Uzma Yunus

Department of Chemistry, Allama Iqbal Open University, H-8, Islamabad, Pakistan

Rashid Iqbal

Department of Chemistry, Quaid-I-Azam University, Islamabad, Pakistan

Ekkhard Winterfeldt

Institute fur Organische Chemie, Universitat der Hannover, Schneiderberg, Germany

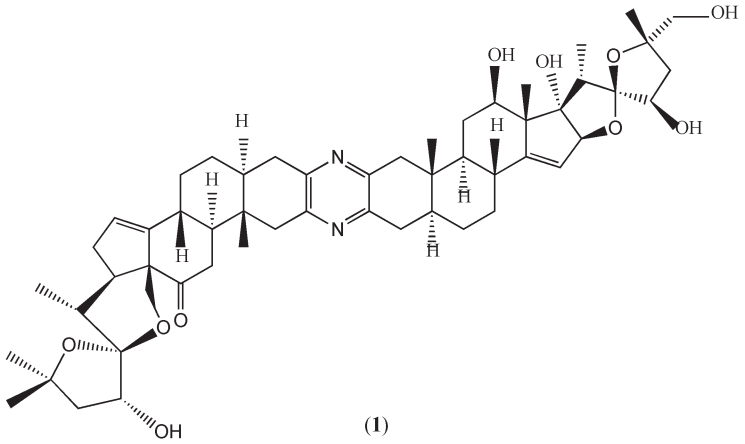
Received July 26, 2004

The present paper describes the synthesis of 5-azido-6-ketones (14) and 6-hydroxy-5-ketone (20) from Hajos Wiechert ketone as chiral building blocks for cephalostatin analogues . The synthesis of symmetric cephalostatin analogue from 6-hydroxy-5-ketone has also been reported. The characterization of the each synthesized compounds was carried out by IR, ^{1}H-NMR, ^{13}C-NMR and High resolution Mass Spectrometry.

J. Heterocyclic Chem., **42**, 1079 (2005).

Introduction.

The present work aimed to synthesize analogues of cephalostatins. Cephalostatins are natural products isolated from the marine worm *Cephalodiscus gilchristi* [1] . Cephalostatins are among the most potent cytostatics ever screened by NCI [2,3] and therefore have potential applications as anti-tumour agents *e.g*., cephalostatin 1 has exhibited remarkable cytotoxic activity against P388 murine leukemia cells with IC_{50} values of 10^{-4}-10^{-6} ng/ml [4]. The structure of cephalostatins consist of a central pyrazine and two C27 steroidal units on each side (1).

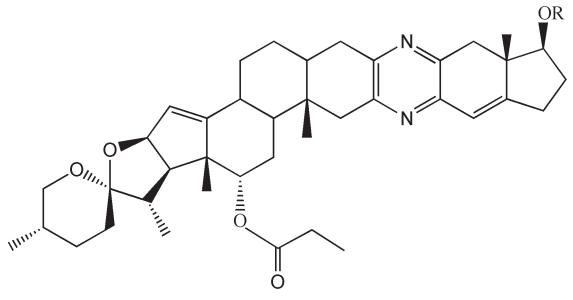


(**1**)

Clinical trials of cephalostatins have stalled because of severe difficulties in harvesting these rare materials [5].

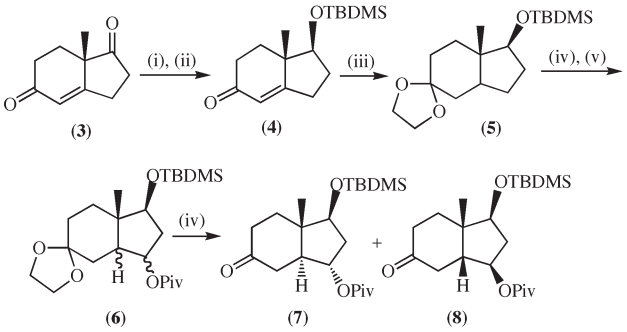
The most important question relating to structure–activity relationship is to find out the structural features essential for such high activity of cephalostatins . In this regard the first question which arises is whether a steroid nucleus is really necessary in cephalostatins to show biological activity. T. Flessner [6] has prepared a cephalostatin analogue which has a steroid nucleus as one half and a hydrindane nucleus as the other half (2). This compound has shown comparable cytostatic activity to that of cephalostatins. Thus T. Flessner's observations gave encouragement to prepare non–steroidal analogues of cephalostatins. Therefore, the synthesis of chiral building blocks for cephalostatin analogues with a hydindane nucleus was undertaken.

