Arch Pharm Res Vol 22, No 6, 575-578, 1999 Medicinal Chemistry

Synthesis of Sesquiterpene Derivatives as Potential Antitumor Agents; Elemane Derivatives

Bo Gil Choi, Eun Yee Kwak, Byung Ho Chung, Won Jea Cho and Seung Hoon Cheon

College of Pharmacy, Chonnam National University, Yongbong-Dong, Buk-Ku, Kwangju, Korea

(Received June 1, 1999)

Derivatives of elema-1,3-diene were synthesized in several steps as polar analogs of β-elemene, antitumor agent under clinical phase. The lactone ring of compound **1** was opened by $LiAlH_4$ to give diol **2** which was selectively protected by TBDPSCl. After acetylation of the secondary alcohol, the acetylated product was ozonolyzed and reduced to give elemane derivative **4** which was converted to diolefin **8** via selenides subsequent deprotection by tetrabutylammonium fluoride gave two compounds **9, 10.**

Key words: β-Elemene, Elema-1,3-diene, Antitumor agent, α-Santonin

INTRODUCTION

β-Elemene (Fig. 1), a new antitumor agent, is one of sesquiterpenes isolated from *Rhizoma zedoariae*. It was synthesized and shown to have potent antitumor activity (Shi, 1981; Fu, 1994) and is under clinical trial. According to Wang (Wang, 1999), β-elemene has a different mechanism of action compared to the conventional chemotherapeutic agents, it was expected to have an excellent antitumor activity with less toxicity in treatment of cancer diseases (Xu, 1996; Zuo, 1998). But it showed the poor oral bioavailability possibly due to its low solubility (Qian, 1996). Recently, a few chemical modifcation of β-elemene was attempted to improve its physicochemical properties (Jia, 1991) but systematic studies were not achieved. Chemical synthesis of β-elemene has been reported by several authors (Patel, 1967; McMurray, 1985), including the method using α-santonin as staring material to establish the correct the stereochemistry. It will be interesting to modify each of the three olefins of β-elemene to a polar functional group because increased polarity may lead to enhanced oral bioavailability and antitumor activity.

In the present study, we tried to synthesize polar analogs of elemene using α-santonin as starting material to obtain the improved antitumor agent.

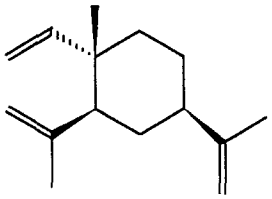


Fig. 1. β-Elemene

Correspondence to: Professor Bo Gil Choi, College of Pharmacy, Chonnam National University, 300, Yongbong-Dong,Buk-Ku, Kwangju, Korea
E-mail: bgchoi@chonnam.ac.kr

MATERIALS AND METHODS

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. ^{1}H-NMR spectra were recorded on Bruker Ac80 fourier transform spectrophotometer for 80 MHz or Bruker AM300 with Me_4Si as internal standard; chemical shifts(δ) are reported in parts per million, and signals are quoted as s(singlet), d(doublet), t(triplet), or m(multiplet). TLC was carried out using precoated plates with silica gel 60F 254 purchased from Merck or from Analtech Co.

5αH,4,6,11βH-Eudesm-2-en-6,12-olide (1)

Compound **1** was prepared by known method (Simonovic, 1963; Grieco, 1977)

Colorless crystal, m.p.142° (lit.142-143°C) (Grieco, 1977); IR (KBr) cm^{-1} 2966, 2937, 2876, 1768, 1456, 1207, 1151, 1020, 985, 688; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, s,-CH_3), 1.16 (3 H, d, J=1.6 Hz, >CH-$\underline{CH_3}$), 1.24 (3 H, d, J=1.6 Hz, >CH-$\underline{CH_3}$) 3.79 (1 H, t, J=10 Hz -CHO-), 5.46~5.56 (2 H, m, -CH=CH-).

