to thank Dr. Cynthia Day of Crystalytics Co. (Lincoln, NE) for the crystallographic analysis and Dr. W. Milhous and MRDC staff at the Walter Reed Army Institute of Research for biological screening data.

Registry No. (±)-**1**, 119241-68-8; (±)-**2**, 119183-85-6; **3**, 18448-47-0; **4**, 76358-53-7; **4** (alcohol), 4845-04-9; (±)**5**, 119183-86-7; (±)-**5** (alcohol), 119183-91-4; (±)-**6**, 119183-87-8; (±)-**7**, 119183-87-8; (±)-**8**, 119183-89-0; (±)-**9**, 119183-90-3.

Supplementary Material Available: Crystal structure analysis report for **9**, Table I (atomic coordinates for non-hydrogen atoms), Table II (anisotropic thermal parameters for non-hydrogen atoms), Table III (atomic coordinates for hydrogen atoms), Table IV (bond lengths), Table V (bond angles), and Table VI (close contacts involving hydrogen atoms) (13 pages). Ordering information is given on any current masthead page.

Simplified Analogues of the Antimalarial Artemisinin: Synthesis of 6,9-Desmethylartemisinin

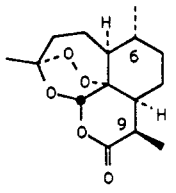
Mitchell A. Avery,* Clive Jennings-White, and Wesley K. M. Chong

Bio-Organic Chemistry Laboratory, Life Sciences Division, SRI International, 333 Ravenswood Avenue, Menlo Park, California 94025

Received September 22, 1988

(±)-6,9-Desmethylartemisinin (**8**) was prepared from pyrrolidinocyclohexene and *cis*-1,4-dichloro-2-butene in eight steps. The intermediacy of bicyclic **2** led to a stereocontrolled route to pivotal syn-substituted cyclohexane **5**. Hydrolysate keto acid vinylsilane **7** underwent abnormal reaction with ozone and subsequent acid-catalyzed cyclization to the title compound.

The natural product (+)-artemisinin has exhibited antimalarial activity against chloroquine-resistant *P. falciparum*.[1] The unique peroxide-containing sesquiterpene structure is depicted here by **1**. Despite its use in ancient Chinese medicine and, more recently, structural elucidation in 1980, many details of the molecular basis for antimalarial activity by artemisinin remain unknown. The emergence of quinine-resistant malaria in tropical regions and the challenge of such a target structure for total synthesis have focused attention upon artemisinin from many laboratories,[2] including our own. We have recently reported the total synthesis of (+)-artemisinin[3] and are presently engaged in a program for the synthesis of novel analogues[4] that are intended to identify a responsible pharmacophore for the design of improved antimalarials.