Ketone (7) was chosen as a suitable starting material that was prepared from Hajos Wiechert ketone (3) by the



(**2**)

Scheme 1

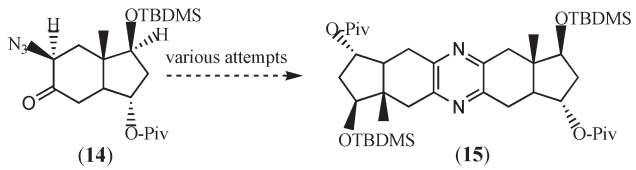


Reagents (yield): (i) $NaBH_4$ (0.27eq), abs. Ethanol, -10 °C to –5 °C, Ar atmosphere, 1.5 hr. (78%); (ii) TBDMSCl (1.2 eq), imidazole (1.8 eq), DMF, Ar atmosphere, rt, 5d. (71%); (iii) ethylene diol (1.5 eq), *p*-TsOH (cat.), toluene, 10 hr. reflux (68%); (iv) Boran-methylsulphide complex (*ca*. 10 *M*) (0.35 eq) , abs. THF, 0 °C 30 min. rt,1 hr. 40 °C , 1hr, rt, ethanol, NaOH, 30% H_2O_2 1 hr. (79%); (v) pivaloyl chloride (1.3 eq), DMAP (1.5 eq), abs pyridine, 100 °C, 24 hr., N_2 atmosphere (85%); (vi) 80% AcOH, 65 °C, 5-10 min.

reaction sequence shown in Scheme 1. Position specific 5-azido-6-ketone (14) and 6-hydroxy-5-ketone (20) were prepared by a series of reactions depicted in Schemes 2 and 3 respectively. A detailed account is given in result and discussion section.

Results and Discussion.

1,2-Azidoketones are well known equivalents of 1,2-aminoketones. The transformation of azide into amine is synthetically well known [7]. Many procedures have been reported for the reduction of azide to amine [8-13]. The proper choice of reducing agent according to the sensitivity of the molecule is known to yield the desired amine. Therefore 5-azido-6-ketone (**14**) was prepared as shown in Scheme 2. Various attempts have been made to reduce azidoketone (**14**) to the aminoketone along with *in situ* intermolecular condensation to pyrazine, but have remained unsuccessful.

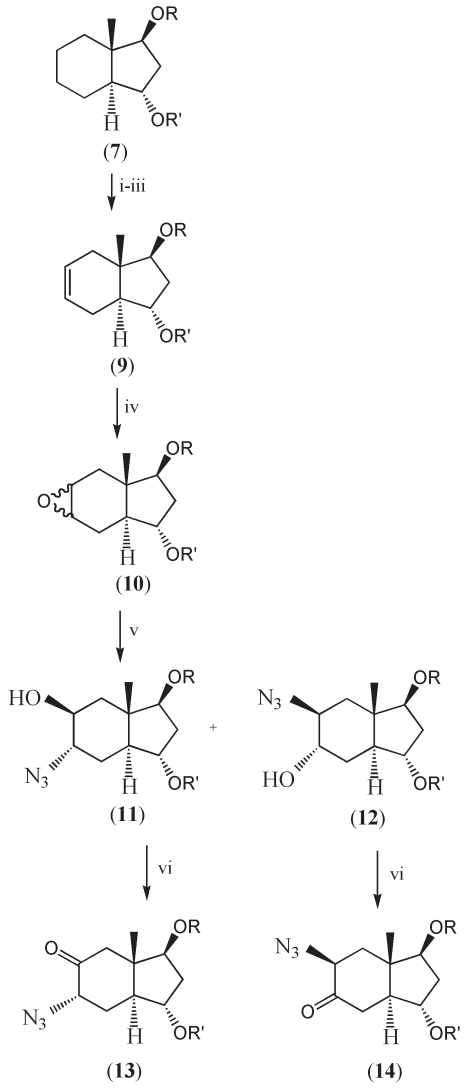


...(1.0)

It was then planned to prepare hydroxyketone (**20**) which could be dimerized to a pyrazine in the presence of alcoholic ammonium acetate [14]. Three slightly different techniques were tried to prepare hydroxyketone (**20**).

(a) Direct Hydroxylation of Ketone (7).

