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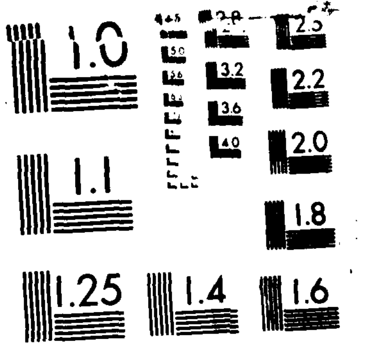

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"ANTIMALARIAL CYCLIC PEROXIDE LACTONES"

ANNUAL REPORT

KUO-HSIUNG LEE

AD-A168 091

February 13, 1984

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

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18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Antimalarial agents; bruceoside-A acetonide; brusatolyl-1-nonenoate; 2,5-α-peroxy-6,11 βH-eudesm-3-en-6,13-olide.

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

Bruceoside-A acetonide was synthesized by an acid-catalyzed transacetalization of bruceoside-A and acetaldehyde diethyl acetal. Brusatolyl-1-nonenoate was 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 1-nonenoyl chloride and deblocking of the silyl moiety with tetrabutylammonium fluoride. Bruceoside-A was obtained directly by extraction of Brucea javanica (Simaroubaceae).

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The synthesis of 2,5-α-peroxy-6, 11 βH-eudesm-3-en-6,13-olide involved the reduction of 1,2-dihydro-α-santonin, prepared by catalytic hydrogenation of α-santonin, with aluminum isopropoxide to a 3-hydroxy derivative. Subsequent conversion of this derivative to 6,11 βH-eudesm-2,4-dien-6,13-olide via a 3-0-mesyl intermediate, followed by photooxygenation gave rise to the desired cyclic peroxide lactone.

Evaluation of these novel compounds as potential antimalarial drugs by Walter Reed Army Institute of Research is currently in progress.

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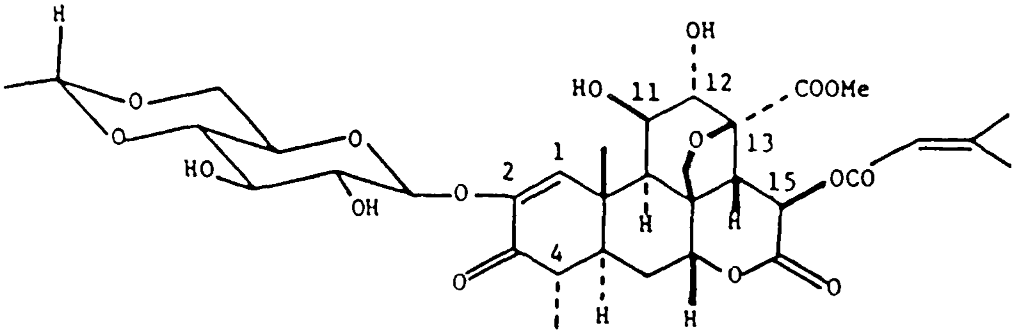
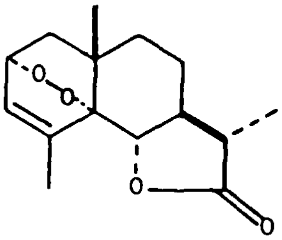
(1) List of structures of all target compounds that have been submitted to the Walter Reed Army Institute of Research for screening between March 15, 1983 - February 10, 1984).

1.



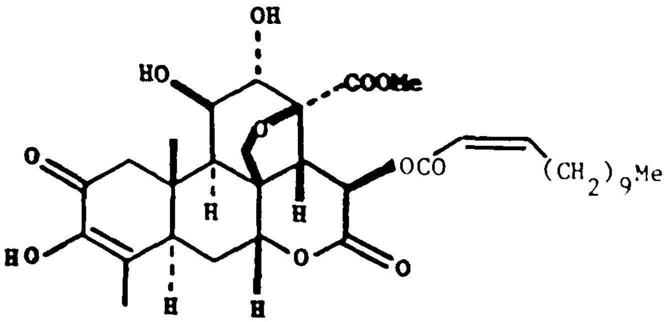
Bruceoside-A Acetonide (500 mg)
(BK 69703)

2.



ST-ST-Peroxide-1 (500 mg)
(BK 70493)

3.



Brusatolyl-1-Nonenoate (500 mg)*

* : To be submitted before March 14, 1984.