1

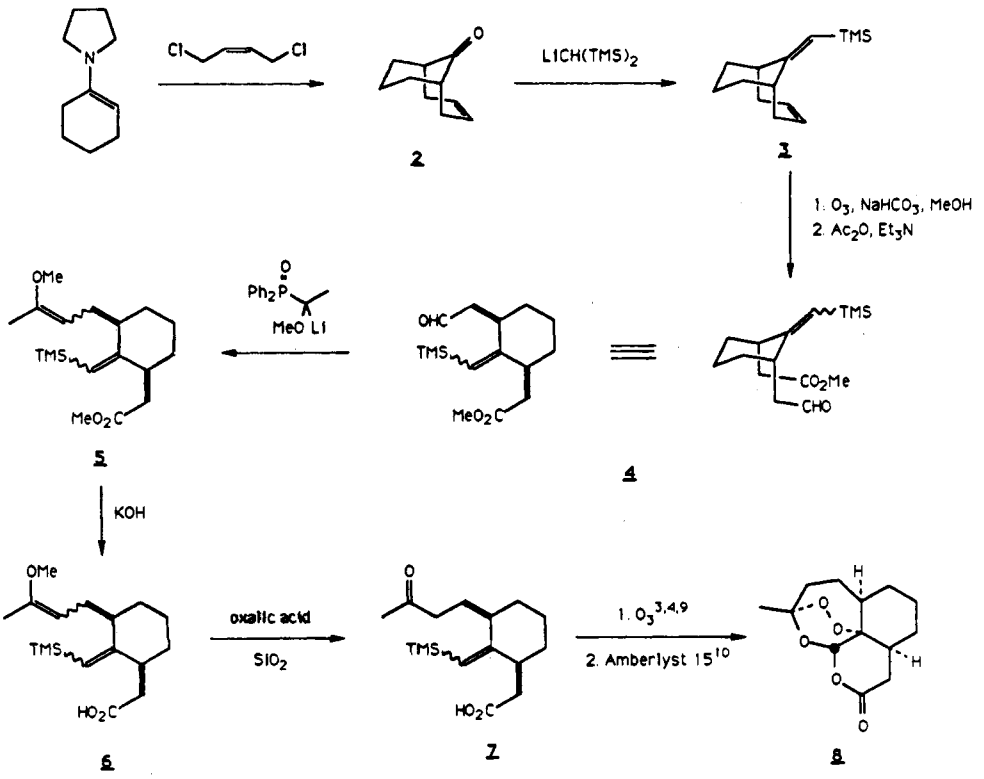
(+)- Artemisinin

Reported herein is the synthesis of a simplified analogue of artemisinin that does not have the C6 and C9 substituent methyl groups. The absence of some of the asymmetric centers allowed a much different synthetic approach from that of our other work: as shown in Scheme I, for starting material bicyclo[4.3.1]decenone **2** was prepared from pyrrolidinocyclohexene and *cis*-1,4-dichloro-2-butene as described by Still.[5] The nonenolizable bridging carbonyl of **2**[6] was condensed in straightforward fashion with bis(trimethylsilyl)methyllithium[7] to the vinylsilane **3** in 78% yield after purification. When the diene **3** was submitted to carefully metered delivery of ozone under conditions developed by Schreiber[8] for the production of aldehyde–esters from disubstituted double bonds, surprisingly selective monocleavage to the desired syn-substituted cyclohexane **4** (as a 1:1 mixture of geometrical vinylsilane isomers) was obtained in 64% yield after chromatography. Ozonolysis of the vinylsilane moiety of **3** or **4** under the experimental conditions was never witnessed. The aldehyde of **4** served as a convenient point for elaboration with lithium diphenyl(1-methoxyethyl)phosphine oxide[9] to the diastereomeric methyl enol ethers **5** in 58% yield, which contained all the necessary carbons for the target analogue. Sequential deprotection was carried out by saponification of esters **5** to acids **6**, which were stirred in a suspension with oxalic acid adsorbed on silica gel to provide keto acids **7** and 94% overall yield from **5**. The final construction of the tetracyclic peroxide utilized methodology that coincided with our prior work,[3,4] and, in this manner, ozone was delivered carefully through a solution of keto acids **7** in methylene chloride at −78 °C. In separate experiments, when starting **7** was no longer present by TLC, the solvent was removed in vacuo to give a material that appeared by NMR (90 mHz) to be diastereomeric [(trimethylsilyl)oxy]dioxetanes[10] (δ 6.17 and

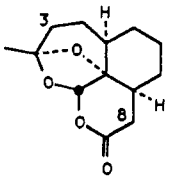
(1) Klayman, D. L. *Science* **1985**, *228*, 1049.
(2) Synthetic approaches to artemisinin: (a) Jung, M.; ElSohly, H.; Croom, E.; McPhail, A.; McPhail, D. *J. Org. Chem.* **1986**, *51*, 5417. (b) Clark, G.; Nidado, M.; Fair, C.; Lin, J. *J. Org. Chem.* **1985**, *50*, 1494. Total syntheses: (c) Zhou, W. *Pure Appl. Chem.* **1986**, *58*, 817. (d) Xing-xiang, X.; Zhu, J.; Da-zhong, H.; Zhou, W. *Tetrahedron* **1986**, *41*, 819. (e) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624. Analogues of artemisinin: (f) Brossi, A.; Venugopalan, B.; Dominguez Gerpe, L.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645.
(3) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *Tetrahedron Lett.* **1987**, *28*, 4629.
(4) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *J. Org. Chem.*, preceding paper in this issue.
(5) Still, W. C. *Synthesis* **1976**, 453.
(6) The possibility of trans or "inside–outside" stereoisomers in such bicyclic bridging ketones (albeit remote in our situation) has recently been addressed. See: (a) Winkler, J. D.; Hey, J. P.; Willard, P. G. *J. Am. Chem. Soc.* **1986**, *108*, 6425. (b) Winkler, J. D.; Henegar, K. E.; Willard, P. G. *J. Am. Chem. Soc.* **1987**, *109*, 2850. (c) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298.
(7) Gröbel, B.; Seebach, D. *Chem. Ber.* **1977**, *110*, 852.
(8) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.
(9) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.
(10) Büchi, G.; Wuest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294.

