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SYNTHESIS OF (+)-8a,9-SECOARTEMISININ AND RELATED ANALOGS

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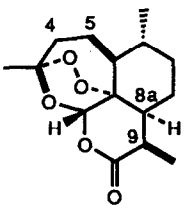
Abstract: An efficient synthesis of (+)-8a,9-secoartemisinin 2, a ring-D cleaved, tricyclic analog of (+)-artemisinin 1, has been accomplished. Dioxetane 7, produced upon ozonolysis of vinyl-silane 5 in methanol, was intercepted with acid to provide the stable bicyclic peroxy-aldehyde 9, which was readily converted to the title compound(s).

The sesquiterpene (+)-artemisinin 1 displays impressive activity against the widespread threat of resistant strains of *Plasmodium falciparum*.[1] Geo-economic and pharmacodynamic considerations further stimulate the ongoing search for the molecular basis of action and minimum structural requirements for high potency in this class of drugs.[2] Increasing efforts to achieve an efficient total synthesis[3] now provide methodology suitable to the synthesis of numerous analogs.[4]



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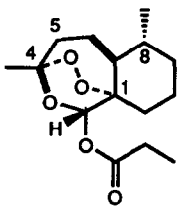
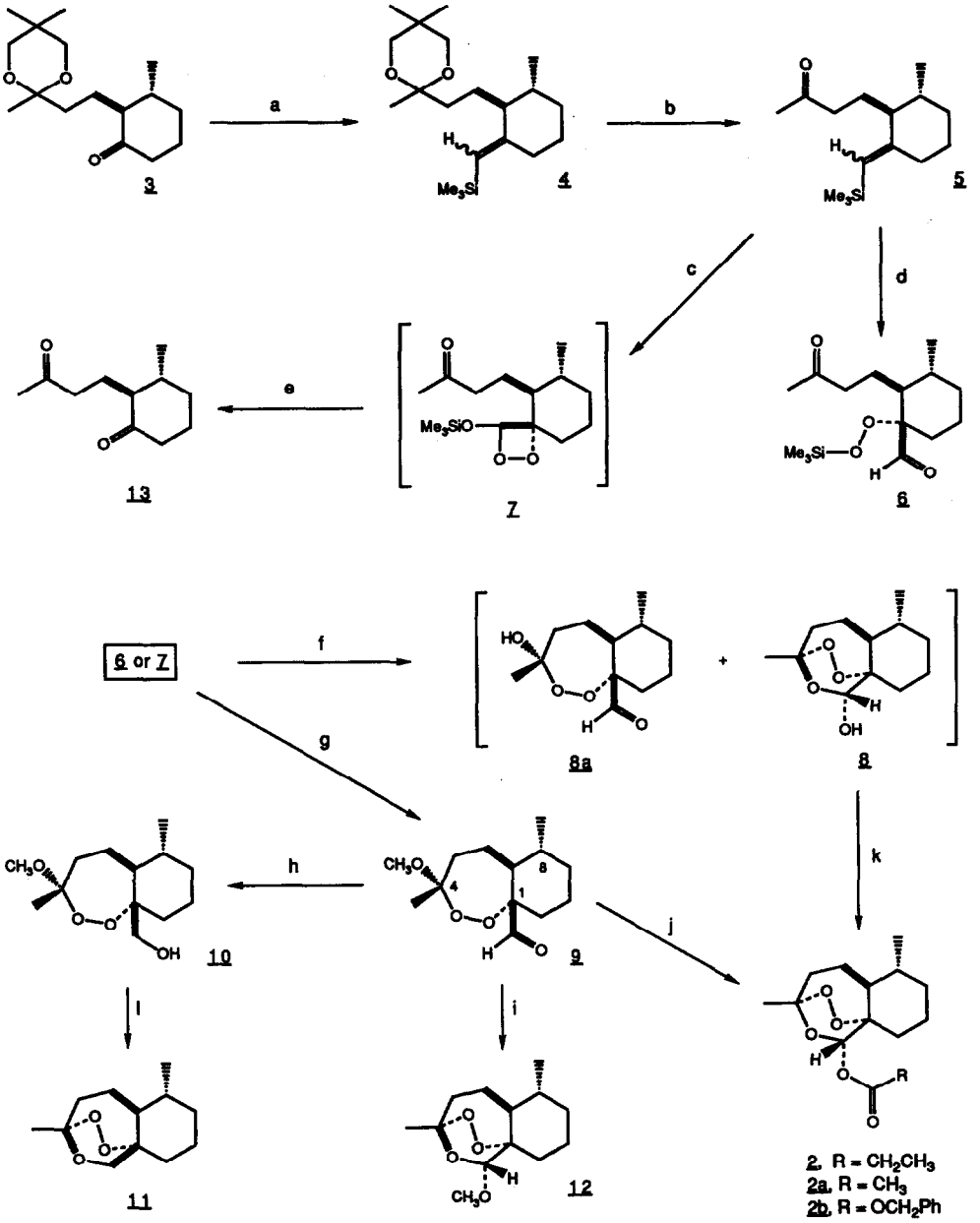


