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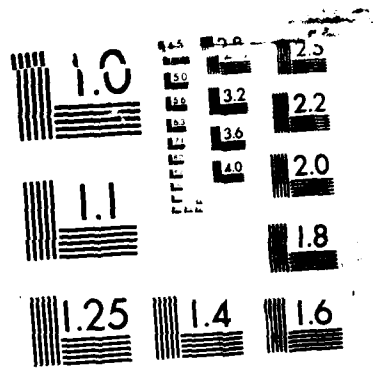

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"ANTIMALARIAL CYCLIC PEROXIDE LACTONES"

ANNUAL REPORT

KUO-HSIUNG LEE

May 15, 1985

Supported by

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Antimalarial agents; 15-methylcarbamoyl bruceolide; 15-phenylalaninyl bruceolide

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

15-Methylcarbamoyl bruceolide and 15-phenylalaninyl bruceolide were synthesized from brusatol, obtained by acid hydrolysis of bruceoside-A, by an initial protection of the 3-hydroxyl group as a dimethyl-t-butylsilyl ether followed by base hydrolysis of the C-15 ester side chain, reacylation with methyl isocyanate and N-t-butoxycarbonyl L-phenylalanine anhydride, respectively, and deblocking of the silyl moiety with 80% acetic acid and tetrabutylammonium fluoride, respectively.

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FIGURE 2

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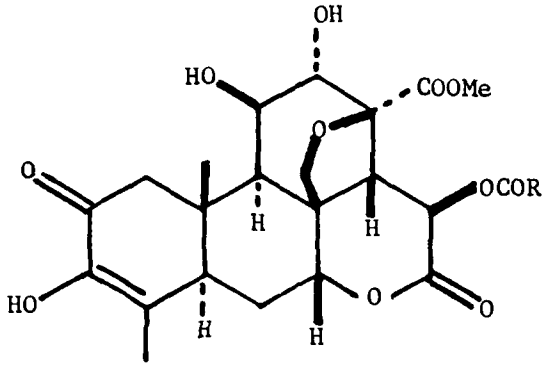
Lee, K. H.
DAMD 17-83-C-3098

ANNUAL REPORT

(1) List of structures of all target compounds that have been submitted to the Walter Reed Army Institute of Research for screening between February 14, 1984 - September 14, 1984.



1. R = $NHCH_3$ (430 mg) (15-methylcarbamoyl bruceolide)
   BK84184

2. R = $\underset{NH_2}{CH}-CH_2-C_6H_5$ (500 mg) (15-phenylalaninyl bruceolide)

(2) Synthetic procedures for each target compound listed above

The synthesis of 15-methylcarbamoyl bruceolide (XII) and 15-phenylalaninyl bruceolide (XVI) was based upon the discussion and recommendation in a telephone conversation with Dr. H. A. Musallam, Department of Medicinal Chemistry, Division of Experimental Therapeutics, Walter Reed Army Institute of Research on March 1, 1984.

1. 15-Methylcarbamoyl bruceolide (XII) (Scheme-1):

a. The synthesis of XII employed a procedure using brusatol as a starting material. Compound IX, prepared from brusatol was described on page 5 of my "annual Report" which was submitted previously on February 13, 1984.

b. Synthesis of Compound XI: To a solution of IX (530 mg) in absolute benzene (50 mL) was added MeNCO (82 mg). The mixture, after stirred at room temp. for 30 hrs., was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$ and evaporated in vacuo to yield a residue. Recrystallization of this residue from ether-petroleum ether afforded XI (480 mg, 82% yield) as white prisms: mp 145-157°; IR ($CHCl_3$) 3450, 3550 (OH and NH), and 1730 (C=O) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.95 (1H, d, J = 15 Hz, H-15), 5.40 (1H, br. s, NH), 4.83 (1H, br. s, H-7), 4.71, 3.75 (2H, d each, J = 7.5 Hz, H-17), 4.24 (2H, br. s, H-11 and H-12), 3.79 (3H, s, $COOCH_3$), 2.80 (3H, d, J = 5.6 Hz, N-CH_3), 1.86 (3H, s, CH_3-4), 1.39 (3H, s, CH_3-10), 0.96 (9H, s, Si-t-butyl group), 0.16, 0.15 (6H, s each, $SiMe_2$) and 2.97 (1H, d, J = 15.0 Hz, H-14).
Anal. Calcd for $C_{29}H_{43}O_{11}$ N Si: m/z 609.2596. Found: m/z 609 (M^+); for $C_{25}H_{34}O_{11}$ N Si (M^+-C_4H_9): m/z 552.1898. Found: m/z 552.1898.