0022-3263/89/1954-1792$01.50/0

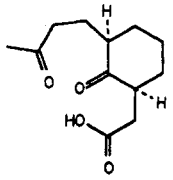
Scheme I



6.06, respectively), intermediates consistent with our earlier observations.[3,4] However, on a routine basis, acid (Amberlyst 15[11]) was added to the post-ozonized, argon-purged solution at −78 °C, which was then allowed to warm to ambient temperature overnight. After workup and flash chromatography, (±)-6,9-desmethylartemisinin (**8**) was afforded in 53% yield, along with nonperoxidic desoxy-6,9-desmethylartemisinin (**9**) and *syn*-2-(2-oxo-3-(3-oxobutyl)cyclohexyl)acetic acid (**10**) in 9% and 20% yield, respectively. The desired analogue **8** exhibited NMR



9

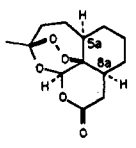


10

spectral characteristics (400-MHz ^1H and ^{13}C) that were very similar to those of the natural product artemisinin. That the identical relative stereochemistry for the resultant tetracycle had indeed been produced, as depicted by **8**, was confirmed by NOE experiments.[12]

(11) Jefford, C. W.; Favarger, F.; Ferro, S.; Chambaz, D.; Bringhen, A.; Bernardinelli, G.; Boukoualas, J. *Helv. Chim. Acta* **1986**, *69*, 1778.

(12) An alternative stereoisomer **i** of **8** can be envisioned from the delivery of ozone onto the opposite face of the vinylsilane, albeit on the same side as the cyclohexyl alkyl substituents. However, our total synthesis of (+)-artemisinin,[3] and in the preparation of other analogues,[4] we have never encountered any other relative stereochemistry in the final cyclization sequence. Isomer **i** was readily eliminated as a possible product on the basis of DNOE experiments (see Experimental Section) that showed H_{12} was not on the same face of the molecule as H_{5a}/H_{8a}.



i

The analogue **8** displayed significant antimalarial activity against resistant strains of *P. falciparum*. Work is in progress to produce other novel analogues of artemisinin via slight modifications of the synthetic sequence presented in Scheme I.

Experimental Section

All melting points were determined on a Thomas capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX90 and a Varian XL400 spectrometer with $CDCl_3$ as solvent unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 1310 instrument. Mass spectral data were obtained through the use of a CEC 21-110B high-resolution, double-focusing spectrometer. Elemental analysis were determined by Desert Analytics, Tucson, AZ.

Synthesis of 10-[(Trimethylsilyl)methylidene]bicyclo-[4.3.1]dec-3-ene (3). As described by Gröbel and Seebach,[7] bis(trimethylsilyl)methyllithium was prepared: to a solution of distilled bis(trimethylsilyl)methane (28.1 mL, 0.131 mol, 1.04 equiv), HMPT (50 mL), and THF (200 mL) at −78 °C was added t-BuLi (77.0 mL of 1.7 M in pentane). The resultant yellow-green solution was maintained at −40 °C for 8 h and then cooled to −78 °C, whereupon to the resultant orange solution was added a solution of bicyclo[4.3.1]dec-3-en-10-one[5] (**2**, 18.9 g, 0.126 mol) in THF (60 mL) over 15 min. The mixture was allowed to warm to ambient temperature overnight. After 15 h, the resultant yellow solution was stirred with H_2O (300 mL) and extracted with hexane (3 × 200 mL). The combined organic layers were washed with H_2O (5 × 100 mL) and brine (2 × 200 mL), dried over Na_2SO_4, and evaporated at reduced pressure to afford 30.7 g of yellow oil, which was purified via flash chromatography with hexane and SiO_2 and subsequent distillation, bp 94–95 °C at 0.25 Torr. In this fashion, 21.2 g (78%) of vinylsilane **3** was obtained as a colorless oil, suitable for analysis. NMR (400 MHz): δ 5.68 (m, 2 H, C*H*=C*H*), 5.19 (s, 1 H, =C*H*($SiMe_3$), 2.85 (br s, 1 H, bridgehead), 2.55 (br m, 1 H, bridgehead), 2.64 (br m, 4 H, CH_2CH=), 2.05 (m, 1 H), 1.71 (m, 4 H), 1.28 (m, 1 H), 0.080 (s, 9 H, $Si(CH_3)_3$). IR (NaCl): 2960, 2920, 1610, 1250, 875, 840 cm^{-1}. EIMS *m/e* (rel intensity): 220 (19), 146 (72), 73 (100), 59 (27). Anal. Calcd for $C_{14}H_{24}Si$: C, 76.28; H, 10.97. Found: C, 76.20; H, 11.06.