(2) Synthetic procedures for each target compound listed above

1. Bruceoside-A Acetonide:

a. The starting material bruceoside-A was obtained by an initial extraction of air-dried fruits of *Brucea javanica* according to an exact procedure described in the literature[1] by the P.I., followed by column and preparative scale high performance liquid chromatographic purification.

b. Treatment of bruceoside-A (100 mg) with acetaldehyde diethyl acetal (4.0 mg) and p-toluene sulfonic acid (10 mg) in chloroform (20 mL) at room temperature for two days followed by silica gel column chromatography (1 g) of the resulting product yielded bruceoside-A acetonide as amorphous powder (60% yield): mp 185-190°; IR 3450 (br, OH), 1730-1760 (br, C=O) and 1640 (C=C) cm^{-1}; NMR (250 mHz, $CDCl_3$, TMS) δ 1.17 (3H, d, J = 7.0 Hz, MeCHOO), 1.60 (3H, s, Me-10), 1.39 (3H, d, J = 5.0 Hz, Me-4), 1.6-2.1 (5H, m, H-5, H-6, H-9 and H-14), 1.94 (3H, d, J = 1.5 Hz, Me-23), 2.20 (3H, d, J = 1.5 Hz, Me-23), 2.4-2.6 (1H, m, H-4), 3.35-3.80 [10H, m, sugar CH-O (6H) + 4 OH], 3.81 (3H, s, COOMe), 4.15-4.28 (2H, m, H-11 and H-12), 4.44 (1H, br. s, H-15), 4.6-4.8 (4H, m, H-7, H-17 and anomeric H), 5.62 (1H, s, H-22), 6.20 (1H, br. MeCHOO) and 6.85 (1H, s, H-1).
Anal. Calcd for $C_{34}H_{44}O_{16}$: m/z 708.2626. Found: m/z 708.2620.

c. This compound (500 mg) was prepared and submitted based upon the discussion and recommendation during the site visit of Drs. R. O. Pick and H. A. Musallam on July 26, 1983.

2. ST-ST-Peroxide-1 - see Scheme-1

a. 1,2-Dihydro-α-Santonin (II) - This known compound was prepared from α-santonin (I) according to an exact literature procedure[2] in quantitative yield.

b. 3-Hydroxy-6, 11βH-eudesm-4-en-6, 13-olide (III) - This compound was prepared based upon Corey's procedure[3] in his synthesis of an analogous compound. A solution of II (11.7 g) and aluminum isopropoxide (26 g) in dry 2-propanol (150 mL) was allowed to boil gently in a 250-mL flask fitted with a Vigreux column. The acetone vapor formed was allowed to escape from the reaction mixture. After 6 hr. the 2-propanol was distilled and the reaction mixture was reduced to ca. a 50-mL volume. Cold 1 N hydrochloric acid was added, and the resulting acidic solution was extracted with methylene chloride. The extracts were washed with saturated sodium bicarbonate and saturated sodium chloride solutions and dried over sodium sulfate to afford an oily mixture (III) in ca. 80% yield. Compound III: IR ($CHCl_3$) 3620 (OH), 3030 (C=C), 1775 and 1765 cm^{-1} (mixture lactone C=O) cm^{-1}; NMR (250 mHz, $CDCl_3$, TMS) δ 1.18 (s, Me-10), 1.21 (d, J = 7.5 Hz, Me-11), 1.93 (s, Me-4), 2.85 (br. s, OH) (disappeared upon addition of D_2O), 3.94 (t, J = 7.5 Hz, H-3), 4.62 (d, J = 9 Hz, H-6) and 2.32 (m, H-11).

c. 6, 11βH - Eudesm-2,4-dien-6,13-olide (V) - This compound was synthesized from III via IV. To a solution of III (3 g) in anhydrous tetrahydrofuran (50 mL) was added 4 mL of triethylamine. The mixture was cooled to < 5° and treated with mesyl chloride (2 g). Stirring was continued for 2 hr. at < 5°. The resulting triethylamine hydrogen chloride salt was filtered and the filtrate was evaporated *in vacuo*.