5αH,4,6,11βH-Eudesm-2-en-6,12-diol (2)

The suspension of $LiAlH_4$ (0.78 g, 20.6 mmol) in ether

(20 ml) was slowly added to the solution of lactone **1** (1.34 g, 5.7 mmol) in ether (40 ml) at 0°C and then refluxed for 4 h. The reaction was quenched by using EtOAc and ammonium chloride. The solution was extracted by ether several times and ethereal layer was dried and concentrated to give white residue which was separated by column chromatography using hexane/EtOAc (1:1) to give white crystal (1.15 g, 84.7%). m.p.: 162-164°C; IR (KBr) cm^{-1}: 3322, 2950, 2929, 1056, 1056, 694; ^1H NMR ($CDCl_3$) : δ 0.85 (3 H, s, $-CH_3$), 0.9 (3H, d, J=1.65, >CH-$\underline{CH_3}$), 1.22 (3 H, d, J=1.65, >CH-$\underline{CH_3}$), 3.48~3.60 (3 H, m, $\underline{CH}OH$ & $\underline{CH_2}OH$), 5.39 ~5.52 (2 H, m, -CH=CH-).

6α-Acetoxy-12-(*t*-butyldiphenylsilyl)oxy-5αH,4,6,11βH-eudesm-2-ene (3)

To the solution of diol **2** (1.07 g, 4.5 mmol) and imidazole (0.884 g, 13.0 mmol) in DMF (20 ml) was slowly added t-butyldiphenylsilyl chloride (1.3 ml, 4.96 mmol) in DMF (5 ml) at 0°C and was stirred at room temperature for 4 h. The reaction mixture was evaporated under vacuun pressure to give colorless oil which was separated by column chromatography using hexane/EtOAc (10 : 1) to yield colorless oil, 12-(*t*-butyldiphenylsilyl)oxy-5αH,4,6,11H-eudesm-2-en-6α-ol (2.04 g, 95.7%); IR (neat) cm^{-1}: 3481, 2928, 2361, 1653, 1456, 1388, 1109, 694; ^1H NMR ($CDCl_3$) : δ 0.78 (3H, d, >CH-$\underline{CH_3}$), 0.87 (3H, s, $-CH_3$), 1.06 (9H, s, $-C(CH_3)_3$), 3.35~3.65 (3H, m, >$\underline{CH}$-OH & $-CH_2$-OSi), 5.40~5.60 (2H, m, -CH=CH-), 7.25~7.74 (10H, m, aromatic).

A solution of above compound (0.3 g, 0.63 mmol) in Ac_2O/pyridine (10 ml) was reacted at 60°C overnight and concentrated under vacumm pressure. The crude yellowish oil was separated by column chromatography to give colorless oil; IR (neat) cm^{-1} 2931, 1731, 1471, 1427, 1373, 1240, 1110, 823, 738, 701, 609, 505 ; ^1H NMR ($CDCl_3$) : δ 0.77 (3 H, d, >CH-$\underline{CH_3}$), 0.88 (3 H, s, $-CH_3$), 1.02 (3 H, d, >CH-$\underline{CH_3}$), 1.06 (9 H, s, $-C(CH_3)_3$), 2.06 (3 H, s, $-COCH_3$), 3.50 (2H, d, J=7.0Hz, $-CH_2$-OSi-), 5.03 (1 H, t, J=10 Hz, -CHO-), 5.40~5.49 (2 H, m, -CH=CH), 7.28~7.72 (10 H, m, aromatic).

2,3-Dihydroxy-6α-acetoxy-12-(*t*-butyldiphenylsilyl)oxy-5αH,4,6,11βH-elemane (4)

A solution of the acetate **3** (0.2 g, 0.385 mmol) in MeOH (10 ml) cooled at -78°C was treated with a saturated ozone solution in CH_2Cl_2 (10 ml). After 20 min, $NaBH_4$ (16 mg) was added at -78°C and the same amount of $NaBH_4$ was added every 15 min for 45 min. The reaction mixture was warmed to room temp and the solvent was removed under reduced pressure and crude residue was dissolved to water. The solution was extracted with ether several times and ethereal layer was washed with saturated NH_4Cl solution and dried over Na_2SO_4. The solution was evaporated to give white powder which was crystallized to colorless foam (0.12 g, 56.2%); IR (KBr) cm^{-1} : 3331, 2957, 1730, 1429, 1385, 1232, 1113, 1035, 806; ^1H NMR ($CDCl_3$) : δ 0.90 (6H, br d, J=1.9 Hz, >CH-$\underline{CH_3}$ × 2), 1.08 (9H, s, $-C(CH_3)_3$), 2.02 (3H, s, $-COCH_3$), 3.47 (2H, d, J=7.0 Hz, $-CH_2$-OSi), 4.2 (2H, br s, -OH × 2), 5.06 (H, t, J=10 Hz, -CHO-), 7.20~7.69 (10H, m, aromatic).