Scheme 2



R= *tert*-Butyldimethylsilyl group and R' = Pivaloyl group

Reagents and conditions (yield): (i) $NaBH_4$ (0.3 eq.), abs. ethanol, 0-5 °C, 2 hrs at RT – quenched with a little acetone (92%); (ii) TosCl (2 eq., dimethylaminopyridine (eq.), CH_2Cl_2, 24 hrs. at RT- excess TosCl was precipitated with a mixture of petroleum ether and diethyl ether and removed by filtration (90%); (iii) Abs. toluene, alumina basic (5 eq.), 90 °C , 6 hrs. – filtered hot and washed with CH_2Cl_2 (75%); (iv) *meta*-chloro per benzoic acid (1.5 eq.), CH_2Cl_2, 0 °C – RT , 5 hrs. at RT., quenched with saturated Na_2SO_3 and extracted with CH_2Cl_2 (89%); (v) Dimethyl acetamide: water (8:2), NaN_3 (1.27 eq.), 5 days at 100 °C , cooled and quenched with water and extracted with methyl *tert*-butyl ether (80%); (vi) [Bis (acetoxy)iodo]benzene (BAIB) (1.0 eq.), 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (0.1 eq), 10 hrs. at RT-quenched with saturated Na_2SO_3 and extracted with CH_2Cl_2 (85% (**13**) and 79% (**14**); Note: All reactions were carried out under Nitrogen atmosphere. All products were purified by flash column chromatography.

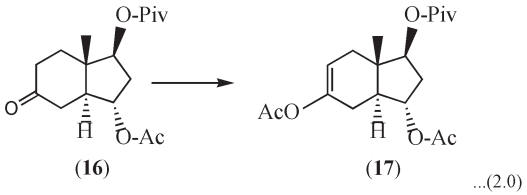
The less substituted enolate of a ketone can be obtained by a kinetically controlled deprotonation of the ketone

with a hindered base like lithium diisopropylamide (LDA), potassium hexamethyldisilazide (KHMDS), *etc*. Thus attempts were made to convert ketone (**7**) to hydroxyketone (**20**) through its enolate by using different bases such as LDA, KHMDS and potassium hydride under different conditions. The oxidants used were oxaziridine [15], dimethyldioxirane (DMDO), oxodiperoxymolybdenum(pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pryimidinone (MoOPH) [16] and *meta* chloroperbenzoic acid (*m*-CPBA).

In case of the use of oxaziridine at –78° no hydroxylation was observed. Instead starting material was isolated. Whereas at -15° the starting material was found decomposed. Similarly, MoOPD, which has been claimed to be a harmless non-carcinogenic and safe alternative to MoOPH for carrying out α-hydroxylations of α-methyleneketone enolates, was also attempted as oxidant in the present work. Even this did not furnish hydroxyketone, only a mixture of many unidentified products was obtained.

(b) Hydroxylation on Fixed Enolate (**17**).

In view of the failure of the attempts on direct hydroxylation of ketone (**7**), the hydroxylation on fixed enolate was planned. For this purpose, the enol acetate (**17**) of ketone (**16**) was prepared by perchloric acid catalyzed enolization [17] and quenching of enol as acetate. The enol acetate was obtained in quantitative yield from ketone (**16**), (eq 2). The enol acetate has been reported to give epoxidation product which can be rearranged to α-hydroxyketone by heating [18].



...(2.0)

Many different reagents and conditions were tried for the epoxidation of enol acetate (**17**) but in no case could hydroxyketone (**20**) be obtained. The reagents tried for epoxidation included methyl(trifluoromethyl)dioxirane which is known to be the most reactive in the dioxirane series , *meta*-chloroperbenzoic acid (*m*-CPBA), dimethyl dioxirane (DMDO).

It seems surprising that all the reagents mentioned above cause epoxidation/hydroxylation of steroids smoothly and conveniently, however, they failed to bring about the required hydroxylation of ketones (**7** and **16**) in the present work. It may be emphasized that the α- epoxide in steroids is the predominant product because the angular β-methyl group directs the epoxidation in the direction α to the A ring.