2

As part of our program, we have employed a disconnective approach to understanding the requirements for antimalarial activity of 1. Analogs of 1 that lack the 4,5-bond (A-ring seco) display conformational flexibility about the trioxane/lactone rings and a concomitant reduction of activity.[5] A similar conceptual scission of the D-ring (bond 8a,9) provides derivatives, such as 2, that must mimic the relative orientation of the A,B, and C rings of 1 and are thus of considerable interest.[6] As described below, we have employed vinylsilane ozonolysis methodology[7] to install the crucial functional arrangement for the construction of 2.

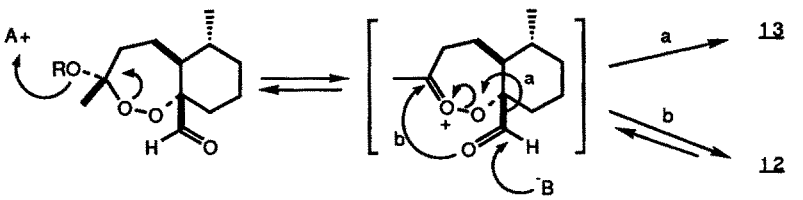
The synthesis of 2 is shown in Scheme 1. Reaction of dimethyl(methoxy)silyl(trimethylsilyl)methyllithium[8] with the chiral ketone 3 in pentane afforded the E/Z vinylsilane 4 in 50% yield (93% based on recovered 3). Hydrolysis of 4 with aqueous oxalic acid impregnated silica gel in dichloromethane provided the requisite keto-silane 5 in 81% yield. Upon exposure of 5 to ozone in CH_2Cl_2 at low temperature, the stable silyl-peroxy aldehyde 6 was the sole product. In contrast, ozonolysis of 5 in methanol led to clean production of the dioxetane 7, as was evidenced by NMR (δ6.0, $CDCl_3$). The dioxetane 7 was reasonably stable but slowly underwent cycloreversion to the diketone 13 on standing at room temperature for several hours. However, if boron trifluoride etherate was added directly to the ozonolysis mixture, then conversion to a stable bicyclic aldehyde 9 was witnessed (69% isolated yield). Assignment of structure 9 to this material rested on NMR (APT, COSY, HETCOR, NOESY)[9] and was recently confirmed by analogy to parallel studies by another group in a racemic system lacking the 8α-methyl group.[10]

Scheme 1[a]



[a]Key: (a) $MeOMe_2SiCH_2SiMe_3$, t-BuLi, pentane; (b) aq. oxalic acid, silica gel, CH_2Cl_2; (c) O_3/O_2, MeOH, -78°C; (d) O_3/O_2, CH_2Cl_2, -78°C; (e) $CDCl_3$, 23°C; (f) moist $CHCl_3$, TFA; (g) c followed by BF_3 etherate; (h) $NaBH_4$, MeOH, O°C; (i) BF_3 etherate, MeOH, $(MeO)_3CCH_3$; (j) RCOX, Amberlyst-15, solvent; (k) RCOX, DMAP, CH_2Cl_2; (l) p-TsA, CH_2Cl_2.

The aldehyde 9 proved useful for conversion to 8a,9-secoartemisinin 2, or to a variety of other analogs. Treatment of 9 in propionic anhydride, with or without co-solvent, with Amberlyst-15 gave 2 in 30% yield.[11] The reaction was successful with acetic anhydride as well, affording 2a in 35% yield,[12] but failed with benzoic anhydride. Reduction of 9 with sodium borohydride in methanol provided the alcohol 10, which upon brief treatment with pTsA in CH_2Cl_2 was converted directly to the tricyclic trioxane 11 in 79% yield.[13] In an effort to improve upon the conversion of 5 to 2 and make the route applicable with other acylating reagents (for the production of analogs), hydrolysis of the dioxetane 7, or of the silyl-peroxide 6, to the tricyclic alcohol 8 was examined. Under a variety of conditions (e.g., TFA/$CDCl_3$ or THF/aq. HCl), 7 gave rise to a chromatographically inseparable mixture of 8, 8a, and diketone 13 (1:2:1 ratio, respectively), from which 13 could be removed by bisulfite wash. Aldehyde 6 underwent hydrolysis under neutral conditions (aq. methanol) to give a similar mixture of 8/8a/13. Upon treatment of the resultant 1:2 mixture of 8/8a (from 7) with propionic anhydride and DMAP in CH_2Cl_2, the only isolable products were 2 (20%) and 13 (60%). Similar results were observed under these conditions with benzyl chloroformate, which furnished 2b (confirmed by x-ray crystallography) in 21% yield[14], or with acetic anhydride (2a, 24%). The unwanted occurrence of the diketone 13 is presumably the product of a fragmentation reaction:



Treatment of either 6, 7, or 9 in methanol with acid and a dehydrating agent (trimethylorthoacetate) gave rise to a mixture of 9 (20%) and the acetal 12 (4:1 mixture of diastereomers, 15% yield).[15] Equilibration of 9 with catalytic acid in dry CH_2Cl_2 provided 12, but with attendant fragmentation to 13 (3:2:1 ratio of 13:9:12, respectively).

