a]	Reaction time (h)	Yield (%)
3	CH_3	THF	72	80
3	CH_3	CH_2Cl_2	24	77
3	CH_3	C_6H_6	24	80
4	CH_2CH_3	CH_2Cl_2	72	55
5	$CH_2CH_2CH_3$	CH_2Cl_2	72	79
6	$CH_2(CH_2)_3CH_3$	CH_2Cl_2	56	74
7	$CH_2CH{=}CH_2$	CH_2Cl_2	4	65
8	CH_2CH_2OH	CH_2Cl_2	31	70
9	$CH_2(CH_2)_2CH_2OH$	CH_2Cl_2	55	73
10	$CH_2(CH_2)_6CH_2OH$	CH_2Cl_2	32	70
11	$CH_2(CH_2)_8CH_2OH$	CH_2Cl_2	25	53
12	$CH_2(CH_2)_{10}CH_2OH$	CH_2Cl_2	8	60
13	$CH_2(CH_2)_{14}CH_3$	CH_2Cl_2	7	56
14	p-$CH_2C_6H_4$-$COOCH_3$	CH_2Cl_2	18	49

[a] After reduction in THF, THF was removed under reduced pressure and replaced with CH_2Cl_2 or C_6H_6.

In a typical experiment, $NaBH_4$ (0.1 g) was added over 5 min to a stirred mixture of artemisinin (0.2 g) and Amberlyst-15 (1.0 g) in THF (20 ml) and the reaction was stirred at room temperature for 30 min. MeOH (2 ml) was added and the reaction mixture was stirred at rt for a further 72 h. The resin was removed by filtration, the filtrate was concentrated and the crude product chromatographed to give 0.17 g (80% yield) of artemether as a mixture of α- and β-isomers isolated in the ratio[8] 1:3. The etherification step was faster when after the reduction step, THF was removed under reduced pressure and replaced by CH_2Cl_2 or benzene. Several ethers were prepared using this procedure in 53–82% yields (Table 1).[9,11]

Alternatively, the reaction can be stopped after the reduction step. In this case, simple filtration followed by the concentration of the filtrate and chromatographic purification of the crude product furnishes dihydroartemisinin in acceptable yields. The reaction was very slow when Amberlite 120 instead of Amberlyst-15 was used. Of the several solvents used (THF, DME, 1,4-dioxan, etc.), THF gave the best results. The resin could be recovered, regenerated and reused without loss of activity.

Thus, we have developed a one-pot process suitable for the industrial synthesis of ether derivatives of dihydroartemisinin. Absence of aqueous work-up and recycling of the acid catalyst are special features of the process.

Acknowledgements

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8. Ratio of α- and β-isomers was calculated on the basis of ^{1}H NMR.
9. Preparation of compounds **5**–**6** and **9**–**14** has been reported earlier.[1b,10]
10. Kanchan, R. Ph.D. Thesis, Poorvanchal University, Jaunpur, India, 1999.
11. Selected spectral data: α-Artemether **3** [^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (d, 3H, $J=7.1$ Hz, CH_3), 0.96 (d, 3H, $J=5.6$ Hz, CH_3), 1.45 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 4.35 (d, 1H, $J=9.2$ Hz, C-10), 5.30 (s, 1H, C-12); FABMS: m/z 299 (M^++H), 267 (M^+–OCH_3)] and β-artemether **3** [^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, 3H, $J=7.2$ Hz, CH_3), 0.95 (d, 3H, $J=6$ Hz, CH_3), 1.44 (s, 3H, CH_3), 3.42 (s, 3H, OCH_3), 4.67 (d, 1H, $J=3.3$ Hz, C-10), 5.38 (s, 1H, C-12); FABMS: m/z 299 (M^++H), 267 (M^+–OCH_3)].
α-Hydroxy ethyl ether derivative of dihydroartemisinin **8** [^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (d, 3H, $J=7.2$ Hz, CH_3), 0.96 (d, 3H, $J=5.7$ Hz, CH_3), 1.42 (s, 3H, CH_3), 3.74 (m, 2H), 3.85 (m, 2H), 4.47 (d, 1H, $J=9.2$ Hz, C-10), 5.37 (s, 1H, C-12); FABMS: m/z 329 (M^++H), 311 (M^+–OH), 267 (M^+–OCH_2CH_2OH)] and β-hydroxy ethyl

ether derivative of dihydroartemisinin **8** [^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, 3H, $J=7.6$ Hz, CH_3), 0.95 (d, 3H, $J=5.7$ Hz, CH_3), 1.43 (s, 3H, CH_3), 3.73 (m, 4H, $OC\underline{H}_2C\underline{H}_2OH$), 4.84 (d, 1H, $J=3.3$ Hz, C-10), 5.44 (s, 1H, C-12); FABMS: m/z 329 (M^++H), 311 (M^+–OH), 267 (M^+–OCH_2CH_2OH)].

α-*p*-Carbomethoxy benzyl ether derivative of dihydroartemisinin **14** [^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (d, 3H, $J=7$ Hz, CH_3), 0.98 (d, 3H, $J=7.9$ Hz, CH_3), 1.46 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.51(d, 1H, $J=9.3$ Hz, C-10), 4.68 (d, 1H, $J=13.3$ Hz, $-OC\underline{H}_2C_6H_4COOCH_3$), 5.03 (d, 1H, $J=13.3$ Hz, $-OC\underline{H}_2C_6H_4COOCH_3$), 5.34 (s, 1H, C-12) 7.43 and 8.00 (2×d, 2×2H, $J=8.3$ Hz, aromatic protons); FABMS: m/z 433 (M^++H), 267 (M^+–$OC\underline{H}_2C_6H_4COOCH_3$)] and β-*p*-carbomethoxy benzyl ether derivative of dihydroartemisinin **14** [^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (d, 3H, $J=7$ Hz, CH_3), 0.97 (d, 3H, $J=4.4$ Hz, CH_3), 1.45 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.57(d, 1H, $J=13.3$ Hz, $-OC\underline{H}_2C_6H_4COOCH_3$), 4.91 (d, 1H, $J=3.3$ Hz, C-10), 4.95 (d, 1H, $J=13.3$ Hz, $-OC\underline{H}_2C_6H_4COOCH_3$), 5.45 (s, 1H, C-12), 7.38 and 7.97 (2×d, 2×2H, $J=8.3$ Hz, aromatic protons); FABMS: m/z 433 (M^++H), 267 (M^+–$OC\underline{H}_2C_6H_4COOCH_3$)].