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AN EFFICIENT PARTIAL SYNTHESIS OF (+)-ARTEMISININ AND (+)-DEOXOARTEMISININ

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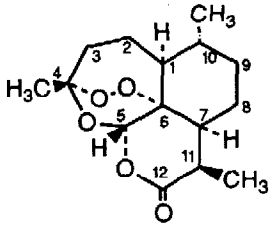
Key Words: Artemisinin, Deoxoartemisinin, Arteannuin B, Arteannuic Acid, Singlet Oxygen, Reductive Elimination, Ketalization, Allylic Oxidation.

Summary: Arteannuic acid and arteannuin B are separately convertible into intermediate **8**, which is transformed by four or five high-yielding steps into the title anti-malarial sesquiterpene peroxides.

The outstanding anti-malarial properties of artemisinin (**1**)[1] and derivatives preparable therefrom (e.g. **2**,[1] **3**[2]) have prompted extensive synthetic efforts to supplement the small amounts[1a] of **1** typically isolable from the leaves of *Artemisia annua L.*



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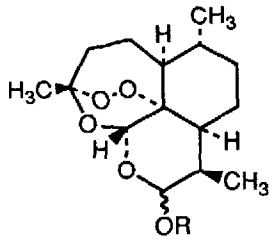

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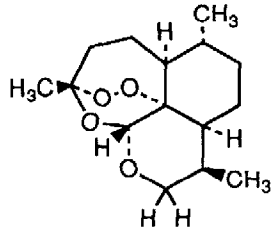

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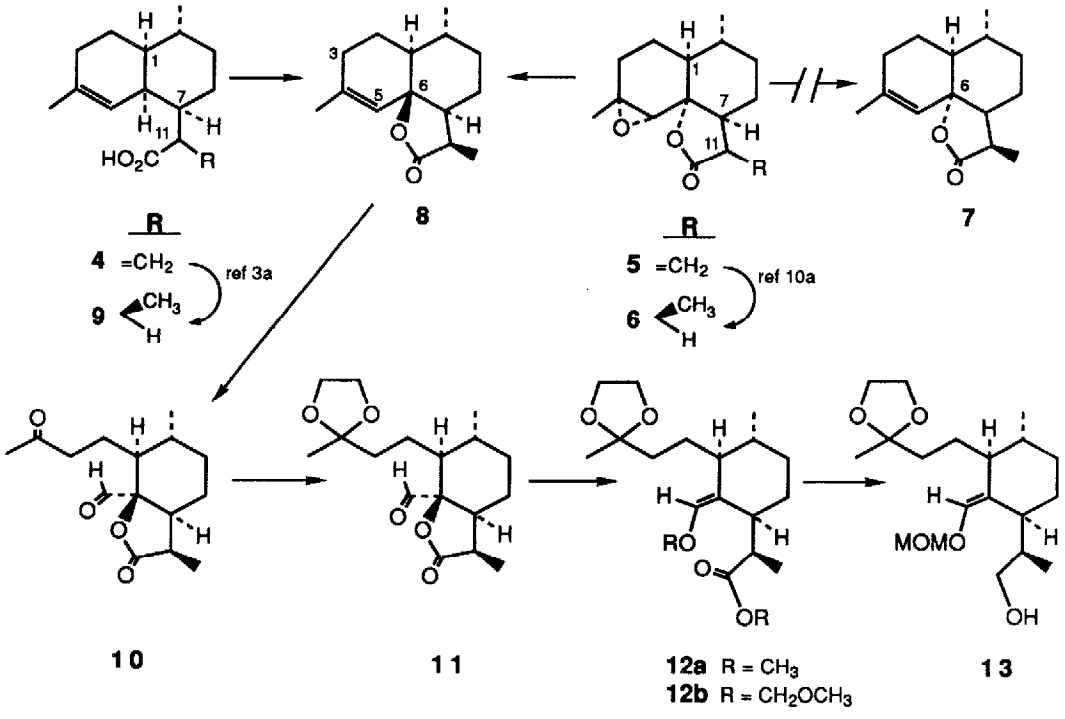
Monoterpenes such as R-(+)-citronellal[3] and (-)-isopulegol[4] have been used as chiral building blocks for skeletal elaboration into **1**. The penultimate step in these syntheses[3,4] was singlet oxygen ($^1O_2$) addition[5] to exocyclic methyl vinyl ethers and acid-induced rearrangement of the resultant dioxetanes to produce the biologically-active 1,2,4-trioxane substructure. Ene reactions and dioxetane cleavage can interfere during such protocols.[5c] Alternatively, Avery[6] utilized the abnormal ozonolysis of vinyl silanes[7], which can lead to siloxydioxetanes, to arrive at **1** and a variety of synthetic analogs. In addition, several brief partial syntheses beginning with sesquiterpene congeners of **1** have been reported[8,9] in which the proper sequential participation of two moles of $^1O_2$ was required, first an ene reaction and then a [2+2] cycloaddition-dioxetane cleavage on a rearranged allylic peroxide. These more complex oxygenation sequences typically give low yields of **1** and **3**, in part because other $^1O_2$ reaction products are equally probable or even more so. We have also been interested in utilizing relatively more abundant constituents of

Artemisia annua L. for partial synthesis of **1** and **3**, but with specific enol ether $^1O_2$ "targets" incorporated to minimize the above side reactions. This letter reports a successful approach to this problem, in which both arteannuic acid (**4**) and arteannuin B[10] (**5**) are converted to **1** and **3** via a common novel pathway that excludes unwanted epimerizations at C-1 or C-7.