c. Synthesis of 15-Methylcarbamoyl Bruceolide (XII): A solution of XI (222 mg, 0.36 mmol) in 80% acetic acid (2 mL) was heated at 80°C for 1.5 hr with stirring. After the acetic acid was evaporated in vacuo, the residue was added with water (10 mL). The water-insoluble substances were filtered. The filtrate was evaporated under reduced pressure to give an oil (150 mg) which showed two spots on TLC (silica gel - EtOAc). Separation and isolation of Compound XII (80 mg) was achieved by PTLC (silica gel - EtOAc). Compound XII (50% yield) was recrystallized from acetone-ether: mp 204-206°; IR (IBr) 3600-3200 (br., OH, NH), 1730 (ester and lactone CO), 1640 (OCONHMe), and 1660 (α,β-unsat. CO) cm^{-1}; NMR (250 MHz, DMSO-d_6-TMS) δ 7.77 (1H, br. s, NH), 5.44 (1H, br. s, H-15), 4.92 (1H, br. s, H-7), 4.42, 3.69 (2H, d each, J = 7.5 Hz, H-17), 4.06 (1H, s, H-12), 4.02 (1H, d, J = 7.5 Hz, H-11), 3.69 (3H, s, $COOCH_3$), 2.86 (3H, s, N-CH_3), 2.76 (1H, d, J = 15.0 Hz, 14-H), 2.76 (2H, q, J = 5.0 Hz, H-1), 2.11 (1H, dd, J = 15.0 Hz and 2.0 Hz, H-5), 1.81 (2H, dt, J = 15.0 Hz and 2.0 Hz, H-6), 1.69 (3H, s, CH_3-4) and 1.17 (3H, s, CH_3-10).
Anal. Calcd for $C_{23}H_{29}O_{11}$ N: m/z 495.1739. Found: m/z 495.1722.

d. Considerable efforts were made to remove the dimethyl-t-butylsilyl protecting group from IX in order to make XII. When XI was treated with tetrabutylammonium fluoride in THF at room temperature, Compound XIII instead of Compound XII was obtained in ca. 80% yield.

2. 15-Phenylalaninyl bruceolide (XVI) (Scheme-1):

a. Synthesis of Compound XIV - To a stirred solution of IX (600 mg) in anhydrous benzene (30 mL) was added freshly distilled anhydrous pyridine (2 mL) and N-tert butoxycarbonyl-L-phenylalanine anhydride[1] (700 mg). After 20 hr, the mixture was washed with water, diluted HCl, water, $NaHCO_3$, saturated NaCl and water. The benzene layer was dried over anhydrous $MgSO_4$ and evaporated in vacuo to yield a residue (800 mg). Recrystallization of this residue from ether afforded XIV as colorless needles (630 mg, 72% yield): mp 233-235°; IR (KBr) 3600-3400 (OH and NH), 1740 (lactone CO), 1725 (ester CO), 1670 (NHCO), 1640 (C=C-CO) and 1610 (C=C-CO) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 0.15, 0.16 (3H each, s) ($SiMe_2$), 0.93 (9H, s, $SiMe_3$), 1.35 (9H, s, $O\text{-}CMe_3$), 1.38 (3H, s, Me-10), 1.83 (3H, s, Me-4), 2.02 (H-9), 2.34 (2H, m, H-6 and H-1), 2.92 (2H, m, H-6 and H-1), 3.19 (1H, d, J = 7.50 Hz, H-14), 3.79 (3H, s, COOMe), 4.24 (2H, brm, H-11 and H-12), 3.75, 4.69 (2H, d each, J = 7.50 Hz, H-17), 4.78 (1H, s-like, H-7), 6.30 (1H, d, H-15) and 7.27 (5H, aromatic protons).
Anal. Calcd for $C_{41}H_{57}O_{13}N\,Si$: m/z 799.3583. Found: m/z 742 [M^+-57 (t-BOC group)] and m/z 784 [M^+-15 (Me group)].

b. Synthesis of XV - Tp a stirred solution of XIV (1.23 g, 1.53 mmol) in THF (8 mL) was added $Bu_4N^+\,F^-$ (4 mL, 4 mmol) at 0°. After 10 min., the reaction mixture was poured into iced water (20 mL) and extracted with chloroform. The chloroform extract was washed with water, 3% aqueous Na_2CO_3 and water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give a residue. Recrystallization from EtOAc-ether yielded XV as colorless prisms (990 mg, 94% yield): mp 213-215°; TLC [silica gel, EtOAc-$CHCl_3$ (1:1), Rf = 0.3]; IR (KBr) 3550-3300 (OH and NH), 1740 and 1720 (lactone and ester CO), 1640 (NHCO) and 1610 (α,β-unsat. CO) cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.35 (9H, s, CMe_3), 1.39 (3H, s, Me-10), 1.84 (3H, d, J = 1.0 Hz, Me-4), 3.20 (2H, d-like, J = 13.0 Hz, CH_2Ph), 3.81 (3H, s, COOMe), 4.26 (2H, m, H-11 and H-12), 4.53 (1H, m, $CH\text{-}CH_2Ph$), 3.75, 4.70 (1H each, d, J = 7.5 Hz, H-17), 4.77 (1H, s-like, H-7), 5.00 (1H, d, J = 11.0 Hz, NHCO), 6.32 (1H, d, J = 13.0 Hz, H-15) and 7.27 (5H, m, aromatic protons).
Anal. Calcd for $C_{35}H_{43}O_{13}N$: m/z 685.2747. Found (FAB): m/z 686 (M^+ + H) and
m/z 586 [M^+-99 (t-BOC)].

