

Studies on α -Bromination of Ketone in Hydrindane Ring System

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The present paper describes the results of various attempts to synthesize 5-bromo-6-ketone (**11**). When standard procedures for the α -bromination were tried, a mixture of 5-bromo-6-ketone (**11**) and 7-bromo-6-ketone (**12**) was obtained. However, when bromination was carried out under buffered conditions, the desired 5-bromo-6-ketone (**11**) could be obtained in a good yield.

Keywords: α -Bromoketone; Hajos-Wiechert ketone; Hydrindane ring system; Bromination.

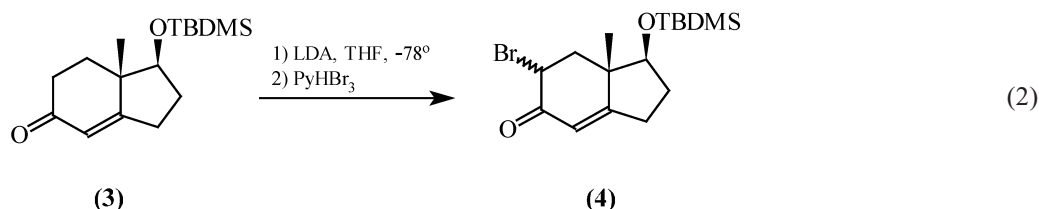
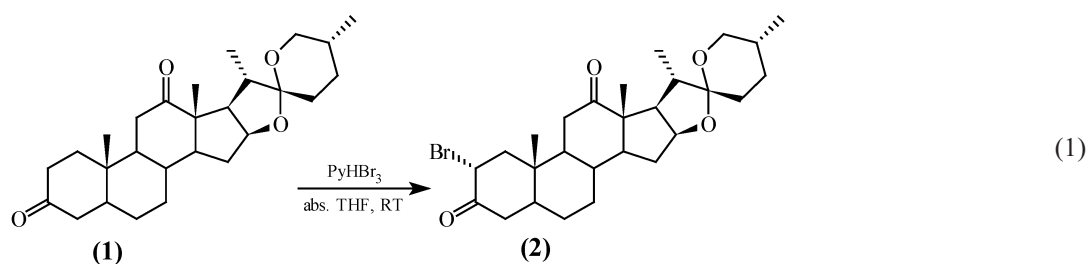
INTRODUCTION

Bromoketones are well known intermediates in organic synthesis,¹ as they can be transformed into a number of other functionalities under moderate reaction conditions.²⁻⁴ Many new reagents have been introduced in recent years for the preparation of α -bromoketones.⁵⁻⁶ In a project which aimed to prepare analogues of marine natural products, cephalostatins,⁷⁻⁹ we required 5-bromo-6-ketone (**11**) as an intermediate. The plan was to transform bromoketone to enaminketone, which on reduction dimerizes to dihydropyrazine. Autooxidation of the latter results in pyrazine.

RESULTS AND DISCUSSION

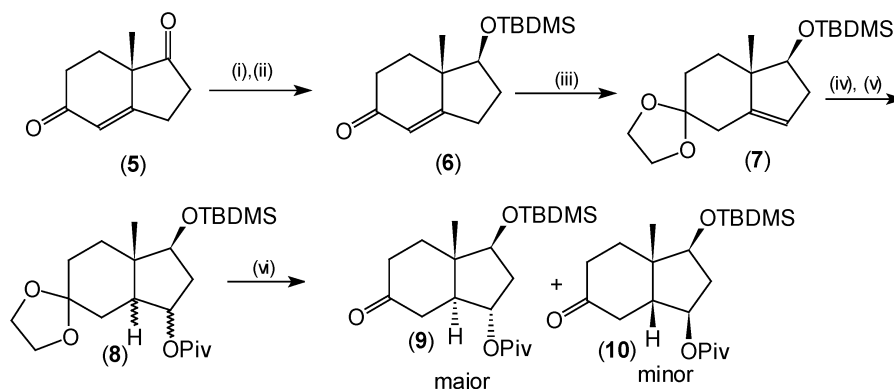
In steroid chemistry, it is a well known observation¹⁰ that the 3-keto steroids on bromination yield 2-bromo-3-ketone exclusively. In the bromination of ketone derived from hecogenin (**1**) too, the bromination occurred stereospecifically alpha to the ring A (**2**) (Eq. 1). This observation is in line with previous studies where in a hydrindane nucleus too, α -bromination at the desired position was reported by Flessner¹¹ (Eq. 2).