The residue was added with water and extracted with methylene dichloride, dried over anhydrous magnesium sulfate and distilled under reduced pressure to yield crystalline residue (IV) upon cooling. Without further purification this residue was dissolved in DMSO (10 mL) and treated with DBU (1,5-diazabicyclo [5·4·0] undecene-5) (1.5 g). After stirring for 15 hr, the mixture was added 50 mL of ice-water and the resulting oil was extracted with methylene dichloride, washed with HCl, water, sodium bicarbonate and water, dried over anhydrous magnesium sulfate and evaporated in vacuo to furnish a residue. Recrystallization from ether-hexane gave V as colorless crystals in 25% yield. Compound V: MP 148°; IR (KBr) 3030 (C=C) and 1770 (lactone C=C) cm^{-1}; NMR (250 MHz, $CDCl_3$, TMS) δ 1.05 (3H, s, Me-10), 1.25 (3H, d, J = 7.5 Hz, Me-11), 1.97 (3H, d, J = 2.0 Hz, Me-4), 2.28 (1H, m, H-11), 4.51 (1H, d, J = 11.0 Hz, H-6) and 5.72 (2H, m, H-2 and H-3).

Anal Calcd for $C_{15}H_{20}O_2$: m/z 232.1462. Found: m/z 232.1467. Considerable efforts were directed toward the improvement of yield for the conversion of IV to V. Table-1 lists various reaction conditions which were carried out for this purpose. The reason for this low-yield step is due to the formation of Va.

d. ST-ST-peroxide-1 (or 2,5-α-peroxy-6,11βH-eudesm-3-en-6,13-olide) (VI) - A solution of V (300 mg) and eosin Y (20 mg) in pure benzene (300 mL) was irradiated with a 260-w photoflood lamp while a finely dispersed stream of purified oxygen was bubbled through the reaction mixture. After 30 hr of irradiation, benzene was distilled under reduced pressure and the resulting oil was column chromatographed on silica gel (30 g). The benzene-ethyl acetate (1:1) eluate yielded 200 mg (60% yield) of the desired peroxide V as colorless prisms after recrustallization from ether. Compound VI: mp 143-145°; IR (KBr) 3030 (C=C) and 1760 (lactone C=O) cm^{-1}; NMR (250 MHz, $CDCl_3$, TMS) δ 0.99 (3H, s, Me-10), 1.24 (3H, d, J = 7.5 Hz, Me-11), 2.07 (3H, d, J = 2.0 Hz, Me-4), 4.35 (1H, d, J = 11.0 Hz, H-6), 4.58 (1H, m, H-2), 6.31 (1H, dd, J = 7.5 and 2.0 Hz, H-3) and 2.32 (1H, m, H-11).

Anal. Calcd for $C_{15}H_{20}O_4$: m/z 264.1360. Found: m/z 264.1360.

3. Brusatolyl-1-Nonenoate (X) - see Scheme-2.

a. The synthesis of this target compound was also based upon the discussion and recommendation during the site visit of Drs. R. O. Pick and H. A. Musallam on July 26, 1983.

b. The synthesis of X employed a procedure (Scheme-2) which was reported as a short meeting abstract by Honda et al.[4]

c. 3-O-dimethyl-t-butylsilyl brusatol (VIII) - Brusatol (VII, 1.04 g, 2 mmol), obtained by hydrolysis of bruceoside-A according to literature 1, was silylated by use of dimethyl-t-butylsilyl chloride (360 mg, 2.4 mmol), imidazole (340 mg, 5 mmol) in dimethyl formamide (2 mL) at 40-50° for 1.5 hr. The reaction mixture was poured into water and the resulting crystals were filtered and recrystallized from ether-petroleum ether to yield colorless crystals (1.14 g, 89.5% yield) of VIII: mp 242-243°; IR (KRr) 3500 (OH), 1735 (ester and lactone C=O), 1670 (α,β-unsat. C=O) and 1610 (C=C) cm^{-1}; NMR (250 MHz, $CDCl_3$, TMS) δ 0.15 and 0.18 (3H each, s, Me_2 Si), 0.96 (9H, s, Me_3 C-), 1.39 (3H, s, Me-10, 1.84 (3H, s, Me-4), 1.93 and 2.19 (3H each, s, Me_2 = C), 3.78 (3H, s, COOMe), 4.20 (1H, m, H-11), 4.26 (1H, m, H-12), 4.80 (1H, m, H-7), 5.62 (1H, s, H-22) and 6.27 (1H, br. s, H-15).