2-Hydroxy-3-o-nitrophenylseleno-6α-acetoxy-12-(*t*-butyldiphenylsilyl)oxy-5αH,4,6,11βH-elemane (5)

To the solution of diol **4** (9.4 g, 16.9 mmol) and *o*-nitrophenylselenocyanate (7.68 g, 33.8 mmonl) in THF (50 ml) and pyridine (50 ml), tri-*n*-butylphospine (8.4 ml, 33.8 mmol) was added slowly and stirred at room temperature for 2.5 h. After removal of solvent at reduced pressure, the residue was treated with ether and washed with d-HCl, saturated $NaHCO_3$ and NaCl solution. The ethe-real solution was dried over Na_2SO_4 and evaporated to yield crude brown oil which was separated by column chromatography to give yellowish oil **5** (10.5 g, 82.2%). ^1H NMR (DMSO-d_6) : δ 0.83 (3H, s, $-CH_3$) 0.85 (3H, d, , >CH-$\underline{CH_3}$), 0.98 (3H, d, >CH-$\underline{CH_3}$), 1.0 (9H, s, $-(CH_3)_3$), 2.04 (3H, s, $-COCH_3$), 3.50 (2H, m, $-\underline{CH_2}$-OH), 5.0 (1H, t, J=10 Hz), 7.20~8.36 (14H, m, aromatic).

2-Hydroxy-6α-acetoxy-12-(t-butyldiphenylsilyl)oxy-5αH,4,6,11βH-elema-2-ene (6)

To the solution of monoselenide **5** (10.5 g, 13.9 mmol) in THF (130 ml) at 0°C was slowly added 50% aqueous hydrogen peroxide solution (6.4 ml). After adding, the reaction mixture was stirred at room temperature for 3h and diluted with water (200 ml), and concentrated to remove the organic solvent. The aqueous solution was extracted with ether 3 times and ethereal layer was dried and evaporated to give crude residue which was separated by column chromatography using hexane/EtOAc (25 : 1) to give yellowish solid **6** (6.7g, 89.8%).; IR (KBr) cm^{-1}: 3442, 2931, 1729, 1469, 1373, 1238, 1110, 910, 823, 701, 503; ^1H NMR ($CDCl_3$) : δ 0.78 (3H, d, J=1.6 Hz, >CH-$\underline{CH_3}$) 0.87 (3H, d, J= 1.6 Hz, >CH-CH_3), 1.00 (3H, s, $-CH_3$), 1.06 (9H, s, $-(CH_3)_3$), 2.04 (3H, s, $-COCH_3$), 4.90 5.90 (3H, m, $-CH=CH_2$), 7.30~7.80(10H, m, aromatic).

2-o-Nitrophenylseleno-6α-acetoxy-12-(t-butyldiphenylsilyl)oxy-5H,4,6,11β-elema-2-ene (7)

A solution of monoolefin **6** (5.7 g, 10.62 mmol) in THF (200 ml) was treated with 2-nitrophenylselenocyanate (4.81 g, 21.2 mmol) and tri-*n*-butylphospine (5.3 ml, 21.2 mmol) was added slowly at room temperature and stirred for 4 h. After removal of solvent in vacuum pressure, the residue was extracted with ether, washed with water

and dried over Na_2SO_4. The ethereal solution was concen-trated to red residue which was separated by column chromatography to give yellowish oil **7** (4.8 g, 61.4%); IR(neat) cm^{-1}: 2929, 2352, 1729, 1589, 1515, 1332, 1236, 1097, 730, 703; ^1H NMR ($CDCl_3$) : δ 0.85 (3 H, d, J=1.6 Hz, >CH-CH_3) 0.97 (3H, d, J=1.6 Hz, >CH-CH_3), 1.07 (9 H, s, -$(CH_3)_3$), 2.31 (3H, s, -$COCH_3$), 2.93 (H, m, J=6.9 Hz), 3.50 (1H, d, J=6.9 Hz) 7.26~8.37 (14H, m, aromatic).

