Pergamon

Tetrahedron Letters 42 (2001) 3997–4000

TETRAHEDRON LETTERS

First synthesis of (+)-deoxoartemisitene and its novel C-11 derivatives

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Received 26 February 2001; revised 10 April 2001; accepted 13 April 2001

Abstract—A short, regiospecific and first synthesis of (+)-deoxoartemisitene and its novel C-11 derivatives with non-acetal at C-12 was achieved from artemisinic acid.

Artemisinin **1**, a sesquiterpene lactone endoperoxide isolated from *Artemisia annua*, and its derivatives have been important as antimalarial drugs with the most effective activity against multidrug resistant forms of *Plasmodium falciparum*.[1] To overcome low solubility, instability in acidic condition, and recently appearing neurotoxicity of artemisinin and its C-12 derivatives with acetal at C-12 such as arteether, artemether, and artelinic acid, we prepared deoxoartemisinin[2] **2** and its C-12 derivatives with non-acetal at C-12.[3] Although some C-11 derivatives of artemisinin were prepared by 1,4-conjugated addition[4] from artemisitene **3** and artemisinic acid **5** and show an effective antimalarial activity, their compounds are still acetal-type at the C-12 position, which are neurotoxic and acid unstable. However, deoxoartemisitene **4**, as a versatile intermediate, and its C-11 derivatives with non-acetal at C-12 have never been prepared. Therefore, the structure–activity relationship of C-11 derivatives of deoxoartemisitene is unknown. In this letter, we report the first synthesis of (+)-deoxoartemisitene **4** and its novel C-11 derivatives with non-acetal at C-12 from readily available artemisinic acid **5** to elucidate their structure–activity relationship and overcome the expected acid instability and neurotoxicity of the C-11 derivatives with acetal at C-12 (Fig. 1).

There are only a few oxidations and reductions known for transformation of artemisinin derivatives[2] due to the unstable endoperoxide moiety. Mild and partial reduction of methyl artemisinate **6**, prepared from artemisinic acid **5**, with DIBAL-H cleanly afforded dehydroartemisinyl alcohol **7** (82% yield). Photooxidative cyclization of the alcohol **7** with oxygen, rose bengal and irradiation, followed by in situ treatment with trifluoroacetic acid, gave deoxoartemisitene **4**[5] in 35% yield. Although the yield for the photooxidative cyclization is low, this step represents the shortest synthetic route to **4**. Deoxoartemisitene is a versatile intermediate for the preparation of a variety of C-11 derivatives of deoxoartemisinin. We found the endoperoxide of deoxoartemisitene is intact under ozonolysis, oxidations and reductions, etc. Thus, conversion of deoxoartemisitene into C-11 derivatives with non-acetal

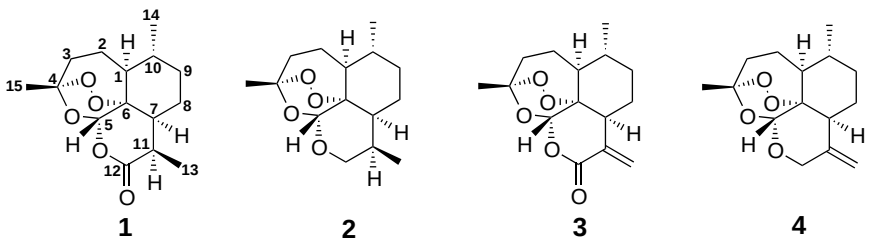

Figure 1.

Keywords: artemisinin; deoxoartemisinin; artemisitene; deoxoartemisitene.