d. 3-O-dimethyl-t-butylsilyl bruceolide (IX) - To a solution of VII (500 mg) in methanol (30 mL) was added 1 N potassium methoxide in methanol (100 mL) at 0°. After 12 hr, the reaction mixture was neutralized with Dowex 50W-X2 cation exchange resin and evaporated in vacuo. The residue was extracted with chloroform, washed with sodium bicarbonate, water, dried over anhydrous magnesium sulfare and distilled under reduced pressure to furnish IX in 70% yield as amorphous powder: mp 158-160°; IR ($CHCl_3$) 3580 (OH), 1730 (ester and lactone C=O), 1670 (α,β-unsat. C=O) and 1610 (C=C) cm^{-1}; NMR (250 MHz, $CDCl_3$, TMS) δ 0.13 and 0.18 (3H each, s, Me_2 Si), 0.96 (9H, s, Me_2-C), 1,38 (3H, s, Me-10), 1.84 (3H, s, Me-4), 3.84 (3H, s, COOMe), 4.21 (1H, m, H-11), 4.26 (1H, m, H-12), 4.72 (1H, m, H-7) and 5.28 (1H, d, J = 11 Hz, H-15).

e. Brusatolyl-1-nonenoate (X) - Synthesis of X from IX is currently in progress and is expected to be completed shortly.

(3) Literature references -

1. K.H. Lee, Y. Imakura, Y. Sumida, R.Y. Wu, I.H. Hall and H.C. Huang, J. Org. Chem., 44, 2180 (1979).
2. A.E. Greene, J. Muller and G. Ourisson, J. Org. Chem., 39, 186 (1974).
3. E.J. Corey and A.G. Hortmann, J. Am. Chem. Soc., 87, 5736 (1965).
4. T. Honda, K. Imao, M. Inoue, N. Nakazuka, T. Tachioka and T. Nakanishi, Abstract of 1983-Annual Meeting of Japanese Pharmaceutical Society, Tokyo, Japan.

(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 -

These will be considered upon the completion of biological testing.

(6) List of personnel receiving contract support -

1. Dr. Narihiko Fukamiya (6/1/83-8/31/83), an Assistant Professor of synthetic organic chemistry on leave from Hiroshima University, Japan, was appointed as Postdoctoral Fellow for the synthesis of target compounds.
2. Dr. Shohei Tani (7/15/83-present), an Associate Professor of Pharmaceutical Chemistry on leave from Kobe Gakuin University, Japan, was appointed as Postdoctoral Fellow to replace Dr. Fukamiya's position.
3. Dr. Hiroshi Irie (11/4/83-12/14/83), a Professor of Synthetic Pharmaceutical Chemistry on leave from Nagasaki University participated in synthetic work of this contract research. Dr. Irie is a distinguished Synthetic Organic Chemist well-known in Japan.

Scheme 1 : Synthesis of ST-ST-Peroxide-1 (BK 70493)

