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Replacement of the Nonperoxidic Trioxane Oxygen Atom of Artemisinin by Carbon: Total Synthesis of (+)-13-Carbaartemisinin and Related Structures.

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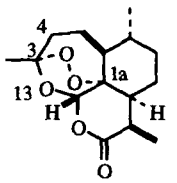
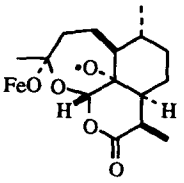
Abstract: Provided by total synthesis, endoperoxides **17**, **19** and **21** underwent intramolecular oxymercuration-demercuration leading respectively to formation of an isomeric tetracycle, (1aS,3S,5aS,6R,8aS,9R,12S)-10-deoxo-13-carbaartemisinin **18**, (+)-10-deoxo-13-carbaartemisinin **20**, and (+)-13-carbaartemisinin **4**. Neither target **4** nor **20** displayed substantial antimalarial potency *in vitro* against *Plasmodium falciparum*, but the isomeric peroxide **18** possessed reasonable antimalarial potency *in vitro*.

Much effort has been expended to develop new antimalarial drugs based on the natural product lead structure, (+)-artemisinin **1**.[4] The unusual peroxy moiety of this cadinane sesquiterpene was found to be essential for antimalarial activity,[5] and prompted by Meshnick's observation of the reaction of hemin with **1**,[6] Posner has elegantly demonstrated that carbon-centered radical chemistry apparently surrounds the mode of antimalarial action of this class of drugs.[7] In Posner's *in vitro* studies, cleavage of the oxygen-oxygen bond of structures such as **1** by Fe(II) leads to an intermediate oxygen radical (e.g. **2**) which then abstracts, in an intramolecular 1,5-fashion, a hydrogen atom from C-4.[8] The fate of this resultant carbon radical **3** is as yet not understood, although Meshnick's group continues to study the biochemical course of reaction of **1** *in vivo*.[9] The importance of intermediate carbon radicals in the mechanism of action of simpler artemisinin analogs has also been demonstrated by Jefford.[10]



1, (+)-Artemisinin



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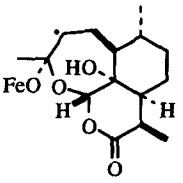

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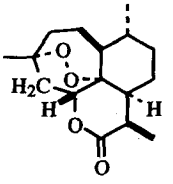
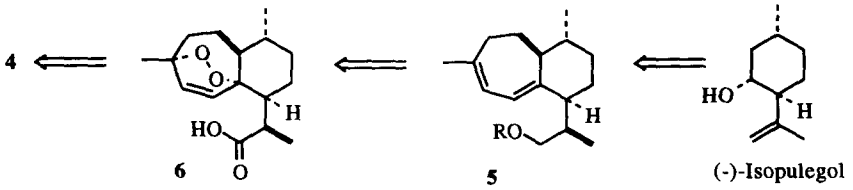


4, (+)-13-Carbaartemisinin

From our perspective, it was unclear whether this sissioning process (**1** to **2**/**3**) would be followed by unraveling of the tetracycle and whether this unraveling process would be detrimental to potency. It was felt that insertion of carbon for oxygen at what was fomerly O-13, i.e. as in 13-carbaartemisinin **4**, would inhibit further fragmentation of the intermediates (**2** or **3**) and would allow us to determine the importance of this process. We

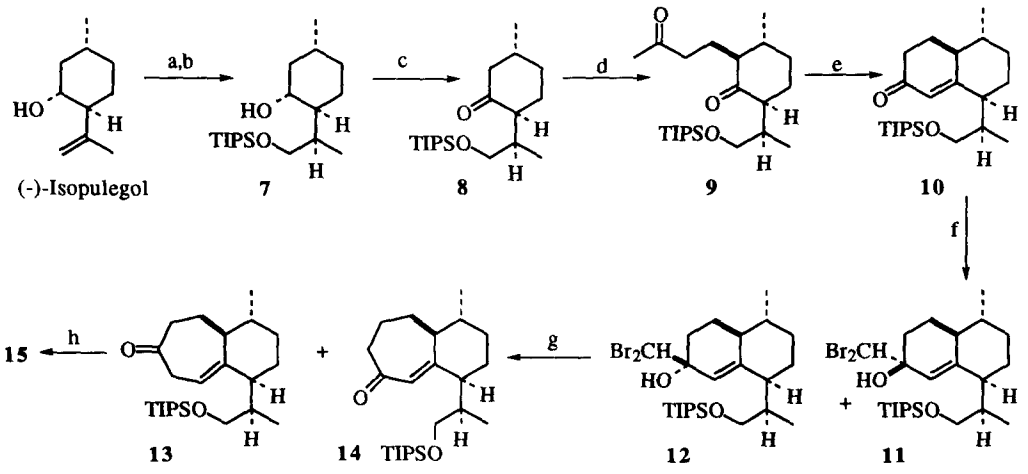
therefore set about the synthesis of **4** from a chiral pool, specifically (-)-isopulegol as outlined retrosynthetically below:



(-)-Isopulegol was envisaged as a suitable precursor for Robinson annelation, ensuing ring expansion and appropriate manipulation of functionality would then furnish the diene **5**. Addition of singlet oxygen to provide **6** followed by an intramolecular oxymercuration would then complete the sequence leading to **4**.

