Journal of Biosphere, 1: 16-18, 2012 ISSN 2278 – 3342

Synthesis of pityol: a tetrahydrofuran analogue *via* co-halogenation reaction

Pankaj Gupta, Neha Mahajan and S.C. Taneja

Abstract: A facile and efficient methodology for the synthesis of pityol, a tetrahydrofuran analogue, was developed using co-halogenation as a key step. Both the diastereoisomers (*syn***:***anti* = 44:56**)** of pityol were prepared in >70% yield, using abundantly available racemic sulcatol as a starting material.

Key words: Diasteroisomers; pheromones; racemic sulcatol.

1. Introduction

Pheromones are substances which occur in nature and are involved in chemical communication between animals. The term pheromone (from the Greek *pherein* = to transfer and *hormon* = to excite), coined by Karlson and Luscher,[1] is a substance which is secreted by an individual and received by a second individual of the same species, in which it releases a specific reaction, for example, a specific behaviour or a development process. The major ways of exploiting pheromones in pest control are: monitoring, mating disruption and mass trapping.[2] Such pheromone applications provide significant cost reduction and environmental benefits to the farmer, to the consumer and to the society.

Pheromones are usually obtained in μg to mg quantities which are insufficient for the determination of their absolute configuration as well as for the biological studies to examine their practicality in the field. Pheromone synthesis is therefore important in order to rigorously establish the structure of a new pheromone and also to provide a plenty of material to carry out extensive biological tests.

Two enantiomers out of the four possible isomers of Pityol **1** are the naturally occurring pheromones. The (2*R*,5*S*)-isomer serves as the male specific attractant for the spruce bark beetle *Pityophorus pityographus* and (2*R*,5*R*)-isomer was identified as the aggregation pheromone of the elm bark beetle *Pteleobius vitattus*. Due to its commercial importance various syntheses have been reported in the past. In 1990, K. Ishihara *et al*.[3] converted 2-methyl-2-hepten-6-one to mixture of Pityol and a tetrahydropyran isomer via ketal formation followed by reduction. Later on in 1992, Ruthenium (VII) oxide catalyzed cyclization was used to obtain predominantly *anti* isomer of Pityol by Suhan Tang *et al*.[4] . Recently, using racemic sulcatol as a raw material an enantio- and diastereoconvergent synthesis of Pityol isomers was achieved by A. Steinreiber *et al*.[5] wherein the key step was the lipase catalyzed ring closure of oxirane derivative.

Herein we report the synthesis of both the diasteroisomers of pityol in high yields using co-halogenation[6] as a key step.

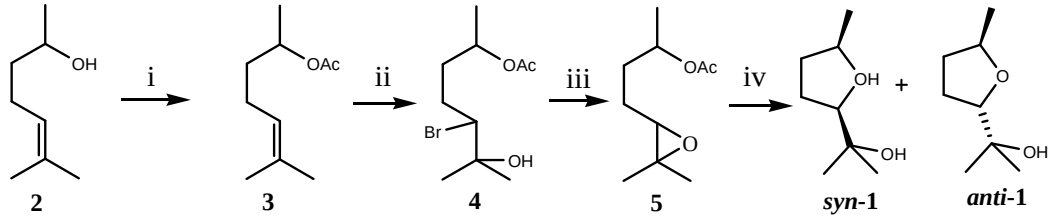
2. Results and Discussion:

In the present synthesis, when racemic sulcatol was treated with N-bromosuccinamide the mixture of products were formed, however when racemic sulcatol **2** was acetylated to **3** and the latter was subjected to bromohydroxylation with N-bromosuccinamide, 6-acetoxy-3-bromo-2-hydroxy-2-methylheptane **4** was obtained as a sole product, which on treatment with DBU gave epoxide **5**. In the next step deacetylation and concomitant cyclization was achieved by potassium hydroxide in buffer with the formation of pityol in >70% yield as depicted in **scheme 1**. The ratio of the *syn* and *anti* isomers was calculated by NMR and GC. Both the diastereoisomers *syn*-**1** and *anti*-**1** were separated by column chromatography and their structural assignments made on the basis of spectral studies.

Pankaj Gupta (✉)
Department of Chemistry,
Govt. Degree College, Kathua- 184104, J&K, India.
e mail: pankajrrl@gmail.com.

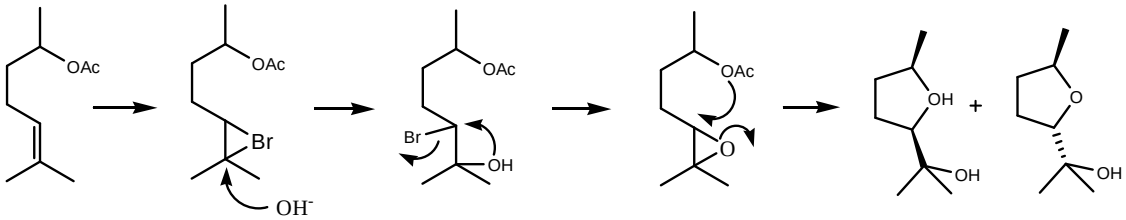
Neha Mahajan
Department of Biotechnology,
Govt. College for Women, Gandhi Nagar,
Jammu -180001, J&K, India.