Methyl *syn*-2-[3-(2-Oxoethyl)-2(*E*,*Z*)-[(trimethylsilyl)-methylene]cyclohexyl]acetate (4). As per Schreiber's proce-

dure,[8] through a stirring suspension of $NaHCO_3$ (120 mg) in a solution of 10-[(trimethylsilyl)methylene]bicyclo[4.3.1]dec-3-ene (**3**, 3.52 g, 16.0 mmol), dry CH_2Cl_2 (50 mL), and absolute methanol (10 mL) at −78 °C was passed a stream of O_3/O_2. The disappearance of starting material was monitored by periodic TLC (SiO_2 in EtOAc/hexane) before the mixture was purged with inert gas, allowed to warm to ambient temperature, filtered, diluted with dry benzene (100 mL), and concentrated at reduced pressure to a colorless solution of approximately 10 mL. This concentrate was diluted with dry CH_2Cl_2 (100 mL) and treated in succession with triethylamine (3.34 mL) and acetic anhydride (4.52 mL). After 4 h at ambient temperature, the resultant solution was washed with 0.1 N HCl (3 × 30 mL) and 12% aqueous KOH (3 × 30 mL), dried over Na_2SO_4, and evaporated to give a yellow oil, which was purified via column chromatography with SiO_2. After elution with EtOAc/hexane, the desired aldehyde **4** was obtained as a colorless oil, 2.78 g (64%), which consisted of a 1:1 mixture of *E*:*Z* isomers by NMR (90 MHz) and which was used immediately. NMR (90 MHz): δ 9.70 (m, 1 H, C*H*O), 5.30 (s, 1 H, =C*H*(TMS)), 3.68, 3.63 (2 s, 3 H, CO_2CH_3), 3.50–2.05 (m, 6 H), 1.90–1.10 (br m, 6 H), 0.06, 0.04 (2 s, 9 H, $SiCH_3$).

Methyl *syn*-2-[3-[4(*E*,*Z*)-(2-Methoxybut-2-enyl)]-2(*E*,*Z*)-[(trimethylsilyl)methylene]cyclohexyl]acetate (5). To a solution of diisopropylamine (1.55 mL, 10.9 mmol) in THF (85 mL) at 0 °C was added dropwise a solution of *n*-BuLi (6.80 mL of 1.6 M in hexane). After 10 min at 0 °C, a solution of (1-methoxyethyl)diphenylphosphine oxide[9] (2.82 g, 10.9 mmol) in THF (40 mL) was added via cannula. After 10 min at 0 °C, the resultant brick red solution was cooled to −78 °C, and a solution of aldehyde **4** (2.70 g, 10.0 mmol) in THF (40 mL) was added via cannula. After 1 h at −78 °C, the resultant yellow solution was allowed to warm over 45 min to ambient temperature, whereupon it was stirred with saturated aqueous NH_4Cl (100 mL) and extracted with Et_2O (2 × 100 mL). The combined ethereal layers were washed with saturated aqueous NH_4Cl (2 × 100 mL), dried over Na_2SO_4, and evaporated to provide 5.42 g of yellow foam, from which a purified sample of diastereomeric adduct mixture was obtained. NMR (90 MHz): δ 8.25–7.24 (br m, 10 H, Ar*H*), 5.75–4.90 (m, 3 H, *H*OCH, =C*H*), 3.69, 3.68, 3.65, 3.63 (4 s, 3 H, CO_2CH_3), 3.69, 3.68, 3.66, 3.64 (4 s, 3 H, OCH_3), 3.30–0.69 (m, 15 H), 0.07 (m, 9 H, $SiCH_3$).