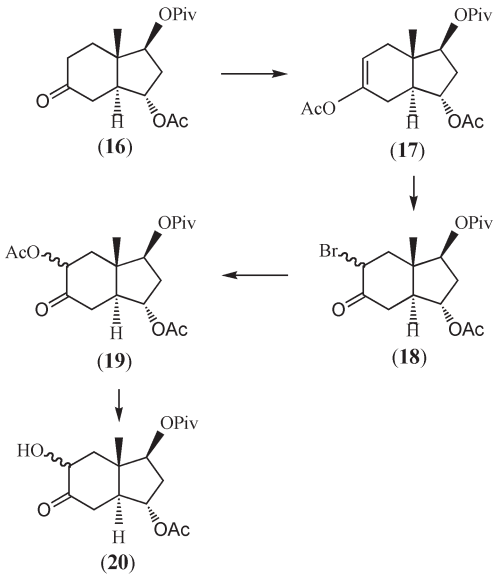
In view of the fact that our substrate ketones (**7** and **16**) have a β-methyl group in addition to two extra bulky groups on the adjacent ring, the only apparent reason for the failure seems to be the steric crowding on starting ketone.

(c) Preparation of Hydroxyketone *Via* Nucleophilic Substitution.

Since all efforts to carry out direct hydroxylation on the ketone remained unsuccessful, it was decided to synthesize hydoxyketone (**20**) *via* hydrolysis of acetoxyketone (**19**) obtained by substitution of bromide in bromoketone (**18**) with acetate ion, Scheme 3 illustrates the sequence of reactions. A number of efforts have been made to bring this transformation *e,g*, fluoride salts like KF, CeF were used in combination with basic solvent (DMF), glacial acetic acid was used as a source of acetate ion. The role of fluoride is to substitute the bromide in substrate which is a better leaving group and can be replaced easily by acetate ion, but in these attempts the bromoketone proved to be extremely stable and recovered unchanged.

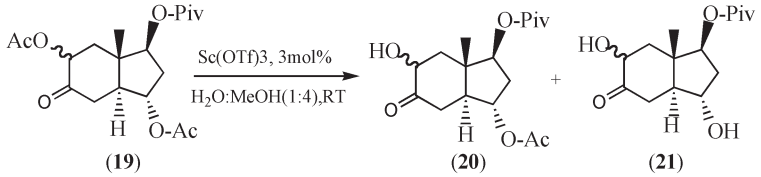
In another attempt phase transfer catalyst like 18-crown-6 ether was used along with acetonitrile as a solvent to increase the solvation of acetate ion, this effort remained unsuccessful. Another attempt for preparing acetoxyketone from bromoketones (**18**) was made by involving the use of silver acetate along with glacial acetic acid at 65-70°. This attempt successfully led to acetoxyketone (**19**). The bromoketone (**18**) on reaction yielded 58% of the pure acetoxyketone (**19**) after flash chromatography.

Scheme 3



Hydrolysis of 6-Acetoxy-5- ketones (**19**).

Since acetoxyketone (**19**) consisted of two different ester groups *i.e*. the acetate and the pivalate group, a number of attempts had been made to selectively hydrolyze the 6-acetoxy group *e.g*. basic hydrolysis, *trans* esterification, microwave irradiation *etc*. However all such efforts remained unsuccessful. However, when aectoxyketone (**19**) was treated with scandium triflate ($Sc(OTf)_3$) in a mixture of methanol and water (1:4) at 60-65 °C for 24 hours, the desired 6-hydroxy-5-ketone (**20**) was obtained in 30% yield, along with 3,6-dihydroxy-5-ketone (**21**) in 13% yield. It may be emphasized that (**20**) was obtained in relatively better yield because formation of (**20**) from (**19**) by use of $Sc(OTf)_3$ had involved the carbonyl group adjacent to the acetate group during hydrolysis. The other acetate group, which did not have an adjacent carbonyl group, was found to hydrolyze to a relatively lesser extent. This observation appears to be in line with the coordination approach suggested by Kajiro [19]. Additionally the use of $Sc(OTf)_3$ in the present case resulted in hydrolysis of acetate group selectively and there was no indication of hydrolysis of the pivalate group. Both the hydrolysis products (**20**) and (**21**) were found to have the pivalate group retained in there structure. Equation 3 explains the reaction.



...(3.0)

The complete spectral data is given in the experimental section. The weak absorption of hydroxy group in infra red spectrum suggests hydrogen bonding between the hydroxyl group and the keto group as shown below (Figure 1).

Preparation of Pyrazine (**22**).