In summary, a wide variety of optically active analogs of artemisinin 1 are now readily accessible by this methodology. Studies in progress focus on the synthesis of new analogs, for structure-activity relationship studies, derived from 2a by ester-enolate alkylation. In vitro antimalarial bioassay of 2, 2a, 2b, 9, 11, and 12 is in progress and will be reported in due course.

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5. W. Inman, M. A. Avery, W. Chong, and P. Crews, accepted for publication in J. Org. Chem. . 4,5-secoartemisinin derivatives exist in an array of conformers in solution (NMR), while X-ray data show a chair-chair-chair conformation.
6. Energy minimization (MMP2) of several conformational isomers of artemisinin (resulting from rotation about the C1-O2-O3-C4 dihedral angle) demonstrates a clear preference for the conformer corresponding to the solid-state structure (X-ray) as well as the solution structure (NOESY). Unlike the 4,5-seco derivatives, 8a,9-scission provides analogs (type 2) having only one tricylic conformation that nicely overlaps with the A-B-C rings of the natural product (1).
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8. T. F. Bates and R. D. Thomas, J. Org. Chem., **54**, 1784 (1989).
9. Crystals of 9 from hexane, m.p. 100-102°C. $[\alpha]_D^{23}$ = +317° (c = 1.18, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (ddd, J = 4, 12, 14.5 Hz, 1H,11α), 0.94 (d, J = 6.4 Hz, 3H, 8α-Me), 1.19 (d, J = 1.2 Hz, 3H, 4β-Me), 1.26 (dddd, J = 2.8, 3, 12, 12 Hz, 1H, 7α), 1.28 (m, 1H, 10β), 1.32 (m, 1H, 9α), 1.52 (dddd, J = 1.5, 12, 12, 14.5 Hz, 1H, 6β), 1.66 (dddd, J = 1.5, 4, 6.5, 14.5 Hz, 11β), 1.69 (m, 1H, 10α), 1.85 (dddd, J = 2, 3, 8, 14.5 Hz, 1H, 6α), 1.93 (m, 1H, 9β), 1.94 (dddd, J = 1.2, 2, 12, 14.5 Hz, 1H, 5α), 2.07 (ddd, J = 1.5, 8, 14.5 Hz, 1H, 5β), 2.18 (dddq, J = 4, 6.4, 12, 12 Hz, 1H, 8β), 3.34 (s, 3H, 4α-OMe), 9.51 (d, J = 2.8 Hz, 1H, 1β-CHO). ^{13}C NMR ($CDCl_3$): d 19.6 (C-4β), 20.4 (C-8αMe), 21.9 (C-6), 22.0 (C-10), 30.2 (C-9), 32.3 (C-8), 35.2 (C-11), 40.5 (C-5), 49.1 (OMe), 56.6 (C-7), 91.8 (C-1), 108.6 (C-4), 198.2 (C-1β-CHO).
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11. Pure 2 isolated as an oil, $[\alpha]_D^{22}$ = +26.3° (c = 1.90, hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 6.3 Hz, 3H, 8α-Me), 0.99 (m, 1H, 9α), 1.20 (t, J = 7.6 Hz, 3H), 1.26 (m, 2H), 1.38 (s, 3H, 4-Me), 1.39 (ddd, J = 6.6, 11.5, 11.5 Hz, 1H, 7α), 1.44 (m, 1H, 8β), 1.51 (dddd, J = 4.8, 11.5, 13.4, 13.8 Hz, 1H, 6β), 1.62 (m, 2H), 1.91 (dddd, J = 3.1, 3.5, 6.6, 13.8 Hz, 1H, 6α), 2.02 (ddd, J = 3.1, 4.8, 14.6 Hz, 1H, 5β), 2.14 (ddd, J = 2, 3.5, 10.1 Hz, 1H, 11β), 2.39 (ddd, J = 4.1, 13.4, 14.6 Hz, 1H, 5α), 2.47 (q,J = 7.6 Hz, 2H), 6.45 (s, 1H, 12β).