As shown in Scheme I, manipulation of (-)-isopulegol as described previously provided smooth access to the Robinson precursor: hydroboration of (-)-isopulegol with oxidative workup followed by selective protection provided alcohol **7**, Swern oxidation of which then gave **8**. Generation of the kinetic enolate of **8** with LDA at low temperature followed by Michael addition to 3-trimethylsilyl-3-buten-2-one gave diketone **9**. Aldol cyclization and elimination of water from **9** to generate bicyclic enone **10** was much more difficult than anticipated due to facile epimerization of the propanol side-chain. It was found that this epimerization could be

Scheme I



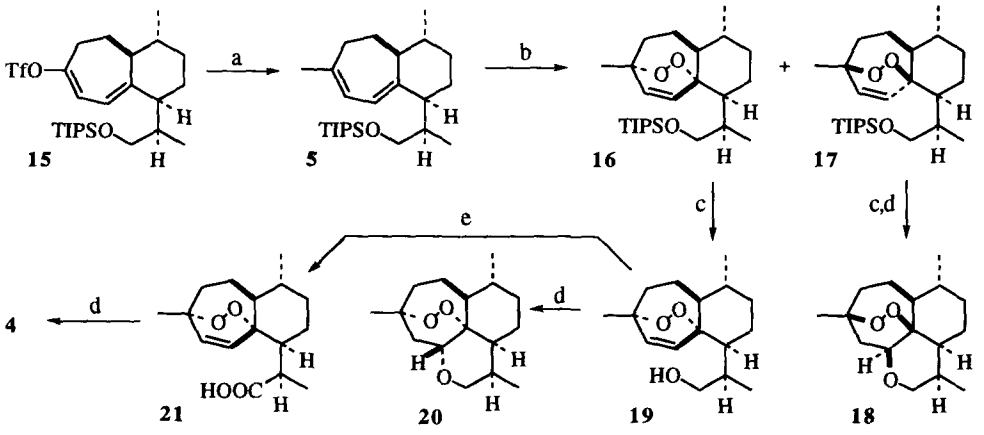
Key: a) BH_3-THF, then H_2O_2, NaOH, 40%; b) $(i\text{-}Pr)_3SiCl$, DMAP, Et_3N, 96%; c) $(COCl)_2$, DMSO; Et_3N, 95%; d) LDA, 3-trimethylsilyl-3-butene-2-one, then pH 2, 73%; e) *l*-proline, MeOH, 43%; f) Br_2CH_2, LDA, -95°C, 88%; g) BuLi, THF, -95°C, 53% of **13**; h) KH, DME, Tf_2NPh, 89%.

inhibited to some extent upon treatment of **9** with 1.5 equivalents of *l*-proline, leading directly to the bicyclic enone **10**. Addition of dibromomethyllithium at low temperature afforded a mixture of diastereomers **11** and **12**, of which only isomer **12** underwent desired ring expansion. Thus, treatment of **12** with butyllithium at

-95°C furnished a mixture of β,γ-unsaturated enone **13** along with α,β-unsaturated enone **14** (3:1 mixture of **13**:**14**). Dienol triflate **15** was then regiospecifically formed upon treatment of enone **13** with KH in THF followed by addition of Tf_2NPh. The triflate **15** was stable enough to be chromatographed rapidly over silica gel, although it had to be utilized for the next reaction directly.

The final steps in the overall sequence were then carried out as demonstrated in Scheme II. Coupling of the enol triflate with dimethylcopper lithium provided the diene **5** in excellent yield. Singlet oxygenation of **5** was then investigated with a variety of dyes in different solvents. We were surprised to find that a mixture of diastereomeric peroxides were obtained, only varying slightly with conditions, and that the desired peroxide **16** could only be obtained in about 30% yield. The unexpected predominant diastereomer **17**, obtained in 54% isolated yield, was carried through the sequence of silyl group deprotection and Hg(II) cyclization (Scheme II) to arrive at the diastereomeric peroxide **18**.[11] In any event, the desired peroxide **16** was then deprotected with tetrabutylammonium fluoride in THF to give the alcohol **19**.

