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# Semi-synthesis of deoxyartemisinin

**Asish K. Bhattacharya,*[a,b] Ashish K. Pathak[b,c] and Ram P. Sharma[b]**

[a] *Combi Chem-Bio Resource Centre and Division of Organic Chemistry: Synthesis, National Chemical Laboratory, Pune-411 008, India. Fax: +91 20 2589 3153; e-mail: ak.bhattacharya@ncl.res.in*
[b] *Phytochemical Technology Division, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow-226 015 (UP), India*
[c] *Southern Research Institute, P.O. Box 55305, Birmingham, AL 35255-5305, USA*

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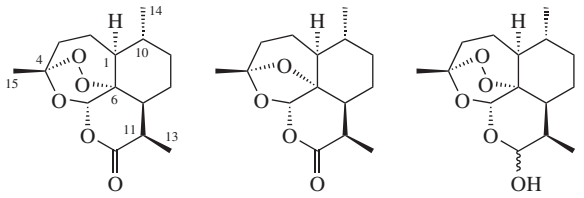
**The reaction of artemisinin with aluminium–nickel chloride hexahydrate in THF or nickel boride in MeOH furnishes deoxyartemisinin in an excellent yield.**

Artemisinin **1**, a unique sesquiterpene lactone endoperoxide isolated from the Chinese plant *Artemisia annua*, and a number of its semi-synthetic derivatives (*e.g.*, arteether, artemether and sodium artesunate) possess antimalarial properties and are clinically used in several countries.[1,2] They are effective against *Plasmodium* parasites, which are resistant to the newest and commonly used antimalarial drugs.[3] Interestingly, deoxyartemisinin **2** is naturally occurring in the plant *A. annua*,[4] albeit in low yield, and is the major metabolite isolated from the urine of patients treated with artemisinin **1**.[5] Total synthesis of deoxyartemisinin **2** has been reported by Zhou *et al.*[6,7] Deoxyartemisinin **2** and the dimer of dihydrodeoxyartemisinin have shown cytotoxicity to cloned murine Ehrlich ascites tumour (EAT) cells (MTT assay, $IC_{50}$ 70 μM) and against murine bone marrow using a clonogenic assay for committed progenitor cells of the granulocyte–monocyte linkage (CFU-GM assay, $IC_{50}$ 4.8 μM).[8,9]



**1** **2** **3**

The Al–$NiCl_2 \cdot 6H_2O$ reagent system selectively affects transformations of several functional groups.[10–13] However, this reagent system has not been employed on artemisinin **1**. In continuation of our studies[14–16] with metal–metal salt reduction and also to devise a cheap method for the reduction of artemisinin **1** to dihydroartemisinin **3**, which is several fold[1,2] more active than **1**, the reaction of **1** with Al–$NiCl_2 \cdot 6H_2O$ in THF was studied. One major product was obtained (96% yield) as a solid.† On the basis of spectral data[6,7] and co-TLC with an authentic sample, the product was found to be deoxyartemisinin **2**. Note that deoxyartemisinin **2** gave *m/z* 264 ($M^+ - 2$) instead of 266 ($M^+$) at 70 eV.

The reaction of artemisinin **1** with nickel boride generated *in situ* from $NaBH_4$ and $NiCl_2 \cdot 6H_2O$ in MeOH at room temperature also furnished deoxyartemisinin **2** in quantitative yield.†

In conclusion, a short semi-synthesis of **2**, which would facilitate a preparation of its other derivatives for cytotoxic studies, as well as other biological studies, is reported.

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† Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded in KBr on a Perkin Elmer 1710 FT-IR spectrophotometer. The NMR spectra were recorded on a Bruker WM-400 instrument (400 MHz) in $CDCl_3$ with TMS as an internal standard. Chemical shifts $\delta$ are expressed in ppm. Mass spectra were recorded on a JEOL JMS D-100 spectrometer. Elemental analysis was carried out on a HERAEUS CHN-O-RAPID elemental analyzer. For TLC, silica gel G (E. Merck, India) was used. Sodium borohydride was purchased from Aldrich. All the solvents were purified before use. THF was distilled over $LiAlH_4$. Hexane refers to the fraction with bp 65–70 °C. Work up reaction mixtures were dried over anhydrous $Na_2SO_4$.

*Deoxygenation of artemisinin* **1** *with Al–$NiCl_2 \cdot 6H_2O$–THF.* To a stirred solution of the substrate **1** (100 mg, 0.35 mmol) in freshly distilled THF (5 ml), Al powder (270 mg, 10 mmol) and $NiCl_2 \cdot 6H_2O$ (3.56 g, 15 mmol) were added. A vigorous exothermic reaction took place immediately, which subsided after few minutes. After completion of the reaction (TLC), the resulting mixture was diluted with THF (100 ml) and filtered. Evaporation of the dried ($Na_2SO_4$) filtrate furnished **2** as a solid, mp 110–112 °C (EtOAc–hexane, 2:8) in 96% yield; $[\alpha]_D^{25}$ –134.6° (*c*, 0.5, $CHCl_3$). IR (KBr, $\nu$/cm$^{-1}$): 1745. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$: 5.70 (s, 1H, H-5), 3.19 (m, 1H, H-11), 1.54 (s, 3H, 15-Me), 1.20 (d, 3H, 13-Me, *J* 7 Hz), 0.94 (d, 3H, 14-Me, *J* 7 Hz); MS (EI), *m/z*: 264 ($M^+ - 2$), 222, 209, 194, 43 (100). Found (%): C, 67.62; H, 8.30. Calc. for $C_{15}H_{22}O_4$ (%): C, 67.65; H, 8.33.

*Deoxygenation of* **1** *with nickel boride.* A solution of **1** (100 mg, 0.35 mmol) in dry MeOH (3 ml) was stirred at room temperature and $NiCl_2 \cdot 6H_2O$ (250 mg, 1.06 mmol) was added. To the stirred solution, $NaBH_4$ (125 mg, 3.29 mmol) was added for 15 min. After completion of the reaction (TLC), the resulting mixture was diluted with $H_2O$ (100 ml) and extracted with $CH_2Cl_2$ (3×50 ml). The dried $CH_2Cl_2$ extract was evaporated to furnish a solid (94 mg, quantitative), which was found identical to **2** in terms of mp, mix-mp, TLC, co-TLC and $^1$H NMR.[6,7]

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