c. Synthesis of XVI - A solution of XV (830 mg) in anhydrous EtOAc (20 mL) was cooled to 0°, and anhydrous HCl gas was introduced

into this solution for about 40 min. The reaction mixture was allowed to stand at 0° for 30 min in the nitrogen atmosphere. The resulting crystals were filtered, washed with cold EtOAc and dried to furnish XVI (700 mg, 93% yield) as colorless needles: mp 225-227°; TLC (silica gel, EtOAc, Rf = 0.40); IR (KBr) 3500-3200 (OH and NH_2), 1760 (lactone CO) and 1740 (ester CO) cm^{-1}; NMR (250 MHz, CD_3OD) 1.38 (3H, s, Me-10), 1.84 (3H, s, Me-4), 1.90 (1H, d, J = 5.1 Hz, H-9), 3.00 (1H, H-5), 2.55, 2.86 (1H each, d, J = 15.0 Hz, H-1), 3.44 (1H, d, J = 15.0 Hz, H-14), 3.69 (3H, s, COOMe), 3.06, 3.34 (1H each, q, J = 15.0, 4.0 and 15.0, 7.0 Hz, H-23), 4.38 (1H, q, J = 4.0 and 7.0 Hz, H-22), 4.18 (1H, d, J = 5.6 Hz, H-11), 4.32 (1H, s-like, H-12), 3.72, 4.70 (1H each, d, J = 7.0 Hz, H-17), 4.92 (1H, m, H-7), 6.37 (1H, d, J = 15.0 Hz, H-15) and 7.35 (5H, m, aromatic protons).

Anal. Calcd for $C_{30}H_{35}O_{11}N \cdot HCl \cdot \frac{5}{3} H_2O$: C 55.25%, H 6.08 and N 2.14%. Found: C 55.09%, H 6.30% and N 2.51%.

Also Anal. Calcd for $C_{30}H_{35}O_{11}N$ (FAB): m/z 585 (M^+). Found: m/z 586 ($M^+ + H$).

(3) Literature references -

1. D. H. Rammler and H. G. Khorana, J. Am. Chem. Soc., 85, 1997 (1963).

(4) Biological test data -

These are not available as testing on compounds listed above in (1) is in progress by Walter Reed Army Institute of Research.

(5) Publication and patents -

1. These will be considered upon the completion of biological testing.

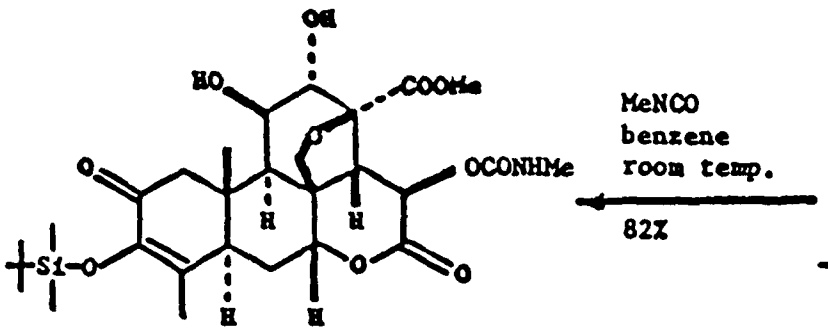
2. "Antimalarial Agents. 1. α-Santonin-Derived Cyclic Peroxide as Potential Antimalarial Agent" by S. Tani, N. Fukamiya, H. Kiyokawa, H. A. Musallam, R. O. Pick and K. H. Lee, J. Med. Chem., in press. This publication is based upon data presented in my Annual Report submitted February 13, 1984, p. 4.

(6) List of personnel receiving contract support -

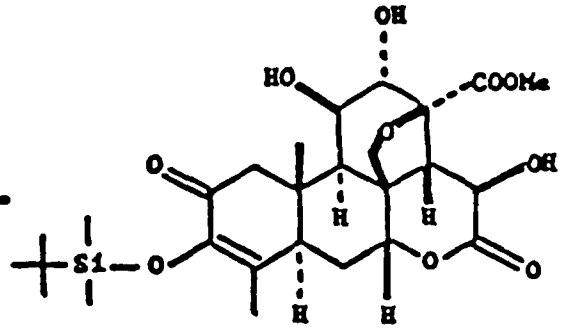
1. Dr. Shohei Tani (2/14/84-9/14/84), Associate Professor of Pharmaceutical Chemistry, on leave from Kobe Gakuin University (Ph.D. from Kyoto University) worked continuously very hard on this project.