To a solution of crude adduct in dry THF (45 mL) was added NaH (330 mg of 80% oil dispersion). After 3.5 h at ambient temperature, the resultant suspension was stirred with saturated aqueous NH_4Cl (150 mL) and extracted with Et_2O (2 × 100 mL). The separated organic layer was washed with saturated aqueous NH_4Cl (2 × 50 mL) and brine (150 mL), dried over Na_2SO_4, and evaporated to afford 4.28 g of orange oil, which was purified by column chromatography with SiO_2. After elution with EtOAc/hexane, enol ether **5** was obtained as a yellow oil, 1.87 g (58% from aldehyde **4**), which was a mixture of four diastereomers as reflected in the NMR and TLC (SiO_2 in EtOAc/hexane). NMR (90 MHz): δ 5.10 (m, 1 H, =C*H*), 4.18 (br m, 1 H, C*H*(OMe)), 4.48 (m, 3 H, OCH_3), 3.17–0.90 (m, 15 H), 0.11, 0.07 (2 s, 9 H, $SiCH_3$).

***syn*-2-[3-[4-(2-Oxobutyl)]-2(*E*,*Z*)-[(trimethylsilyl)methylene]cyclohexyl]acetic Acid (7).** To a solution of ester **5** (90.0 mg, 0.278 mmol) in MeOH (10 mL) was added 6 N KOH (0.69 mL, 15 equiv). The solution was heated at reflux for 12 h and allowed to stir at ambient temperature for an additional 12 h. The resultant yellow solution was acidified with saturated aqueous NH_4Cl (35 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over Na_2SO_4, and evaporated to give acid **6** as a yellow oil, which was a fairly pure *E*:*Z* mixture by NMR and was used without further purification. NMR (90 MHz): δ 5.23 (m, 1 H, =C*H*), 4.26 (br t, 1 H, *J* = 6.5 Hz, MeOC=C*H*), 3.53, 3.52, 3.48, 3.46 (4 s, 3 H, OCH_3), 3.40–0.90 (m, 15 H), 0.11, 0.07 (2 s, 9 H, $SiCH_3$).

The yellow oil was placed in CH_2Cl_2 (10 mL) and stirred with SiO_2 (70–230 mesh) while adding freshly prepared 10% aqueous oxalic acid (50 mL). After 2 h at ambient temperature, the solid was filtered off and rinsed with CH_2Cl_2 (100 mL). The filtrate was concentrated in vacuo to afford a yellow oil, which was purified by column chromatography with SiO_2. After elution with HOAc/EtOAc/hexane, *E*:*Z* keto acids **7** were obtained as a yellow oil, 77 mg (94% from enol **5**). NMR (90 MHz): δ 5.32, 5.16 (2 s, 1 H, =C*H*), 3.30–2.30 (m, 6 H), 2.13 (s, 3 H, $COCH_3$), 2.00–1.00 (br m, 8 H), 0.11, 0.07 (2 s, 9 H, $SiCH_3$).