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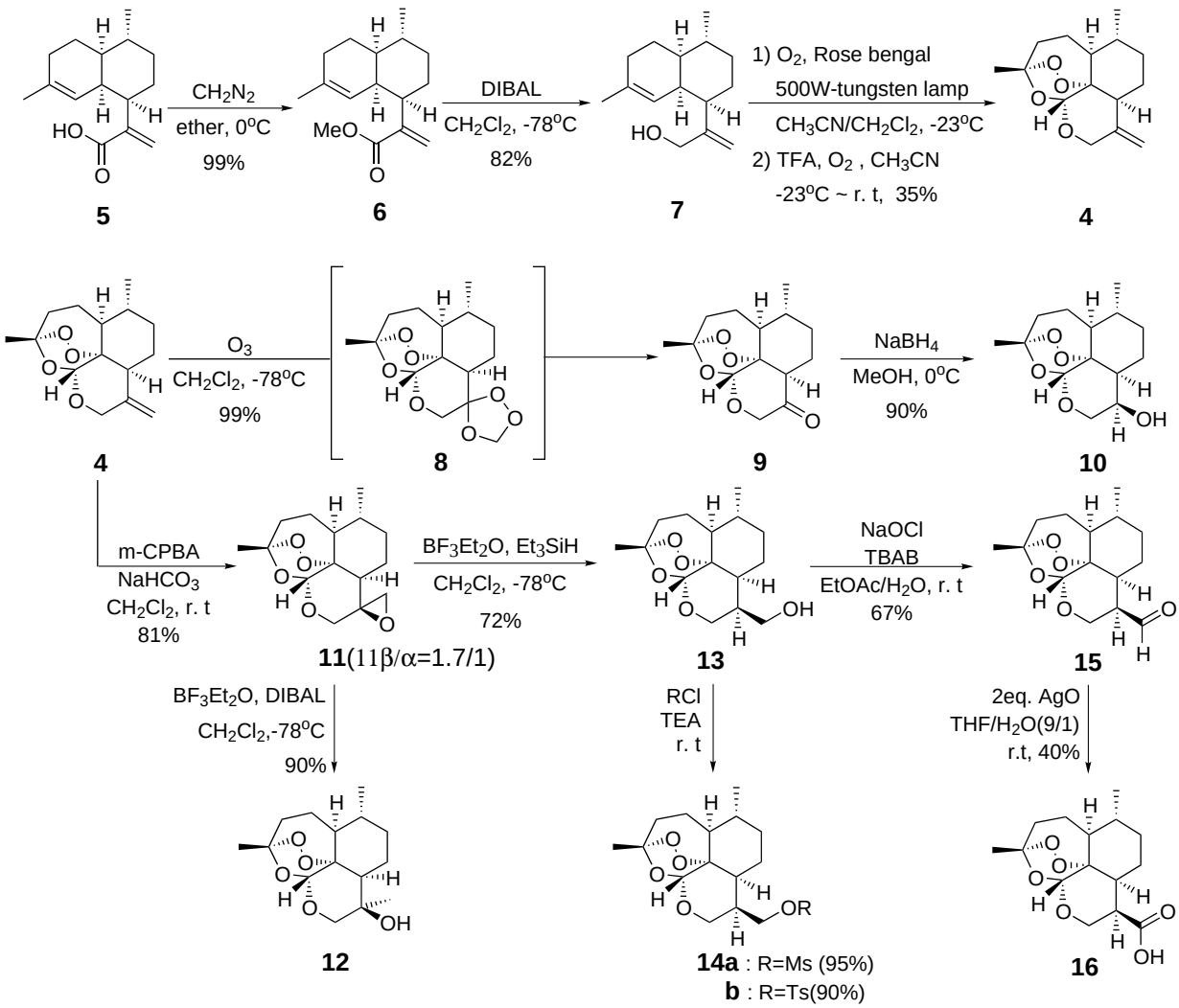
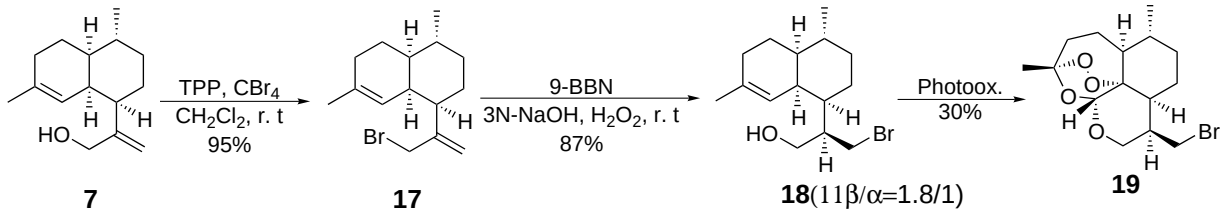
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00641-4

at C-12 was successfully carried out under suitable reaction conditions, as outlined in Scheme 1. Ozonolysis of **4** with 60% ozone afforded deoxoartemisitone **9** in 99% yield with a self-cleavage of the ozonide ring of **8** without a reducing agent. We suggest that this unusual self-cleavage is owing to the sterically hindered spiro ring strain on the ozonide ring of **8**. Reduction of **9** with sodium borohydride exclusively led to the demethyldeoxoartemisin-11-β-ol **10** in 90% yield. Direct preparation of deoxoartemisininol **13** from **4** with hydroboration using 9-BBN or catecholborane was unsuccessful.