As bromoketone is an important intermediate and can be exploited to bring about a number of transformations, it was planned to prepare 5-bromo-6-ketone (**11**) from ketone



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Scheme I



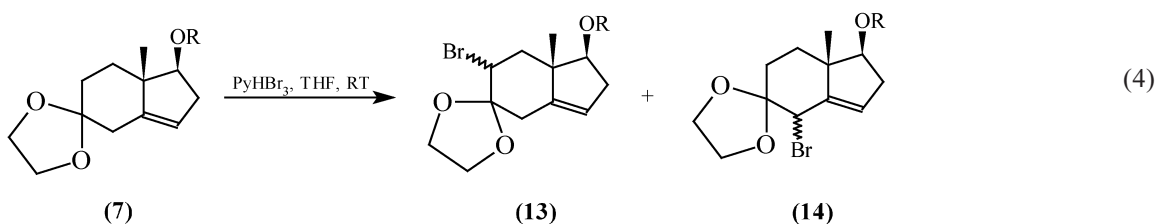
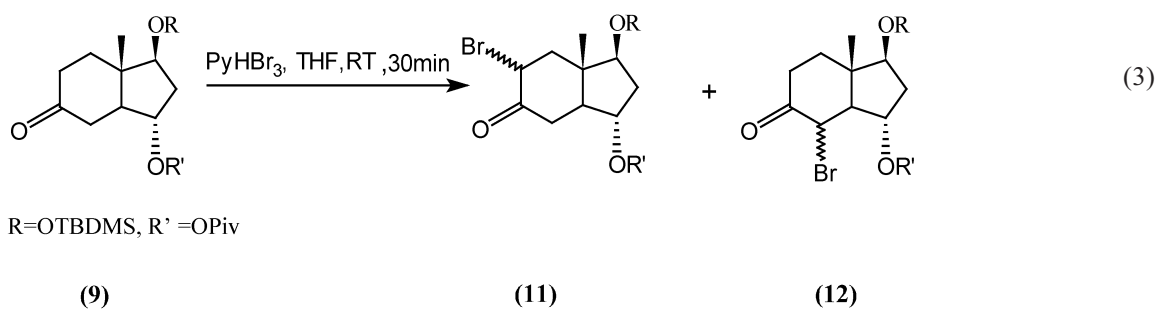
Reagents: (i) NaBH₄ (0.27 eq), abs. Ethanol, -10 °C to -5 °C, Ar atmosphere, 1.5 hr. (ii) TBDMSCl (1.2 eq), imidazole (1.8 eq), DMF, Ar atmosphere, rt, 5d. (iii) ethylene diol (1.5 eq), p-TsOH (cat.), toluene, 10 hr. reflux. (iv) Borane-methylsulphide complex (ca 10 M) (0.35 eq), abs. THF, 0 °C 30 min. rt 1 hr. 40 °C, 1 hr, rt, ethanol, NaOH, 30% H₂O₂ 1 hr. (v) pivaloyl chloride (1.3 eq), DMAP (1.5 eq), abs pyridine, 100 °C, 24 hr. N₂ atmosphere. (vi) 80% AcOH, 65 °C, 5-10 min.

(9) in the hydrindane series. The Hajos Wiechert ketone (5)¹²⁻¹⁴ was chosen as starting material. A series of transformations shown in Scheme I, yielded ketone (9).