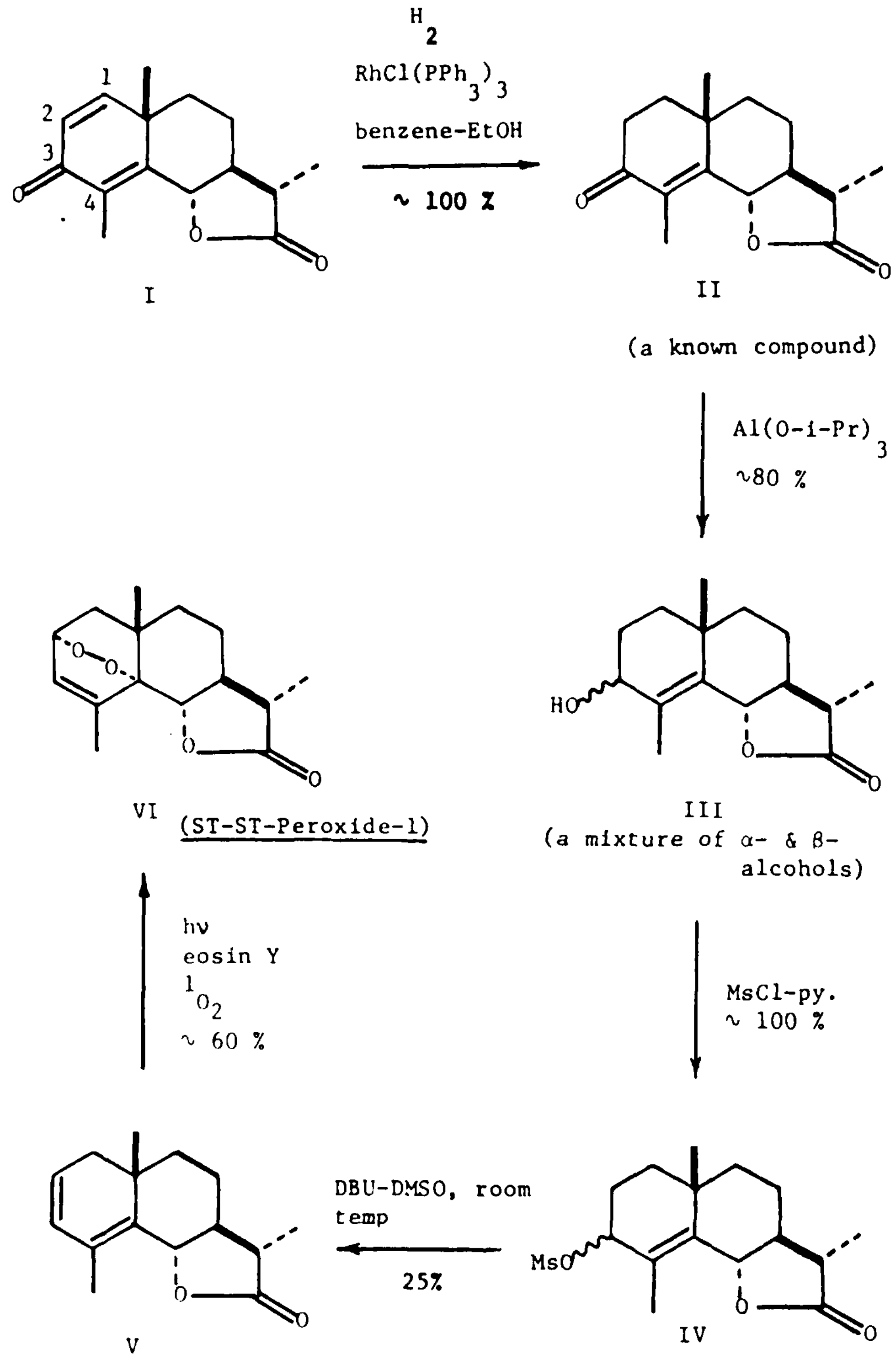
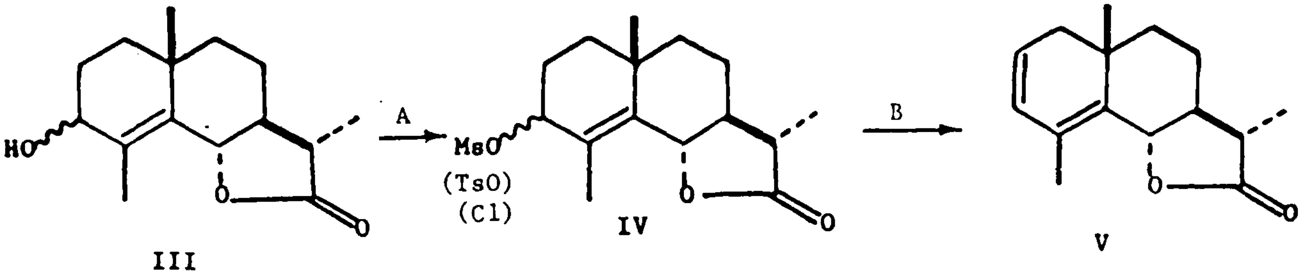


Table 1 : Conversion of Compound III to Compound V Under Various Conditions



Reagents

	A	B	
1	MsCl/Et$_3$N - THF	DBU-DMSO, Δ	I
2	MsCl/Et$_3$N - CH$_2$Cl$_2$	DBU-DMSO, room temp	II
3	MsCl/pyridine - THF	pyridine, Δ	III
4	MsCl/pyridine	t-BuOK-DMSO, Δ	IV
5	SOCl$_2$-pyridine	t-BuOK-DMSO, room temp	V
6	SOCl$_2$-pyridine	Et$_3$N-DMSO, room temp	VI
7	p-TsCl-pyridine	DBU-CHCl$_3$ room temp	VII
8	MsCl/pyridine/DMSO	pyridine-DMSO, Δ	VIII