Epoxidation of **4** with *m*-CPBA and $NaHCO_3$ gave 11(*S*)-(spiroepoxy)deoxoartemisinin **11** and its 11(*R*)-epimer in a 1.7:1 ratio and 81% yield. After many unsuccessful attempts, we found the correct ring-opening conditions of the major epoxide **11** with triethylsilane to give the primary alcohol **13** (yield 72%) and with DIBAL-H to give the tertiary alcohol **12** (yield 90%)[6] both in the presence of $BF_3{\cdot}Et_2O$, respectively. We suggest the bulkiness of the reducing agents affects the direction of the epoxide ring opening of **11**. The triethylsilane reduction represents a new method for the epoxide opening to afford a primary alcohol. Mesylation and tosylation of the alcohol **13** afforded **14a** and **14b** 95 and 90% yield, respectively. While transition-metal or strong-oxidation agents for oxidation of the alcohol **13** caused cleavage of the endoperoxide bridge of molecule, sodium hypochlorite in the presence of tetrabutylammonium bromide as phase-transfer catalyst led cleanly to the aldehyde **15** in 67% yield. In this reaction, the 11β-epimer was obtained exclusively. Further oxidation of the aldehyde **15** with silver oxide at room temperature afforded demethyldeoxoartemisininylic acid **16** in 40% yield. Similarly, the 11α-epimer of **11** was converted into the 11α-epimers of its alcohol **13** and the aldehyde **15**, respectively. Bromination of **13** to prepare **19** failed with various methods. Thus, early bromination of **7** with TPP/CBr_4, hydroboration of **17** afforded **18** and the 11α-epimer of **18** in a 1.8:1 ratio and 87% yield (Scheme 2). Similar photooxidation of **18** gave 13-bromodeoxoartemisinin **19** smoothly in 30% yield. It is noteworthy that the endoperoxide, an indispensable moiety for biological activities of deoxoartemisitene **4**, was left intact during this entire ozonolysis, reductions and oxidations.



Scheme 1.



Scheme 2.

The assignments of the ^{1}H and ^{13}C NMR signals were made on the basis of 2D-COSY and HETCOR spectra of compounds **10**–**13** and **15**–**19**. The relative configuration at the new chiral centers, C-4, 5, 6 and 11, was determined unambiguously, as depicted in **10**–**13** and **15**–**19**, by utilization of two-dimensional NOE (NOESY) techniques.[7] C-11 derivatives with non-acetal at C-12 prepared here showed more water solubility and acid stability than those of acetal-type analogs. For example, the solubility of compounds **13**, **15** and **16** in water is four times greater than that of artemisinin (0.97 mg/mL). The half-life of compounds **13**, **15**, **16**, and **19** in simulated stomach acidic conditions (pH 2.0, 37°C) is 15 times longer than that of artemisinin ($t_{1/2}$= 23.5 h).

In conclusion, our approach is highlighted by its simplicity and efficiency. We outlined the first synthesis of optically active (+)-deoxoartemisitene **4** and its novel C-11 derivatives with non-acetal at C-12 from readily available artemisinic acid. Derivatives **4**, **9**–**16** and **19** are all new compounds that are subject to in vitro biological activities and may overcome low solubility, instability and neurotoxicity of the lead compounds. We presented new reactions to furnish some C-11 derivatives with non-acetal at C-12 directly from artemisinin analogs in the presence of the unstable endoperoxide moiety. In preliminary in vitro antimalarial tests against the clone (3D7 and K1 strains) of *P. falciparum*, **13** is 15 times (IC_{50}=0.1 ng/mL) more potent than artemisinin (IC_{50}=1.51 ng/mL) and six times more potent than artesunate (IC_{50}=0.6 ng/mL).

Acknowledgements

This study was supported by a research grant from the Ministry of Health and Welfare (Project No. HMP-00-B-21500-00106), the Republic of Korea. The authors would like to thank Dr. Simon Croft, LSHTM, London, UK, for preliminary in vitro antimalarial screening.