6α-Acetoxy-12-(t-butyldiphenylsilyl)oxy-5αH,4,6,11βH-elema-2,3-diene(8)

To the solution of above monoselenide **7** (4.8 g, 6.52 mmol) in THF (100 ml) at 0°C was slowly added 50 % H_2O_2 solution (3 ml) and stirred at room temperature for 4 h. The reaction mixture was concentrated to crude oil which was separated by column chromatography (hexane/EtOAc=10 : 1) to give yellowish oil **8** (1.5 g, 44.4%).; IR (neat) cm^{-1} : 3072, 2932, 2858, 1734, 1637, 1473, 1429, 1371, 1242, 1113, 912; ^1H NMR (DMSO-d_6) : δ 0.82 (3 H, d, >CH-$\underline{CH_3}$), 1.06 (9H, s, -$(CH_3)_3$) 1.69 (3H, s, -CH_3), 1.96 (3 H, s, -$COCH_3$), 4.66 (1H, s), 5.75 (1H, dd, J=9.0 Hz, 12.0 Hz, -$\underline{CH}$=CH_2), 4.87~4.92 (3H, m, -CH=CH_2), 5.12 (1H, t, J=10Hz), 7.36~7.65 (10H, m, aromatic).

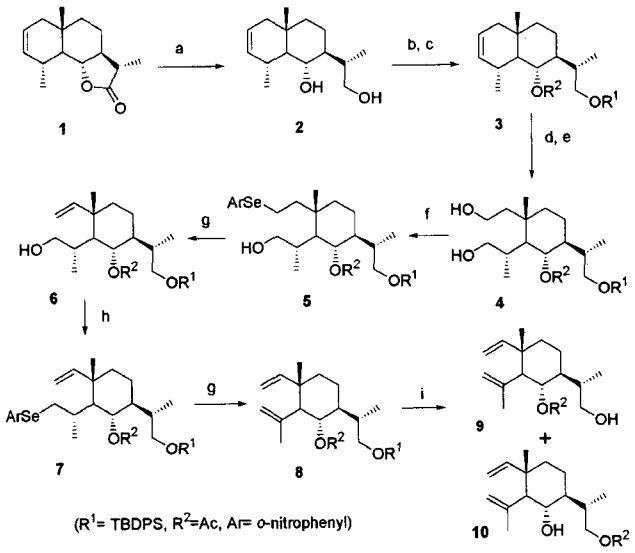
6α-Acetoxy-5αH,4,6,11βH-elema-2,3-diene-12-ol(9) and 12-acetoxy-5αH,4,6,11βH-elema-2,3-diene-6α-ol (10)

To the solution of the diolefin **8** (1.5 g, 2.89 mmol) was added 1M-tetrabutylammonium fluoride solution (3.8 ml, 3.8 mmol) at 0°C and stirred at room temperature overnight. The solution was concentrated and separated by column chromatography to give two alcohols **9** (350 mg, 43.2%) and **10** (370 mg, 45.7%) Compound **9**, IR (neat) cm^{-1}: 3480, 3076, 2934, 2856, 1740, 1637, 1367, 1240, 1035, 910 ^1H NMR ($CDCl_3$) : δ 0.90 (3H, d, J=9.0 Hz, >CH-$\underline{CH_3}$) 1.06 (3H, s, -CH_3), 1.69 (3H, s, -CH_3), 3.50 (2H, d, J=6.0 Hz, -$\underline{CH_2}$OH), 4.65 (1H, s, -$COCH_3$), 4.87~4.93 (3H, m, -CH=CH_2), 5.15 (1H, t, 10Hz, -CHO), 5.75 (1H, m).

Compound **10**, IR (neat) cm^{-1}: 3420, 3082, 2936, 2878. 2631, 1734, 1373, 1028, 910; ^1H NMR (DMSO-d_6) : δ 0.90 (3 H, d, J=6.0 Hz, >CH-$\underline{CH_3}$) 1.00 (3 H, s, -CH_3), 1.78 (3 H, s, -CH_3), 2.06 (1 H, s) 3.69 (1 H, t, J=9.0 Hz, >$\underline{CH}$OH), 4.78 (1 H, s, -$\underline{CH}$=CH_2), 4.87~4.92 (2 H, m, -CH=$\underline{CH_2}$). 5.15 (1 H, s), 5.73 (1 H, dd, J=9.0 Hz, 12.0 Hz).