Hydroxyketones can be dimerized to a pyrazine if heated in an alcoholic solvent in the presence of excess ammonium acetate. The nitrogen atoms in pyrazine come from the ammonia of ammonium acetate and the intermediate seems to be an aminoketone, which dimerizes quickly to a dihydropyrazine and by auto oxidation to pyrazine (Eq. 4).

In order to prepare pyrazine (**22**), the 6-hydroxy-5-ketone (**20**) was refluxed in methanol with five times excess of ammonium acetate, for a period of 3 hours. The work up and purification of the crude product is described in the experimental section. The pyrazine (**22**) was obtained in a relatively low yield of 14% as a colourless oil. Equation 4 illustrates the formation of pyrazine (**22**).

EXPERIMENTAL

General Remarks.

All solvents were purified before use by standard purification methods. All reactions were carried out in absolute solvents under inert atmosphere (argon or nitrogen). Melting points were recorded on Gallenkamp MPD-350, melting point apparatus and are not corrected.

Infra-red spectra were measured with Perkin-Elmer FT-1710 Spectrometer. Mass spectra were recorded at Finnigen MAT-312 instrument at an Ionization Potential of 70 eV. The measuring temperature is given along with data and relative intensities are

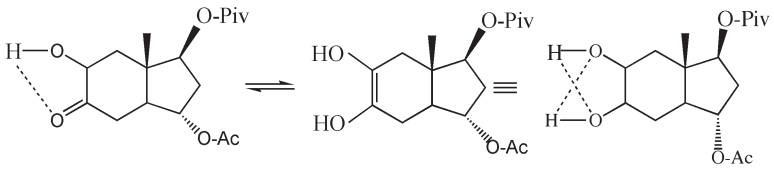
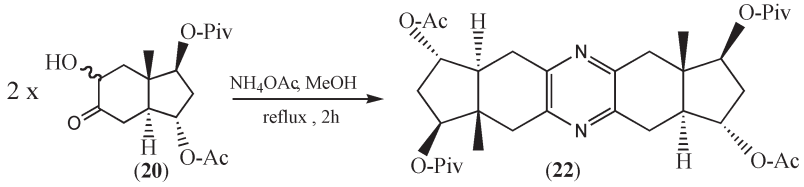


Figure 1. Hydrogen bonding in 6-hydroxy-5-ketone.



...(4.0)

given in small bracket (%). FAB spectra (FAB-MS) were determined with VG-Autospec on Nitrobenzyl alcohol matrix (NBA-matrix). Low resolution measurements have been made. High resolution mass spectra (HRMS) were measured according to peak matching method on VG-Autospec.

^{1}H-NMR spectra were recorded on an AM-400 (400 MHz) and Avance 400 (400 MHz) instruments from Bruker. ^{13}C-NMR spectra were recorded with the AM 400 (100 MHz), AVS 400 (100 MHz, Avance) spectrometer from Bruker. All measurements were made in deuterated solvents. In case where TMS could not be taken as internal standard, solvent signal was used for calibration ($CDCl_3$ = 77.0 ppm). Analytical thin layer chromatography was carried out on pre coated Aluminum sheet with silica gel 60 F_{254}, obtained from Merck. The detection was made with the help of UV lamp (λ = 254 nm) and with cerium (IV) sulphate/phosphormolybdane acid reagent. Preparative column chromatography was done according to the principle of flash chromatography with silica gel from Baker (diameter 0.03 - 0.06 mm) by applying weak pressure (*ca*. = 0.5 bar). Elemental analysis was carried out with vario EL from elementar Analysen systeme GmbH and CHN Rapid from Heraeus.

2',2'-Dimethylpropionic Acid-3-acetoxy-6-bromo-7a-methyl-5-oxo-octahydro-inden-1-yl-ester (18).

a) Formation of Δ^2 Enolacetate (**17**).

Reagent for acetylation was prepared according to the proceduregiven in the literature [20]. This reagent is 1 *M* in Ac_2O and 10^{-3} *M* in $HClO_4$; 1 ml of this reagent was used for every 10 mg of ketone.

A solution of ketone (**16**) was prepared by dissolving 261 mg (0.841 mmol) of (**16**) in 26 ml of the above mentioned reagent under nitrogen atmosphere and stirred at room temperature for about 10 minutes (TLC monitored), then washed with saturated sodium hydrogen carbonate solution and dried over anhydrous sodium sulphate and solvent removed in vacuum. To remove traces of acetic anhydride, a drop of pyridine and 5 ml of methanol was added and again evaporated to dryness, and kept for 2 hours on vacuum pump. ^{1}H-nmr of the crude enol -acetate showed only Δ^2-enol-acetate (**17**).

b) Solvent for Bromination.