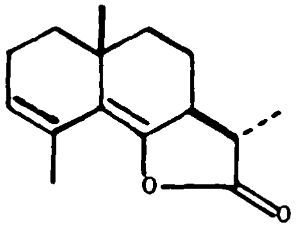
Best Conditions

A2-BVI (25% yield) or

A2-BII (25% yield) or

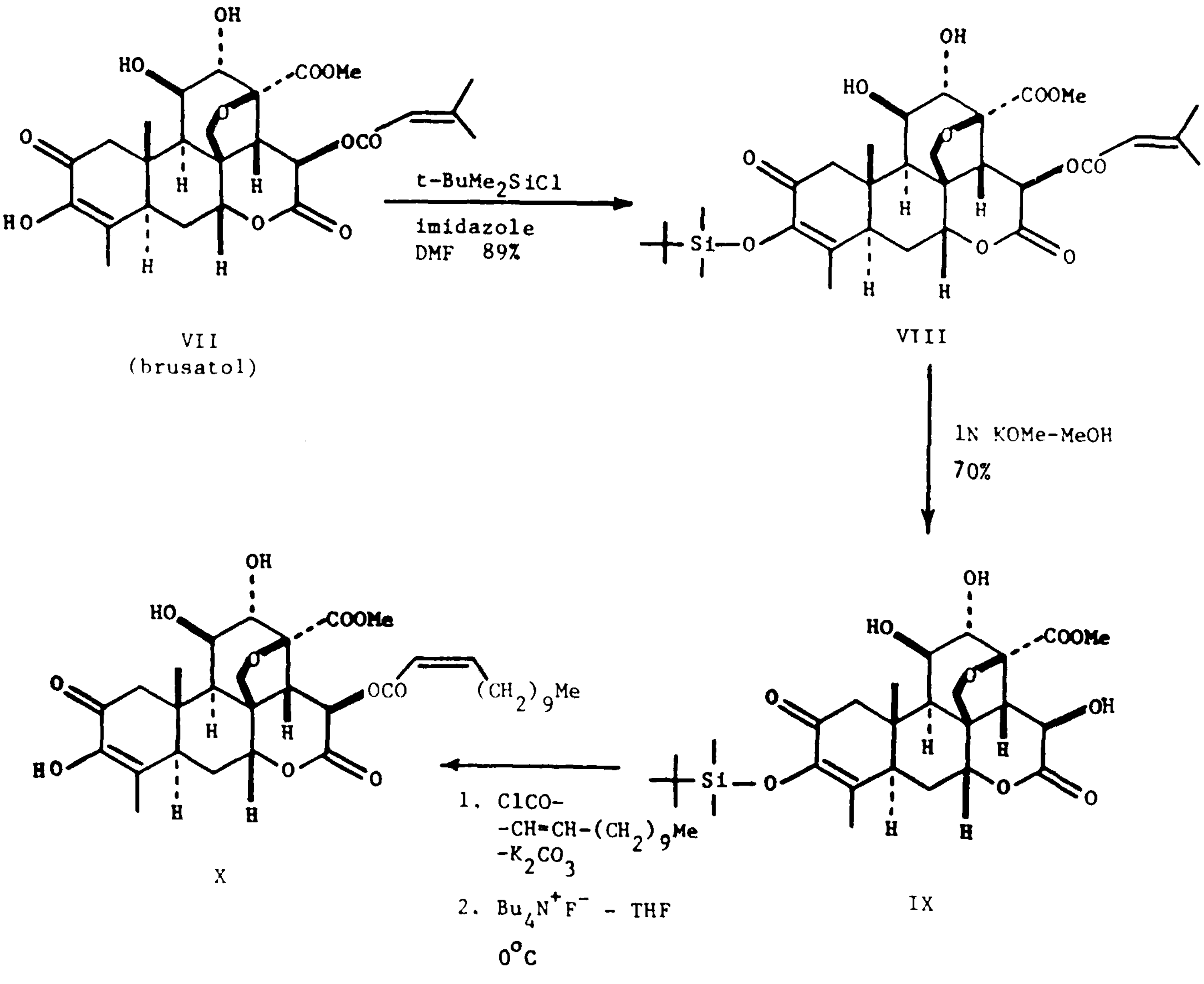
A2-BVIII (25% yield)

The other combination of reaction conditions all produced less than 25% yield.



Va

Scheme 2 : Synthesis of Brusatolyl 1-Nonenoate



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