(±)-Octahydro-3-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one ((±)-6,9-Desmethylartemisinin (8)). Through a solution of keto acid **7** (1.03 g, 3.49 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was passed a stream of O_3/O_2. After the resultant solution was purged with argon, Amberlyst 15 (1.0 g) was added, and the mixture allowed to warm to ambient temperature. After 21 h, the resin was filtered off, and the filtrate concentrated in vacuo to 0.76 g of yellow oil, which was further purified via flash column chromatography with SiO_2 and EtOAc/hexane. In this fashion, 277 mg (53%) of 6,9-desmethylartemisinin (**8**) was obtained as white crystals, which upon recrystallization with EtOAc/hexane provided analytically pure microprisms, mp 130.0–130.5 °C. ^1H NMR (400 MHz): δ 5.90 (s, 1 H, H_{12}), 3.18 (dd, 1 H, *J* = 18.3, 7.1 Hz, $H_{9\alpha}$), 2.42 (ddd, 1 H, *J* = 14.8, 13.5, 3.8 Hz, $H_{4\alpha}$), 2.25 (dd, 1 H, *J* = 18.3, 1.3 Hz, $H_{9\beta}$), 2.02 (ddd, 1 H, *J* = 14.8, 4.9, 2.7 Hz, $H_{4\beta}$), 1.93 (m, 1 H, $H_{7\beta}$), 1.88 (m, 1 H, H_{8a}), 1.78 (m, 4 H, H_{5a}, $H_{5\beta}$, H_6, H_8), 1.53 (m, 1 H, $H_{5\alpha}$), 1.44 (s, 3 H, CH_3), 1.37 (m, 2 H, H_6, H_8), 1.25 (m, 1 H, $H_{7\alpha}$). ^{13}C NMR: δ 168.7 (C_{10}), 105.4 (C_3), 93.2 (C_{12}), 78.1 (C_{1a}), 43.9 (C_{5a}), 38.4 (C_{8a}), 36.0 (C_4), 32.1 (C_7), 31.6 (C_9), 30.2, 26.6 (C_5), 25.5 (C_{14}), 24.7. The above assignments were based on a combination of selective proton decouplings, APT, and HETCOR experiments in a manner similar to the proton and carbon assignments made for artemisinin.[13] This product (**8**) was differentiated from the possible isomer i by difference NOE experiments as follows. Proton, carbon, APT, and HETCOR experiments were recorded in C_6D_6. ^1H NMR (400 MHz, C_6D_6): δ 5.50 (s, 1 H, H_{12}), 3.00 (dd, 1 H, *J* = 18, 7.2 Hz, $H_{9\alpha}$), 2.19 (m, 1 H, $H_{4\alpha}$), 1.86 (dd, 1 H, *J* = 18, 1 Hz, $H_{9\beta}$), 1.55 (ddd, 1 H, *J* = 14.4, 4.5, 2.7 Hz, $H_{4\beta}$), 1.21 (s, 3 H, CH_3), 1.15 (m, 6 H), 0.88 (m, 1 H), 0.60 (m, 3 H). ^{13}C NMR (C_6D_6): δ 167.1 (C_{10}), 105.1 (C_3), 92.9 (C_{12}), 78.2 (C_{1a}), 44.2 (C_{5a}), 38.7 (C_{8a}), 36.4 (C_4), 32.1 (C_9), 32.0, 29.9, 27.1, 25.8 (C_{14}), 24.9.

Irradiation of the H_{12} singlet at δ 5.50 led to a 13% NOE enhancement solely of the multiplet centered at δ 0.60 (the characteristic "fingerprint-like" multiplicity of the δ 0.60 signal was unaltered). The three protons in the δ 0.60 multiplet were shown to have cross peaks (HETCOR) to the three different carbons at δ 32.0, 29.9, and 24.9. Further, these carbons were shown to be methylene carbons by APT and had second cross peaks to the proton multiplet at δ 1.15. The absence of an NOE enhancement in the δ 1.15 multiplet which contains the two methine signals (APT, HETCOR) for H_{5a} and H_{8a}, allowed for the exclusion of isomer i as a possible product. Inspection of Dreiding models showed that in structure **8**, the closest protons to H_{12} were $H_{5\beta}$, $H_{6\beta}$, and $H_{8\beta}$. Thus, by analogy to NOE experiments with the natural product[13] and the observations made above, the assignment of structure **8** and the multiplet at δ 0.60 to $H_{5\beta}$, $H_{6\beta}$, and $H_{8\beta}$ are reasonably made. A confirming complementary experiment was run in which the δ 0.60 multiplet was irradiated, leading to a 28% NOE enhancement of the H_{12} singlet at δ 5.50. IR (KBr): 2925, 1735, 1210, 1005 cm^{-1}. CIMS ($^+NH_4$) *m*/*e*: 272 (M + $^+NH_4$), 255 (M + ^+H). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.39; H, 7.17.

The chromatographic separation also provided desoxy-6,9-desmethylartemisinin (**9**), 69 mg (9%) of white rhombic prisms, mp 117–118 °C, and *syn*-2-[2-oxo-3-(3-oxobutyl)cyclohexyl]acetic acid (**10**), 161 mg (20%) of white crystalline powder, mp 87–88 °C.