RESULTS AND DISCUSSION

The starting material **1** was prepared by catalytic hydrogenation, epimerization and Shapiro reaction from α-santonin according to the published methods (Simonovic, 1963; Grieco, 1977). The diol **2** was easily obtained in high yield from lactone **1** by treatment with $LiAlH_4$/ether (Cardona, 1992) (Scheme 1). By taking advantage of the different reactivity of primary and secondary alcohol, selective protection of primary alcohol using *t*-butyldiphenylsilyl chloride in the presence of imidazole in DMF was achieved in high yield and subsequent acetylation of the secondary alcohol using Ac_2O/pyridine gave compound **3** in high yield. This olefin was treated with ozone at 78°C followed by reduction with $NaBH_4$, gave the diol **4**. We attempted to synthesize bis-*o*-nitrophenyl selenide from **4** to afford divinyl compound directly *via* oxidation but we could not obtain bis-selenide. Conversion of **5** to divinyl compound was accomplished in four steps. The mono-selenide was obtained from diol in high yield using *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine. Oxidative elimination of the monoselenide was carried out with hydrogen peroxide to give the olefinic alcohol, **6** which was subjected to another selenation followed by oxidative elimination to yield diolefin **8**. The compound **8** was deprotected by *tetra*-butylammonium fluoride to give separable mixture of two compounds **9** and **10**.



Reagents: (a) $LiAlH_4$, ether; (b) TBDPSCl, imidazole, DMF; (c) Ac_2O, Py; (d) O_3, CH_2Cl_2,MeOH; (e) $NaBH_4$, MeOH; (f) ArSeCN, Bu_3P, THF-Py; (g) 50%H_2O_2, THF; (h) ArSeCN, Bu_3P, THF; (i) TBAF,THF

Scheme 1. Synthesis of Elemane derivatives

ACKNOWLEGEMENTS

This paper is supported by RESEARCH FUND for SABBATICAL YEAR, 1996, Chonnam National University and it was greatly appreciated.

REFERENCES CITED

Cardona, L., Garcia, B., Gimenez, J. E., and Pedro, J. R.,

A shorter route to the synthesis of (+)-Junenol, Isojunenol, and their coumarate esters from (-)-santonin, *Tetrahedron*, 48, 851 (1992).

Fu, N. W., Jin, L. P. and Huo, Y. T., Antitumor and pharmacological studies of β-elemene, *Bull. Chin. Med.*, 9, 35 (1994).

Grieco, P. A. and Nishizawa, M., Total synthesis of (+)-Costunolide, *J. Org. Chem.*, 42, 1717-1720 (1977).

Jia, W. M., Yang, L. M., Li, Z. H. and Hu, J. H., Synthesis of the antitumor β-elemene derivatives, *Youji Huaxue*, 11, 608-610 (1991).

McMurray, J. E., and Kocovsky, P., Synthesis of helmithogermacrene and β-elemene, *Tetrahedron Lett.*, 26, 2171 (1985).

Patel, L. J., Kulkarni, K. S., and Rao, A. S., Tepenoids: Part LXXVIII-Synthesis of Tetrahydroelemol, *Indian J. Chem.*, 4, 400 (1988).

Qian, J. Pharmacology and clinical studies of β-elemene, a new anticancer agent, *Chin. J. Clin. Oncol.*, 23, 453-5 (1996).

Shi, J. H. Pharmacological studies on antitumor activities of β-elemene, *Bull. Chin. Med.*, 2, 32 (1981)

Simomovic, D. M., Somasekar, R. and Bnattacharyya, Terpenoids-XXXIX, *Tetrahedron*, 19, 1061 (1963)

Wang, X. W., Elemene, *Drugs of the Future*, 23, 266-270 (1998).

Xu, H. U., Li, J., and Tun, L., Effect of elemene on serum superoxide dismutase activity in patients with with brain tumors, *Chin. J. Clin. Oncol.*, 23, 527-9 (1996)

Zuo, Y., The Study of elemene of induction apoptosis on ascites hepatoma cell line Hca-F25/Cl-16A3, *Chin. J. Cancer Res.*, 9, 10-13 (1998).