2. Dr. Hiroshi Irie, Professor of Pharmaceutical Chemistry at Nagasaki University participated in the discussion and the work of the synthetic analogs related to artemisinine beginning July 1, 1984 through August 31, 1984. Dr. Iris is a distinguished synthetic organic chemist with more than 80 publications in the synthesis of natural products.

Scheme 1



MeNCO
benzene
room temp.
82%

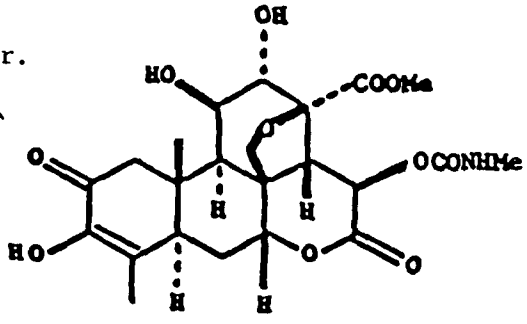


XI

IX

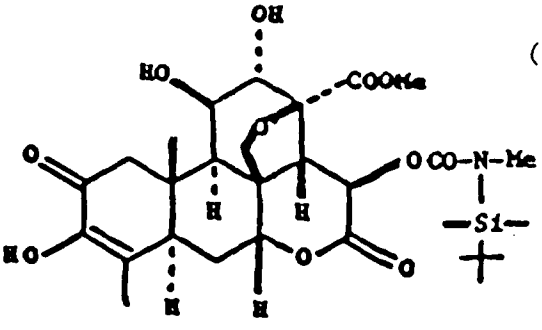
80% AcOH
80°C
1.5 hr.
50%

$Bu_4N^+ F^-$ -
THF, room temp.
80%

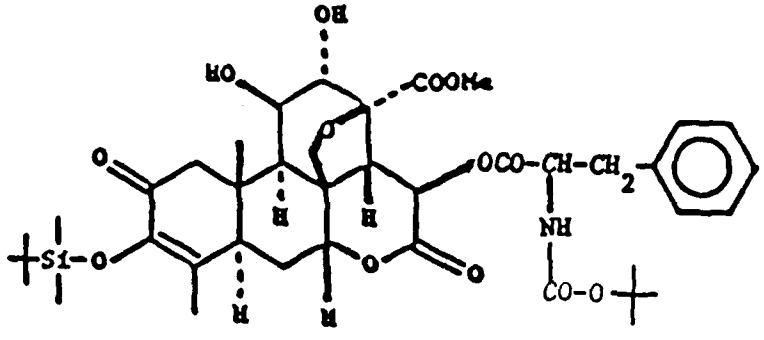


XII
(15-Methylcarbamoyl bruceolide)

$O(COCHCH_2\text{-}Ph)_2$
NHCOO+
pyridine
72%

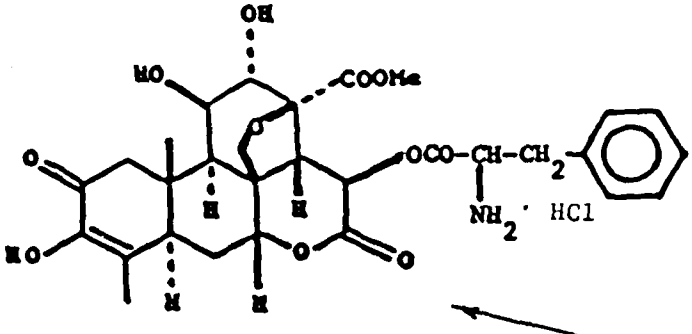


XIII



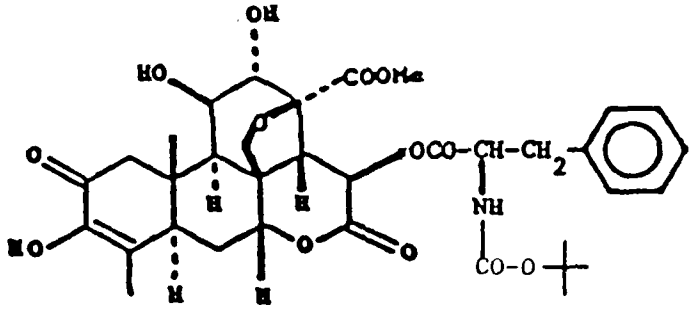
XIV

$Bu_4N^+ F^-$
THF, 94%



XVI
(15-Phenylalaninyl bruceolide)

HCl -
EtOAc, 0°C
93%



XV

END

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