The ketone (9) was treated with pyridinium tribromide (PyHBr₃) in absolute THF at room temperature. In contrast to steroids, in the present case a mixture of 5-bromo-6-ketone (11) and 7-bromo-6-ketone (12) was obtained instead of the only desired 5-bromo-6-ketone (11) (Eq. 3). 25% pure (11) could be isolated by flash column

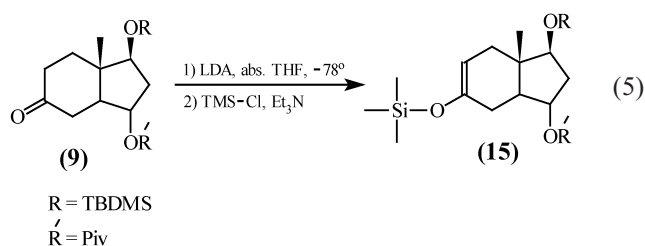
chromatography. In another attempt the ketal (7) was subjected to bromination at the 6-position. In this case again an inseparable mixture of 2- and 4-bromoketal (13&14) was obtained, where 4-bromoketal (14) was the major product as established by the ¹H-NMR of the mixture of bromoketals. Equation 4 describes the reaction.

In another attempt to brominate ketone (9), it was decided to prepare kinetically controlled enolate using hindered bases at low temperature and the quenching of metal

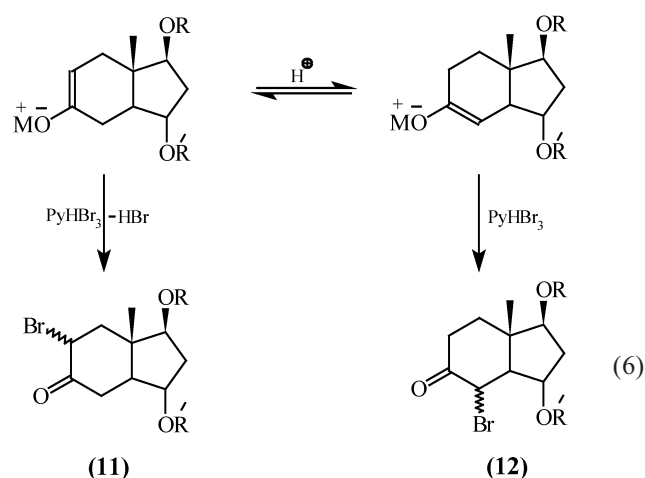


enolate by bromonium ion. Thus ketone (**9**) was subjected to many hindered bases like lithiumdiisopropylamide (LDA), dicyclohexylamide independently, but in each case a mixture of regio-isomeric bromoketones (**11**) and (**12**) was obtained.

A list of reagents and reaction conditions employed for this reaction is provided in Table 1. The use of bulky bases like dicyclohexylamide yielded no product. This observation may be attributed to the heavy bulk of cyclohexyl rings. Probably due to steric congestion it failed to abstract the proton adjacent to the carbonyl group of ketone (**9**). In another independent attempt the enolate was prepared with LDA in THF at $-78\text{ }^{\circ}\text{C}$ and was quenched as trimethylsilyl ether. Here, only a single product was isolated which was identified as 5-enolate (**15**). The enolate formation is represented by (Eq. 5) as confirmed by the $^1\text{H-NMR}$ of (**15**).



This observation provided strong evidence that the desired enolate was formed at an early stage of the reaction. However, as the bromination proceeded, the high concentration of protons, due to the formation of hydrogen bromide, caused the desired enolate to equilibrate with the other enolate, thus yielding the undesired 7-bromo-6-ketone (**12**) (Eq. 6)