12. Pure 2a isolated as an oil, $[\alpha]_D^{21}$ = +9.3° (c = 1.50, hexane). ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 6.3 Hz, 3H, 8α-Me), 0.98 (m, 1H, 9α), 1.25 (m, 2H, 11α/10β), 1.39 (ddd, J = 6.8, 11.3, 11.3 Hz, 1H, 7α), 1.39 (s, 3H, 4-Me), 1.45 (m, 1H, 8β), 1.52 (ddd, J = 4.8, 11.3, 13.5 Hz, 1H, 6β), 1.63 (m, 2H, 9β/10α), 1.91 (dddd, J = 1.2, 3.5, 6.6, 13.9 Hz, 1H, 6α), 2.02 (ddd, J = 3, 4.8, 14.5 Hz, 1H, 5β), 2.14 (m, 1H, 11β), 2.20 (s, 3H, 12α-OAc), 2.39 (ddd, J = 4, 13.2, 14.5 Hz, 1H, 5α), 6.44 (s, 1H, 12β). ^{13}C NMR ($CDCl_3$): δ 170.4 (-OAc), 104.5 (C-4), 88.3 (C-12), 83.1 (C-1), 51.6 (C-7), 37.6 (-OAc), 36.1 (C-5), 34.6 (C-11), 33.9 (C-6), 25.9 (4-Me), 24.9 (C-10), 22.1 (C-9), 21.4 (C-8), 20.1 (8-Me).
13. Crystals of 11 from -78°C pentane, m.p. 69-71°C. $[\alpha]_D^{22}$ = +88.8° (c = 0.267, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (m, 1H, 9α), 0.98 (d, J = 6.1 Hz, 3H, 8α-Me), 1.23 (dddd, J = 3, 4.5,14.2,14.2 Hz, 1H, 10β), 1.30 (ddd, J = 3.3, 13.5, 14.2 Hz, 1H, 11α), 1.34 (s, 3H, 4-Me), 1.37 (m, 2H), 1.80 (ddd, J = 3, 4, 13.5 Hz, 1H, 11β), 1.88 (dddd, J = 3.3, 3.3, 6.3, 14 Hz, 1H, 6α), 2.01 (ddd, J = 3.3, 4.5, 14.5 Hz, 1H, 5β), 2.42 (ddd, J = 3.3, 13.4, 14.5 Hz, 1H, 5α), 4.03 (dd, J = 1.6, 11 Hz, 1H, 12α), 4.20 (d, J = 11Hz, 1H, 12β).
14. Crystals of 2b from hexane, m.p. 110°C. $[\alpha]_D^{22}$ = -17.5° (c = 0.37, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (d, J = 6.2 Hz, 3H, 8α-Me), 1.00 (m, 1H, 9α), 1.27 (m, 2H), 1.38 (ddd, J = 6.2, 11.2, 11.2 Hz, 1H, 7α), 1.40 (s, 3H, 4-Me), 1.44 (m, 1H, 8β), 1.48 (dddd, J = 5, 11.2, 13.2, 13.5 Hz, 1H, 6β), 1.63 (m, 2H), 1.91 (dddd, J = 3.5, 3.8, 6.2, 13.5 Hz, 1H, 6α), 2.03 (ddd, J = 3.5, 5, 14.7 Hz, 1H, 5β), 2.20 (br d, J = 10.4 Hz, 1H, 11β), 2.40 (ddd, J = 3.8, 13.2, 14.7 Hz, 1H, 5α), 5.24 (s, 2H), 6.31 (s, 1H, 12β), 7.38 (m, 5H). The structure of 2b was confirmed by single crystal x-ray crystallographic techniques and will be reported in a fully detailed account.
15. Pure 12 isolated as an oil, $[\alpha]_D^{21}$ = -5.4° (c = 1.05, hexane). ^1H NMR (400 MHz, C_6D_6): δ 0.72 (m, 1H, 9α), 0.73 (d, J = 6.4 Hz, 3H, 8α-Me), 0.98 (mq, J = 6.4 Hz, 1H, 8β), 1.07 (m, 1H, 10β), 1.11 (m, 1H, 11α), 1.14 (m, 1H, 7α), 1.27 (dddd, J = 5, 11.5, 13.5, 14.5 Hz, 1H, 6β), 1.29 (s, 3H, 4-Me), 1.30 (m, 1H, 9β), 1.34 (m, 1H, 10α), 1.59 (dddd, J = 3, 4, 7, 14.5 Hz, 1H, 6α), 1.72 (ddd, J = 3, 5, 14.5 Hz, 1H, 5β), 2.35 (ddd, J = 4, 13.5, 14.5 Hz, 1H, 5α), 2.66 (ddd, J = 2, 3.5, 11 Hz, 1H, 11β), 3.51 (s, 3H, 12α-OMe), 4.95 (s, 1H, 12β).

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