The solvent for bromination was made by dissolving 0.250 g of sodium acetate in 20 ml of glacial acetic acid and 5 ml of carbon tetrachloride.

The above mentioned solvent (24 ml) was used to dissolve 540 mg (1.534 mmol) of Δ^2-enol acetate (**17**). Bromine solution (1 ml of 0.86 ml of bromine dissolved in 10 ml of carbon tetrachloride) was introduced with syringe to the enol acetate solution in 15 minutes under nitrogen atmosphere and stirred at room temperature for another 30 minutes. Then, reaction was quenched with saturated sodium hydrogen carbonate solution, extracted thrice with dichloromethane and the organic layer was dried over anhydrous magnedsium sulphate, and concentrated in vacuum. Flash chromatography (5% ethyl acetate/petroleum ether eluent) provided (85%) of yellow oil. R_f : 0.41 (petroleum ether:diethyl ether, 2:1)); FAB (MS): m/z (%) = 389 (100, M + 1); HREIMS: Calculated mass for $C_{17}H_{25}O_5Br$ = 388.0885; Found = 388.0884; IR (Golden Gate ATR): ν (cm^{-1})= 2971 (w), 2874 (w), 1725 (s), 1480 (w), 1461 (w), 1284 (s), 1156 (s); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 9H, *tert*-butyl group of pivalate), 1.38 (s, 3H, 8-*H*), 1.50-1.80 (m, 2H, 2-*H*), 2.05 (s, 3H, methyl group of acetate), 2.80 (m, 2.24, 2.80 (m, 4H`s, 4, 7-*H*`s), 3.0 (m, 1H, 3a-*H*), 4.36(d, 0.4H, 6-*H*, $J_{1\text{-}2}$ = 4.36 Hz), 4.75-4.80 (m, 2.6H, 1,3 & 6-*H*s).

^{1}H-NMR for Δ^2-enol-2-acetate (54) (characteristic signals only): δ = 1.14 (s, 3H, 8-*H*), 1.21 (s, 9H, pivalate), 2.03 (s, 3H, 3-acetate), 2.11 (s, 3H, 5-acetate), 2.66 (m, 1H, 3a-*H*), 4.83 (m, 2H, 1-*H* and 3-*H*), 5.5 (d, 1H, 6-*H*), (J = 4.76 Hz); ^{13}C-NMR (DEPT, 100 MHz, $CDCl_3$): δ = 14.21 (q, 8-C), 19.04 (q, C of methyl of acetate), 27.10 (q, *tert*-butyl group of pivalate), 32.56 (t, 4-C), 36.59 (t, 7-C), 38.01 (t, 2-C), 43.23 (s, C of pivalate), 48.60 (d, 3a-C), 50.45 (s, 7a-C), 57.61 (d, 6-C), 76.73 (d, 3-C), 78.61 (d, 1-C), 200.02 and 200.29 and 201.48 (s, for three carbonyl groups).

Anal. Calcd. for $C_{17}H_{25}O_5Br$: C,52.56 ; H, 6.44. Found: C, 52.54 ; H, 6.40.

2,2-Dimethylpropionic Acid 3,6-Diacetoxy-7a-methyl-5-oxo-octahydro-inden-1-yl Ester (19).