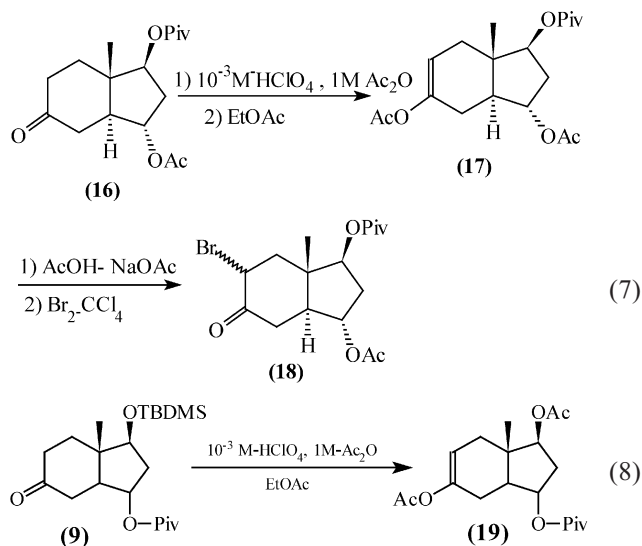


Due to these facts, the strategy to brominate ketones (**9**) and (**16**) had to be changed. Therefore, it was decided to carry out bromination under buffered conditions in order to keep the concentration of hydrogen ions at a low level. This would have hindered the formation of undesired product. Thus, the ketone (**16**) was first converted to its enol acetate (**17**) by using perchloric acid catalysed acetylation.¹⁵ The acetylation went very

smoothly and in only five minutes the acetylation was found complete. The acetylated product (**17**) was isolated and characterized by $^1\text{H-NMR}$. Acetylation was followed by bromination which was carried out in acetic acid/sodium acetate buffer.¹⁶ The bromination resulted in 6-bromo-5-ketone (**18**) in 80% yield. Equation 7 illustrates the steps involved in the conversion of ketone (**16**) to bromoketone (**18**).

However, when ketone (**9**) was subjected to perchloric acid catalyzed enolization the compound (**19**) resulted. This is because the catalytic amount of perchloric acid had hydrolyzed the TBDMS ether as described by Equation 8.

The enol acetate (**19**) was not used further in anticipation of the difficulty to carry out transformations selectively on a molecule having three ester groups i.e. two acetates and one pivalate.



CONCLUSION

Thus the desired 6-bromo-5-ketone was exclusively obtained in 80% yield by carrying out bromination under buffered conditions.

Table 1. Bromination of ketone (9)

Sr. No.	Reagents/Conditions	Results
1.	PyHBr ₃ , MeOH:CHCl ₃ (1:1), 65°, 2 h.	5,7-dibromoketone
2.	LDA, THF, -78°, 1 h, followed by PyHBr ₃ , -78° → RT, 1 h.	A mixture of 5-bromo-6-ketone (11) and 7-bromo-6-ketone (12)
3.	LDA, RT, 2 h, Br ₂ in CH ₂ Cl ₂ at -78°	No reaction
4.	LDA, -78°, 2.5 h, PyHBr ₃ (1.2 eq.), -78°, 1 h → RT.	No reaction
5.	PyHBr ₃ , glacial AcOH, 50-55°, 5 min.	Inseparable complex mixture.
6.	KH, 0°, Br ₂ → RT	Mixture of (11) and (12)
7.	PyHBr ₃ , THF, RT, 30 min.	(11) and (12) and starting ketone (9)
8.	Lithiumdicyclohexylamide, THF, -78°, PyHBr ₃	No reaction, ketone (9) recovered
9.	PTAB, THF, 0°	No reaction, starting ketone (9) recovered
10.	PTAB, THF, 0° → RT in 3 h.	Mixture of (11) and (12)
11.	PyHBr ₃ , EtOH, 50°.	Inseparable complex mixture.

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 a Gallenkamp MPD-350 melting point apparatus and are not corrected.

Infra-red spectra were measured with a Perkin-Elmer FT-1710 Spectrometer. Mass spectra were recorded on a Finnigan MAT-312 instrument at an Ionization Potential of 70 eV. The measuring temperature is given along with data and relative intensities are given in small brackets (%). FAB spectra (FAB-MS) were determined with a VG-Autospec on Nitrobenzyl alcohol matrix (NBA-matrix). Low resolution measurements have been made. High resolution mass spectra (HRMS) were measured according to the peak matching method on a VG-Autospec.

¹H-NMR spectra were recorded on AM-400 (400 MHz) and Avance 400 (400 MHz) instruments from Bruker. ¹³C-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 (δ ¹³C(CDCl₃) = 77.0 ppm).