Initial experiments were performed with 11-R-dihydroarteannuin B[10a] (**6**), obtained from **5** (73% yield) by hydrogenation[11] over pre-reduced Wilkinson's catalyst in 1:1 ethanol/benzene. After examining a variety of protocols for converting **6** into **7**, we settled on the Sharpless procedure[12], using 2:1 n-butyllithium/tungsten hexachloride in THF. Surprisingly, lactone **8** was isolated instead (60% yield), presumably by Lewis-acid-mediated isomerization of the more strained **7**[10a], since some epoxide **6** can be recovered unchanged. The assigned configuration of **8** was supported by NOE enhancement of the C-5 hydrogen signal (5.59 ppm) upon irradiation of the C-11 hydrogen. Further confirmation came from X-ray crystal structure determination[14] of keto-aldehyde **10** (mp 106-106.5°), the ozonolysis product formed in quantitative yield from **8**. The C-6 epimerization of **7** to **8** was not harmful since that stereocenter is removed in subsequent steps. A second and more plentiful source of **8** appeared with the novel discovery that allylic oxidation of 11-R-dihydroarteannuic acid (**9**)[3a] with CrO_3-3,5-dimethylpyrazole[15] in CH_2Cl_2 proceeded rapidly at -20° to the "carboxyl-trapped" γ-lactone, with only slow further C-3 oxidation of **8**. The ketone carbonyl

group in **10** was selectively protected, in the presence of the more hindered aldehyde, by using 1 eq. of 1,2-bis(trimethylsilyloxy)ethane and TMS triflate[16] in CH_2Cl_2 to secure pure **11**[17] in 94% yield. Reductive cleavage of **11** with 2 eq. of sodium naphthalenide in THF at -30° was followed by *in situ* reaction with several alkylating agents (CH_3I, CH_3OCH_2Cl) to produce enol ether-esters[17,18] **12a** and **12b** in 70% and 82% yields, respectively. The hindered aldehyde enolates underwent only O-alkylation, even in the absence of dimethyl sulfoxide, typically used to solvate the sodium counterions. A number of $^1O_2$ reactions[19] were run on **12a** and **12b** in CD_3OD at -78°, with Rose Bengal as photosensitizer, without prior hydrolysis of the ethylene ketal. Warming the dioxetane intermediate[20] gradually to room temperature in the presence of camphorsulfonic acid, followed by solvent removal at reduced pressure and silica gel chromatography led to 30-35% isolated yields of **1**, mp 155-156°, with dioxetane cleavage products[21] as the principal contaminants.

Since deoxoartemisinin (**3**) has *in vitro* and *in vivo* antimalarial activity superior[2] to **1**, we also examined the $^1O_2$ reaction of carbinol **13**[17] (formed in 90% yield by $LiAlH_4$/ether reduction of **12b**), as a direct source of **3**. Pure **3**, mp 106° was isolated in 65% yield with minimal by-product formation, a gratifying outcome when compared with other approaches[9,22], as well as the alternative **12→1→3**[2] sequence (which provided an authentic sample for ^1H and ^{13}C NMR and MS comparison[2]).

In conclusion, both **1** and **3** have been reproducibly prepared in only four or five steps from lactone **8** and the latter is readily accessible from both **4** and **5**. We expect that additional yield optimization will be possible upon scale-up beyond the 10-50 mg reactions described herein. Further experimental details will be provided in the full paper.

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11. The rearranged butenolide and 11-S-dihydroarteannuin B are formed as by-products in yields of 14% and 8%, respectively.
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17. All new compounds were fully characterized by an appropriate combination of IR, ^{1}H NMR (300MHz), ^{13}C NMR (75MHz) and MS, including high resolution exact mass measurements.
18. 2D-NMR studies affirm the expectation, based on 1,3-allyl strain considerations, that both **12a** and **12b** exist in chair or twist-boat conformations in which the allylic H *syn* to the vinyl ether moiety is equatorial. Thus, ene reactions with $^1O_2$ are unlikely[5c] and products therefrom were not detected.
19. In a typical experiment, the substrate is dissolved in CD_3OD (deuterated solvent is used to increase $^1O_2$ lifetime) and Rose Bengal is added, followed by cooling to -78°C. Dry O_2 is bubbled through the solution, which is irradiated by a Sylvania Tungsten Halogen Lamp (120V) filtered through a solution of $K_2Cr_2O_7$. Upon disappearance of the starting material (TLC monitoring), irradiation and O_2 flow are stopped and camphorsulfonic acid monohydrate is added. The reaction mixture is allowed to warm to 0°C over a period of several hours. After ~15 hrs at 0°C, the solution is allowed to warm to rt and the solvent removed by flash evaporation. Compound **1** is isolated by chromatography on florisil by gradient elution with ether-hexane.
20. Isolated from **12b** prior to acid treatment. *Selected data* for dioxetane intermediate: IR (neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 5.94 (1H, s), 5.21 (2H, AB quartet, *J* 6 Hz), 4.68 (2H, AB quartet, *J* 7 Hz), 3.93 (4H, m), 3.44 (3H, s), 3.39 (3H, s), 1.52 (3H, d, *J* 7 Hz), 1.34 (3H, s), 0.99 (3H, d, 6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz), δ177.26, 110.52, 105.74, 96.25, 95.84, 90.52, 64.95, 64.92, 57.80, 56.74.
21. Dioxetane cleavage products were initially diketoesters (from **12**) or diketocarbinols (from **13**); in specific cases, these compounds underwent further aldolization, ester hydrolysis, etc. Structures of such individual products will be discussed in the full paper.
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