Scheme II



Key: a) Me_2CuLi, Et_2O, 94%; b) $^1O_2$, EtOAc, Rose Bengal Salt, 30% **16**, 54% **17**; c) Bu_4NF, THF: 89% **19**; 70% alcohol from **17**; d) $Hg(OTFA)_2$, THF; then $NaBH_4$/NaOH: 76% **20**; 78% **18**; 60% **4**; e) CrO_3, AcOH, H_2O, 64%.

Oxymercuration of the alcohol **19** was readily accomplished using mercuric trifluoroacetate in THF; the organometallic product could then be carefully demercurated with sodium borohydride to provide (+)-10-deoxy-13-carbaartemisinin **20**.[11] Attempted oxidation of alcohol **19** directly to acid **21** using pyridinium dichromate in DMF was not successful as the intermediate aldehyde could not be further oxidized with this reagent. However, alcohol **19** could be oxidized directly to the acid **21** using chromium trioxide in acetic acid. Oxymercuration-demercuration then gave the title compound **4**.[11] The structures of **18** and **20** were unambiguously determined by single crystal x-ray crystallographic analysis,[3] while the structure of **4** was reasonably extrapolated from **20**.

Neither target **4** (IC_{50} = 25 ng/ml) nor **20** (IC_{50} = 5.81 ng/ml) displayed substantial antimalarial potency relative to artemisinin (IC_{50} = 1 ng/ml) *in vitro* against the W-2 clone of *Plasmodium falciparum*,[1,3] a fact that

suggested that the inactivity of C-4α substituted artemisinin analogs could be correlated to their inability to undergo C-4 hydrogen atom abstraction.[7,8] While C-4 radical stability would be predicted to have an impact on antimalarial potency, these results would contradict the notion that improved C-4 radical stability is related, *a priori*, to improved antimalarial activity because the C-4 radical derived from **4** should be more stable than radical **3**. To further complicate this picture, the isomeric peroxide **18** was found to possess reasonably good antimalarial activity (IC_{50} = 1.73 ng/ml). Studies currently underway which address the rearrangement chemistry of **4**, **18**, and **20** with Fe(II) salts or hemin may provide information useful in deciphering these results.

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11. For **18**, ^{1}H NMR: δ 3.86 (dd, 1H, J = 1.1, 11.1 Hz), 3.60 (dd, 1H, J = 1.1, 1.1 Hz), 3.56 (d, 1H, J = 1.1 Hz), 2.32 (dd, 1H, J = 9.2, 14.5 Hz), 2.08 (ddd, 1H, J = 2.7, 14.5, 14.5 Hz), 1.91 (m, 1H), 1.75 (m, 5H), 1.54 (m, 5H), 1.0-1.3 (m, 4H), 1.20 (s, 3H), 0.87 (d, 3H, J = 6.5 Hz); ^{13}CNMR: δ 78.48, 78.31, 74.41, 74.02, 50.09, 46.57, 38.37, 35.59, 35.19, 33.01, 29.63, 27.18, 25.39, 22.34, 20.19, 13.50. The product **20**, m.p. 137-138°C, had: ^{1}H NMR: δ 4.00 (d, 1H, J = 8.3 Hz), 3.60 (dd, 1H, J = 4.2, 11.3 Hz), 3.32 (dd, 1H, J = 11.5, 11.5 Hz), 2.59 (m, 1H), 2.18 (d, 2H, J = 8.3, 14.6 Hz), 1.92 (m, 1H), 1.6-1.78 (m, 4H), 1.4-1.6 (m, 2H), 1.21 (s, 3H), 1.22 (m, 3H), 1.05 (m, 1H), 0.91 (d, 3 H, J = 5.8 Hz), 0.74 (d, 3H, J = 7.3 Hz); ^{13}C NMR: δ 80.73, 78.09, 67.19, 67.06, 53.41, 44.08, 37.27, 37.10, 36.77, 34.51, 28.16, 27.36, 26.76, 20.85, 20.41, 13.65. $[\alpha]_D^{25}$ = + 94.5° (c = 0.152, $CHCl_3$). The product **4**, m.p. 160-162°C, had: ^{1}H NMR: δ 4.92 (dd, 1H, J = 1.5, 9.8 Hz), 3.40 (ddd, 1H, J = 5.1, 7.3, 14.4 Hz), 2.17-2.31 (m, 2H), 2.10 (m, 1H), 1.90 (m, 2H), 1.75 (m, 3H), 1.0-1.4 (m, 5H), 1.23 (s, 3H), 1.18 (d, 3H, J = 7.2 Hz), 0.96 (d, 3H, J = 6.0 Hz); ^{13}C NMR: δ 173.40, 77.10, 79.75, 78.75, 71.50, 51.64, 45.73, 37.52, 37.28, 36.34, 33.79, 33.15, 26.60, 23.77, 19.95, 12.55; IR ($CDCl_3$): 1729 cm^{-1}. $[\alpha]_D^{25}$ = + 69.3° (c = 0.138, $CHCl_3$).

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