Analytical thin layer chromatography was carried out on precoated aluminum sheet with silica gel 60 F₂₅₄ obtained from Merck. The detection was made with the help of a 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 (approx. = 0.5 bar). Elemental analysis was carried out with a Vario EL from Elementar Analysen Systeme GmbH and CHN Rapid from Heraeus.

Preparation of 2',2'-dimethyl-propionicacid-5-bromo-3-(tert-butyl)dimethylsilanyloxy)-3a-methyl-6-oxo-octa-hydro-inden-1-yl ester (11)

To a solution of 500 mg (1.308 mmol) of ketone (9) in abs. THF was added a solution of 459 mg of pyridinium-bromide perbromide (dissolved in 13 mL of abs. THF) and stirred vigorously at room temperature for about 15 minutes. The colour of the reaction changed from orange to light yellow and a solid precipitated. The reaction was quenched with saturated sodium hydrogen carbonate solution and extracted thrice with methyl tert.butyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulphate and concentrated under reduced pressure. A crude mixture of 2-bromoketone (11), 4-bromoketone (12) and unreacted ketone (9) was obtained. Flash chromatography provided the desired 2-bromoketone (11) in 23% yield (138 mg) and 402 mg of an inseparable mixture of 4-bromoketone and unreacted ketone. R_f: 0.65 (petroleum ether:diethyl ether, 2:1).

IR (CHCl₃): ν (cm⁻¹) = 2956 (w), 2932 (w), 2904 (w), 1724 (s), 1460 (w), 1160 (m), 1125 (m). ¹H-NMR (400 MHz, CDCl₃): δ (mixture of α,β -bromoketone) = 0.02 & 0.04 (s, 6H, dimethyl of TBDMS), 0.88 (s, 9H, *tert*-butyl of TBDMS), 1.18 (s, 9H, *tert*-butyl of pivalate), 1.26 (s, 3H, 7a-CH₃), 2.2-2.7 (three sets of multiplets, 6H, 2,4 and 7-Hs), 3.80 (t, 1H, I-H, J_{1-2} = 6.28 Hz), 4.63 (m, (minor iso-

mer) 0.4H, 5-*H*) and 4.30 (d, (major isomer) 0.6H, 5-*H*, $J_{1-2} = 6.16$ Hz), 4.73 (m, 1H, 3-*H*). FAB (MS): m/z (%) = 461 (27, M, Br = 79), 463 (27, M, Br = 81) HREIMS: Calculated mass for $C_{17}H_{28}O_4BrSi = 403.0940$; Found 403.0942 C.H.N. Analysis: C(calculated.): 54.65, C (Found) = 54.89. H (calculated): 8.08 H; (Found) 7.89.

Preparation of 2',2'-dimethyl-propionicacid-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 procedure given in the literature. 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 were added and again evaporated to dryness, and kept for 2 hours on a vacuum pump. 1H -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.

24 mL of the above mentioned solvent was used to dissolve 540 mg (1.534 mmol) of Δ^2 -enol acetate. 1 mL of bromine solution (0.86 mL of bromine dissolved in 10 mL of carbon tetrachloride) was introduced with a 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 magnesium sulphate, and concentrated in a vacuum. Flash chromatography (5% ethyl acetate/petroleum ether eluent) provided (85%) of (**18**) as yellow oil. R_f : 0.41 (petroleum ether:diethyl ether, 2:1) IR (Golden Gate ATR): ν (cm^{-1}) = 2971 (w), 2874 (w), 1725 (s), 1480 (w), 1461 (w), 1284 (s), 1156 (s). 1H -NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (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 ace-

tate), 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*, $J_{1-2} = 4.36$ Hz), 4.75-4.80 (m, 2.6H, 1,3 & 6-*H*s). 1H -NMR for Δ^2 -enol-2-acetate (**54**) Characteristic signals only, $\delta = 1.14$ (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, $CDCl_3$): $\delta = 14.21$ (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). FAB (MS): m/z (%) = 389 (100, M + 1) HREIMS: Calculated mass for $C_{17}H_{25}O_5Br = 388.0885$; Found = 388.0884.

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