Bromo ketone (**18**) (600 mg, 1.54 mmol) was dissolved in 10 ml of glacial acetic acid and 785 mg of silver acetate was added and the mixture was kept at 55 °C (oil bath temperature) for 7 hrs. The mixture was then cooled and neutralized with saturated $NaHCO_3$ and 10 ml of ethyl acetate was added and silver bromide was filtered on a sintered funnel. The crude product was extracted with ethyl acetate and dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash chromatography (PE/EE 9:1) afforded 330 mg (58%) of acetoxy ketone (**19**) and 120 mg of bromoketone (**18**) was recovered. FAB (MS): m/z (%) = 369 (100, M + 1); HREIMS: $C_{19}H_{28}O_7$ (Calc.) = 368.1835 Found = 368.1835; IR (Golden Gate ATR): ν(cm^{-1}) = 2971 (w), 1726 (s), 1367 (m), 1235 (s), 1158 (s); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 9H, *tert*-butyl of pivaloyl), 1.21 (s, 3H, 7a-methyl), 2.18 (s, 3H, methyl of acetyl group), 2.85 (pentat, 1H, 3a-*H*), 4.70 (m, 1H, 3-*H*), 5.34 (m, 2H, 1 & 6-*H*); ^{13}C-NMR (DEPT, 100 MHz, $CDCl_3$): δ = 18.34 (q, 7a-CH_3), 19.79 & 20.20 (q, methyl of acetyl groups), 26.20 (q, methyl of *tert*-butyl of pivaloyl), 34.80, 38.23, 39.00 (t, 2, 4 & 7-C), 51.04 (d, 3a-C), 71.78 (d, 1-C), 74.45 (d, 3-C), 75.58 (d, 6-C), 168.67 (s, C=O of acetyl), 176.46 (s, C=O of pivaloyl), 202.31 (s, C=O, 5-C), 48.06 (s, 7a-C), 43.20(s, C- of *tert*- butyl of pivaloyl)

Anal. Calcd. for $C_{19}H_{28}O_7$: C , 61.95 ; H, 7.60. Found: C, 61.91 H, 7.57.

2,2-Dimethylpropionic Acid-3-acetoxy-6-hydroxy-7a-methyl-5-oxo-octahydro-inden-1-yl Ester (20).

α-Acetoxy ketone (**19**) (280 mg, 0.760 mmol) and 0.074 mg (0.152 mmol) of scandium (III) trifluromethanesulphonate was dissolved in 5 ml of MeOH:H_2O (4:1) and heated to 65 °C for 24 hr. and then brought to room temperature. The reaction was then quenched with water, extracted with ethyl acetate, washed with brine and dried over $MgSO_4$, and the solvent removed under reduced pressure. Flash chromatography using PE/EE (3:1) afforded 75 mg (30.2%) of α-hydroxyketone (**20**), 30 mg (13.8%) of dihydroxyketone (**21**) and 60 mg of acetoxyketone (**19**) was recovered; R_f of (65) = 0.083 PE:EE (2:1); FAB (MS): m/z (%) = 327 (86, M + 1); HREIMS: mass for $C_{17}H_{26}O_6$ (Calc.) 326.1729, Found = 326.1729. IR (Golden Gate ATR): ν (cm^{-1}) = 3436 (w), 2970 (m), 1726 (s), 1245 (m); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.95 (s, 3H, 7a-CH_3), 1.14 (s, 9H, *tert*-butyl group of pivaloyl), 2.02 (s, 3H, methyl of acetyl group), 2.49-2.60 (m, 2H), 2.83 (m, 1H, 3a-*H*), 4.27 (dd, 1H, 3-*H*, J = 19.08 Hz & 7.4 Hz), 4.69 (m, 1H, 6-*H*), 5.33 (m, 1H, 1-*H*); ^{13}C-NMR

(100 MHz, $CDCl_3$): δ = 14.23 (s, C- of *tert*-butyl group of pivaloyl), 20.97 (q, C. of 7a-methyl), 22.23 (q, C. of methyl of acetyl), 27.39 (q, C. of *tert*-butyl of pivaloyl), 32.70, 38.20, 46.00 (t, 2,4 & 7-C) 49.02 (s, 7a-C), 50.20 (d, 3a-C), 71.74 & 76.45 (d, 1 & 3-C), 79.50 (t, 6-C), 171.0 & 177.39 (s, C=O of pivaloyl and acetyl group), 210 (s, C-5 carbonyl).

Anal. Calcd. for $C_{17}H_{26}O_6$: C, 62.57 ; H, 7.97. Found: C, 62.55; H 7.95.

1,7-Bis(2,2-dimethyl-propionate),3,9-bis(ethanoate),6a,12a-dimethyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,12,12a-tetradecahydro-5,11-diaza-dicyclopenta[*b*,*i*]anthracene (22).