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5. Selected spectroscopic data for **4**: mp 95°C; δ_H ($CDCl_3$, 250 MHz) 5.34 (1H, s), 4.98 (1H, s), 4.90 (1H, s), 4.41 (1H, d, J=13 Hz, 12-CH), 4.28 (1H, d, J=13 Hz, 12-CH), 2.39–2.21 (2H, m), 1.41 (3H, s), 0.98 (3H, d, J=6.1 Hz); IR (KBr, cm^{-1}) 3026, 2933, 2881, 1788, 1736, 1466, 1387, 1229, 1117, 1021, 768; MS (EI) m/z 266 (M^+); $[\alpha]_D^{25}$ +10.3° (c 0.123, $CHCl_3$). For **9**: δ_H ($CDCl_3$, 250 MHz) 5.61 (1H, s), 4.65 (1H, d, J=16.4 Hz, 12-CH), 4.08 (1H, d, J=16.4 Hz, 12-CH), 2.41–2.18 (1H, m), 1.44 (3H, s), 1.02 (3H, d, J=6.2 Hz); LC–MS (ESI) m/z 268 (M^+); $[\alpha]_D^{25}$ +9.5° (c 0.15, $CHCl_3$). For **10**: δ_H ($CDCl_3$, 250 MHz) 5.19 (1H, s), 3.99 (1H, dd, J=1.50, 12.5 Hz, 12-CH), 3.84 (1H, dd, J=1.50, 12.5 Hz, 12-CH), 3.62 (1H, m), 3.32 (1H, bs), 2.33 (1H, ddd, J=4.0, 2.4, 4.0 Hz), 1.42 (3H, s), 0.97 (3H, d, J=5.38 Hz); MS (EI) m/z 270 (M^+); $[\alpha]_D^{25}$ +91.1° (c 0.165, $CHCl_3$). For **11**β: mp 89°C; δ_H ($CDCl_3$, 250 MHz) 5.34 (1H, s), 4.00 (1H, dd, J=4.0, 11.9 Hz, 12-CH), 3.52 (1H, dd, J=1.13, 11.9 Hz, 12-CH), 2.97 (1H, d, J=4.77 Hz, 13-CH), 2.80 (1H, d, J=4.77 Hz, 13-CH), 2.35 (1H, ddd, J=3.77, 3.77, 3.79 Hz), 1.43 (3H, s), 0.98 (3H, d, J=6.2 Hz); MS (EI) m/z 282 (M^+); $[\alpha]_D^{25}$ +68.0° (c 0.124, $CHCl_3$). For **12**: δ_H ($CDCl_3$, 250 MHz) 5.22 (1H, s), 3.72 (1H, d, J=11.6 Hz, 12-CH), 3.64 (1H, d, J=11.6 Hz, 12-CH), 2.38–2.25 (1H, m), 1.57 (3H, s), 1.40 (3H, s), 0.95 (3H, d, J=5.95 Hz); $[\alpha]_D^{25}$ +107.1° (c 0.154, $CHCl_3$). For **13**: mp 136°C; δ_H ($CDCl_3$, 250 MHz) 5.20 (1H, s), 4.00 (1H, dd, J=3.8, 11.6 Hz, 12-CH), 3.53 (1H, t, J=11.6 Hz, 12-CH), 3.47 (2H, m, 13-CH_2), 2.71 (1H, m), 2.50 (1H, bs), 2.36 (1H, ddd, J=3.9, 3.3, 3.9 Hz), 1.40 (3H, s), 0.95 (3H, d, J=5.90 Hz); LC–MS (ESI) m/z 284 (M^+); $[\alpha]_D^{25}$ +103.2° (c 0.12, $CHCl_3$). For **15**: δ_H ($CDCl_3$, 250 MHz) 9.24 (1H, s), 5.29 (1H, s), 4.45 (1H, dd, J=1.9, 11.9 Hz, 12-CH), 3.96 (1H, dd, J=1.9, 11.9 Hz, 12-CH), 2.98–2.72 (1H, m), 2.33 (1H, ddd, J=3.8, 3.1, 3.8 Hz), 1.40 (3H, s), 1.01 (3H, d, J=6.0 Hz); LC–MS (ESI) m/z 282 (M^+); $[\alpha]_D^{25}$ +110.0° (c 0.15, $CHCl_3$). For **16**: δ_H ($CDCl_3$, 250 MHz) 5.22 (1H, s), 4.00 (1H, dd, J=3.77, 12.2 Hz, 12-CH), 3.54 (1H, t,

$J=12.2$ Hz), 2.71 (1H, m), 2.39 (1H, ddd, $J=4.1$, 4.0, 4.1 Hz), 1.43 (3H, s), 0.97 (3H, d, $J=5.9$ Hz); IR (KBr, cm^{-1}) 2940, 2874, 1716, 1453, 1387, 1104, 1064, 1018, 946, 762; $[\alpha]_D^{25}$ +97.4° (*c* 0.13, $CHCl_3$). For **18**: δ_H ($CDCl_3$, 250 MHz) 5.17 (1H, s, 5-CH), 3.89 (1H, dd, $J=3.7$, 11.0 Hz, 12-CH), 3.85 (1H, dd, $J=2.8$, 10.2 Hz, 13-CH), 3.71–3.57 (2H, m, 12-CH, 13-CH), 1.91–1.85 (4H, m), 1.60 (3H, s), 0.87 (3H, d, $J=6.4$ Hz); $[\alpha]_D^{25}$ +71.8° (*c* 0.195, $CHCl_3$). For **19**: δ_H ($CDCl_3$, 250 MHz) 5.16 (1H, s), 4.08 (1H, d, $J=12.3$ Hz, 12-CH), 4.00 (1H, t, $J=9.8$ Hz, 13-CH), 3.88 (1H, dd, $J=2.9$, 12.3 Hz, 12-CH), 3.66 (1H, dd, $J=5.3$, 9.8 Hz, 13-CH), 2.31 (1H, ddd, $J=3.8$, 2.9, 3.8 Hz), 2.04 (1H, m), 1.39 (3H, s), 0.95 (3H, d, $J=5.9$ Hz); LC–MS (ESI) m/z 349 (M^+); $[\alpha]_D^{25}$ +91.2° (*c* 0.13, $CHCl_3$).

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