(±)-Octahydro-2-methyl-2,11-epoxy-11*H*-pyrano[4,3-*j*]-benzopyran-9(2*H*)-one (Desoxy-6,9-desmethylartemisinin (9)). NMR (400 MHz): δ 5.72 (s, 1 H, $OCHO_2C$), 2.98 (dd, 1 H, *J* = 17.6, 5.9 Hz, $H_{8\beta}$), 2.26 (dd, 1 H, *J* = 17.6, 1.7 Hz, $H_{8\alpha}$), 2.12 (dddd, 1 H, *J* = 13.4, 5.8, 4.0, 1.6 Hz), 1.82–1.58 (br m, 7 H), 1.51 (s, 3 H, CH_3), 1.47–1.06 (m, 4 H). IR (CH_2Cl_2): 2945, 1745, 1210, 1195, 1105, 915 cm^{-1}. EIMS *m*/*e* (rel intensity): 238 (11), 196 (21), 167 (20), 136 (70), 110 (33), 79 (23). HRMS calcd for $C_{23}H_{18}O_4$ 238.120, found 238.120. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.81; H, 7.68.

(±)-*syn*-2-[2-Oxo-3-(3-oxobutyl)cyclohexyl]acetic Acid (10). NMR (400 MHz): δ 2.87–2.78 (m, 2 H), 2.55 (ddd, 1 H, *J*

(13) Zhongshau, W.; Nakashima, T. T.; Kopecky, K. R.; Molina, J. *Can. J. Chem.* **1985**, *63*, 3070.

= 17.6, 8.8, 6.0 Hz), 2.41 (ddd, 1 H, J = 8.8, 8.6, 6.6 Hz), 2.36 (m, 1 H), 2.24–2.10 (m, 3 H), 2.10 (s, 3 H, $COCH_3$), 1.93 (ddd, 1 H, J = 14.1, 8.3, 6.0 Hz), 1.84 (ddd, 1 H, J = 7.1, 4.4, 2.7 Hz), 1.75 (tt, 1 H, J = 13.1, 3.8 Hz), 1.50 (dddd, 1 H, J = 14.1, 8.6, 6.6, 4.7 Hz), 1.36 (m, 2 H). IR (CH_2Cl_2): 3000 (broad —OH), 2940, 2870, 1710 cm^{-1}. EIMS m/e (rel intensity): 226 (4), 208 (50). HRMS calcd for $C_{12}H_{18}O_4$ 226.120, found 226.120. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.69; H, 8.17.

Acknowledgment. We thank Dr. W. Milhous and the MRDC support staff for the biological evaluation of 6,9-desmethylartemisinin and discussions. This work was supported in part by USAMRDC Contract No. DAMD17-85-C-5011.

Registry No. **2**, 40958-79-0; **3**, 119297-21-1; (±)-(*E*)-**4**, 119297-22-2; (±)-(*Z*)-**4**, 119364-69-1; (±)-**5** (isomer 1), 119297-23-3; (±)-**5** (isomer 2), 119364-70-4; (±)-**5** (isomer 3), 119364-71-5; (±)-**5** (isomer 4), 119364-72-6; (±)-**6** (isomer 1), 119297-24-4; (±)-**6** (isomer 2), 119364-73-7; (±)-**6** (isomer 3), 119364-75-9; (±)-**6** (isomer 4), 119364-76-0; (±)-(*E*)-**7**, 119297-25-5; (±)-(*Z*)-**7**, 119364-74-8; (±)-**8**, 119297-26-6; (±)-**9**, 119297-27-7; (±)-**10**, 119297-28-8; $CH_2(TMS)_2$, 2117-28-4; $(Ph)_2POCH(CH_3)(OMe)$, 64304-77-4; pyrrolidinocyclohexene, 1125-99-1; *cis*-1,4-dichloro-2-butene, 1476-11-5; methyl 2-[3-[3-(diphenylphosphinyl)-2-hydroxy-3-methoxybutyl]-2-[(trimethylsilyl)methylene]cyclohexyl]acetate, 119297-29-9.

Enzymes in Organic Synthesis. 46.[1] Regiospecific and Stereoselective Horse Liver Alcohol Dehydrogenase Catalyzed Reductions of *cis*- and *trans*-Bicyclo[4.3.0]nonanones

Andrzej R. Krawczyk[†] and J. Bryan Jones*[,‡]

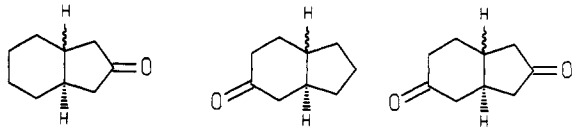
Departments of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 1A1, and Warsaw University, 02093 Warsaw, Poland