Hydroxy ketone (**20**) 75 mg (0.230 mmol) was dissolved in 7 ml of abs. Methanol and 149 mg (2.3 mmol) of Ammonium acetate was added and refluxed for 3 hrs. Then methanol was removed on rotary evaporator under reduced pressure. The concentrate was purified by flash chromatography PE/EE (95:5). 20 mg (14.1%) of pyrazine (**22**) was obtained as colourless oil; FAB (MS): m/z (%) = 614 (25, M + 2), 556 (100, M- C_4H_9); HREIMS: Calculated mass for $C_{34}H_{48}N_2O_8$ = 612.3410 Found = 612.3410; UV ($CHCl_3$): $\lambda_{(nm)}$ 288(s), 305(sh); IR (Golden Gate ATR): ν(cm^{-1}) = 2953 (m), 2853 (m), 1729 (s), 1544 (w); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 4H, 2 & 8-*H*), 1.12 (s, 6H, 13 & 14-*H*), 1.24 (s, 18H, *tert*-butyl groups of pivalates), 2.04 (s, 6H, methyl groups of acetate), 2.45 (heptet, 2H, 3a and 9a-*H*), 2.65-3.00 (m, 8H, 4, 5, 10 and 11-*H*), 4.72 (m, 2H, 3 & 9-*H*), 4.85 (broad multiplet, 2H, 1 & 7-*H*).

Anal. Calcd. for $C_{34}H_{48}N_2O_8$: C, 66.66; H, 7.84; N,4.57. Found: C, 66.62; H, 7.80; N, 4.54.

REFERENCES

[1] G. R. Pettit, T. Tan, J. P. Xu, J. Ichihara, M. D. Williams and M. R. Boyd, *J. Nat. Prod.,* **61**, 955 (1998) and references therein.

[2] A. Ganesan, *Angew. Chem.,* **108**, 667 (1996).

[3] G. R. Pettit, J. Xu, Y. Ichihara, M.D. Williams and M. R. Boyd, *Can. J. Chem.,* **72**, 2260 (1994).

[4] G. R. Pettit, J. Xu, M. D. Williams, N. D. Christie, D. L. Doubek and J. M. Schmidth, *J. Nat. Prod.,* **57**, 52 (1994).

[5] T. G. LaCour, C. Guo, Bhandaru, M. R. Boyd and P. L. Fuchs, *J. Am. Chem. Soc.,* **120**, 692 (1998) and reference [6] therein.

[6] T. Flessner, Doctoral Thesis, Department of Chemistry, Hannover University, Germany (1999).

[7] H. Suzuki and K. Takaoka, *Chem. Lett., The Chemical Society of Japan,* 1732 (1984).

[8a] J. H. Boyer and S. E. Ellzey Jr., *J. Org. Chem.,* **23**, 127 (1958); [b] F. Rolla, *J. Org. Chem.,* **47**, 4327 (1982).

[9a] L. Horner and A. Gross, *Liebigs Ann. Chem.,* **591**, 117 (1955); [b] M.Vaultier, N. Knouzi and R. Carrie, *Tetrahedron Lett.,* **24**, 763 (1983).

[10a] T. Adachi, Y. Yamada, I. Inoue and M. Saneyoshi, *Synthesis,* **45** (1977); [b] B. A. Belinka Jr. and A. Hassner, *J. Org. Chem.,* **44**, 4712 (1979).

[11] A. Hassner and L. A. Levy, *J. Am. Chem. Soc.,* **87**, 4203 (1965).

[12a] D. N. Kirk and M. A. Wilson, *J. Chem. Soc., C*, 414 (1971); [b] S. Polanc, B. Stanovnik and M. Tišler, *Synthesis,* 65 (1978).

[13a] E. Zibral and J. Strob, *Liebigs Ann. Chem.,* **727**, 231 (1969); [b] S. Nagarajan and B. Ganem, *J. Org. Chem.,* **52**, 5044 (1987).

[14] P. N. Vinot and J. Pinsen, *Bulletein de Societie Chimique de France,* **2**, 4970 (1968).

[15] F. A. Davis, A. C. Sheppard, B. C. Chen and M. Serajul Haque, *J. Am. Chem. Soc.,* **112**, 6679 (1990).

[16a] J. C. Anderson and S. C. Smith, *Synlett.,* 107 (1990); [b] E. Vedejs, D. A. Engler and J. E. Telschow, *J. Org. Chem.,* **43**, 188 (1978).

[17] B. E. Edwards and P. N. Rao, *J. Org. Chem.,* **31**, 324 (1966).

[18] C. H. Heathcock and S. C. Smith, *J. Org. Chem.,* **59**, 6828 (1994).

[19] H. Kajiro, S.Mitamura, A. Mori and T. Hijama, *Tetrahedron Lett*., **40**, 1689 (1999).

[20] B. E. Edwards and P. N. Rao, *J. Org. Chem*., **31**,324 (1966).