Received April 26, 1988

Further evidence for the preference of horse liver alcohol dehydrogenase for six-membered rather than five-membered ring ketone substrates is presented. This chemospecificity can be exploited preparatively, as illustrated by the HLADH-catalyzed reductions of (±)-*cis*- and -*trans*-bicyclo[4.3.0]nonane-3,8-diones. In these reactions, the chemospecificity of the enzyme is accompanied by diastereotopic face specificity and enantiomeric selectivity, resulting in good yields of keto alcohol products and recovered diketones of up to 94% enantiomeric excess. The results are fully in accord with the predictions of the cubic space-section model of the enzyme's active site. Enzyme-controlled combinations of specificity of this type have considerable asymmetric synthetic potential and cannot yet be duplicated in a single-step reaction by nonenzymic catalysts.

In recent years, the versatility of enzymes as chiral catalysts for organic synthesis has been widely recognized.[2] Among the major advantages of enzymes as catalysts is their ability to combine several different specificities in a single catalytic step reaction. In this paper, we report on some horse liver alcohol dehydrogenase (HLADH[3]) catalyzed reductions in which regiospecificity, enantioselectivity, and stereoheterotopic selectivity are controlled concurrently.

HLADH is a commercially available, NAD/H-coenzyme dependent, enzyme that catalyzes a broad range of CH(OH) ⇌ C=O oxidoreductions.[1,2,4] The ability of HLADH to combine regio- and stereospecificity in its catalyses has previously been demonstrated for diol oxidations.[5] In order to ascertain if similar discriminations could be exploited in the reduction mode, we have investigated the HLADH-catalyzed reductions of the *cis*- and *trans*-bicyclo[4.3.0]nonane mono- and diketones (±)-**1**–**3a,b**.



(±)-1a,b (±)-2a,b (±)-3a,b

a, C-6α-H, *cis*-series
b, C-6β-H, *trans*-series

[†] Warsaw University.
[‡] University of Toronto.

Results

Preparations of Substrates. The cis substrates (±)-**1**–**3a** were prepared from *cis*-bicyclo[4.3.0]non-3-en-8-one (**4a**),[6] and the trans isomers (±)-**1**–**3b** from *trans*-4,5-bis(hydroxymethyl)cyclohexene[6] as shown in Scheme I.

HLADH-Catalyzed Reductions. The rates of HLADH-catalyzed reductions of (±)-**1**–**3a,b** relative to that of the standard reference substrate cyclohexanone under the same conditions are recorded in Table I, together with the results of the preparative-scale reduction experiments, which were carried out on (±)-**2,3a,b** with ≈1 g of substrate

(1) Part 45. Bur, D.; Luyten, M. A.; Wynn, H.; Provencher, L. R.; Gold, M.; Friesen, J. D.; Clarke, A. R.; Holbrook, J. J.; Jones, J. B. *Can. J. Chem.*, submitted for publication.

(2) (a) Jones, J. B.; Beck, J. F. *Tech. Chem. (NY)* **1976**, *10*, 107. Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. (b) Wong, C. H.; Whitesides, G. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 617. Akiyama, A.; Bednarski, M.; Kim, M. J.; Simon, E. S.; Waldmann, H.; Whitesides, G. M. *Chem. Br.* **1987**, *23*, 645. (c) Klibanov, A. M. *Science* **1983**, *219*, 722; *Chem. Tech.* **1986**, 354. (d) *Enzymes in Organic Synthesis*; Ciba Foundation Symposium 111; Porter, R., Clark, S., Eds.; Pitman: London, 1985. (e) *Biocatalysis in Organic Synthesis*; Tramper, J., von der Plas, H. C., Linko, P., Eds.; Elsevier: Amsterdam, 1985. (f) *Enzymes as Catalysts in Organic Synthesis*; Schneider, M., Ed.; Reidel: Dordrecht, Netherlands, 1986.

(3) Abbreviations used: HLADH, horse liver alcohol dehydrogenase; NAD/H, oxidized and reduced forms, respectively, of nicotinamide adenine dinucleotide; MTPA, (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl; $Eu(fod)_3$, tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)europium (III).

(4) Dodds, D. R.; Jones, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 577.

(5) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 1625.

(6) Mundy, B. P.; Theodore, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 2005.

0022-3263/89/1954-1795$01.50/0