S.C. Taneja
Bio-Organic Chemistry Division,
Indian Institute of Integrative Medicine,
Canal Road, Jammu -180001, J&K, India



i) Ac_2O/Py, ii) DDH/H_2O, 0-5^o, iii) DBU, iv 10% KOH, r.t *syn*: *anti* ; 44:56

Plausible Mechanism



Scheme-1

In conclusion, the co-halogenation methodology has proved to be very successful and versatile tool for the synthesis of pityol, implying the general applicability of this approach for the synthesis of tetrahydrofurans as well.

Experimental

General

^{1}H NMR & ^{13}CNMR, spectra in $CDCl_3$ were recorded on Bruker 200, 400 and 500 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (ppm). Reagents and solvents used were mostly of LR grade. Silica gel coated aluminum plates coated on alumina from M/s Merck were used for TLC. MS were recorded on Jeol MSD-300 and Bruker Esquire 3000 LC-Mass spectrometer.

6-Acetoxy-2-methyl-2-heptene (3): ($C_{10}H_{18}O_2$)

Acetic anhydride (6 g, 0.06 mol) and 5 mg of DMAP was added to a solution of racemic sulcatol **2** (6.4 g, 0.05 mol) in dry dichloromethane and the reaction mixture kept overnight at room temperature. The contents of reaction mixture were poured in ice cold water and extracted with dichloromethane. The organic layer was washed, dried and evaporated to get 6-acetoxy-2-methyl-2-heptene **3** (8.45 g, 99.5%) as colourless liquid; IR (KBr) cm^{-1}: 1021, 1241, 1373, 1737, 2934, 2976; ^{1}HNMR, δ: 1.21 (d, *J* = 6.24 Hz, 3H, C*H*$_3$CO), 1.51 (s, 3H, C*H*$_3$C=C), 1.65 (s, 3H, C*H*$_3$C=C), 1.46-1.67 (m, 2H, C*H*$_2$CO), 1.95-2.08 (m, 2H, C*H*$_2$C=C); ^{13}CNMR, δ: 17.6, 19.7, 21.0, 23.5, 25.6, 35.9, 70.6, 123.4, 132.1, 170.8; ESI-MS (*m/z*): 170(M$^+$).

6-Acetoxy-3-bromo-2-hydroxy-2-methylheptane (4): ($C_{10}H_{19}BrO_3$)

Crude acetate **3** (6.8 g, 0.04 mol) was dissolved in THF/H_2O (1:1) (60 mL) in a flask fitted with a thermometer, a dropping funnel and a nitrogen inlet. 1,3-dibromo-5,5-dimethylhydantion (DDH) (6.5 g, 0.022 mol) was added slowly in small proportions with vigorous stirring under nitrogen atmosphere. The temperature during the addition was maintained between 5-10 ^{o}C. After the reaction completed, it was poured in cold water and extracted with ethyl acetate (3 x 25 mL). The combined layer of the solvent washed with 5% sodium carbonate solution (3 x 15 mL) and then with water (3 x 15 mL). The solvent layer dried over anhydrous sodium sulphate and concentrated under reduced pressure to give a pale yellow oil, identified as 6-acetoxy-3-bromo-2-hydroxy-2-methylheptane **4** (9.1 g, 85 %). IR (KBr) cm^{-1}: 1247, 1374, 1449, 1736, 2934, 2978, 3450; ^{1}HNMR, δ: 1.24 (d, *J* = 6.2 Hz, 3H, C*H*$_3$COAc), 1.33 &1.35 (2 x s, 6H, -C(C*H*$_3$)$_2$), 1.67-1.92 (m, 4H, 2 x C*H*$_2$), 2.06 (s, 3H, -COC*H*$_3$), 4.01 (t, *J* = 10.1 Hz, 1H, -C*H*Br), 4.89-5.00 (m, 1H, -C*H*OAc). ^{13}CNMR, δ (*syn*/*anti*) : 20.4, 21.7, 26.5, 26.9, 29.8 (30.5), 35.2 (35.7), 69.9 (70.2), 71.1, 72.5, 169.7; ESI-MS (*m/z*): 267(M$^+$+1).

6-Acetoxy-2-methyl-2-heptene oxide (5): ($C_{10}H_{18}O_3$)

In a solution of 6-acetoxy-3-bromo-2-hydroxy-2-methylheptane **4** (2.67 g, 10 mmol) in CH_2Cl_2 (40 mL) was added DBU and the solution was allowed to stirr at room temperature until TLC showed the completion of the reaction. The reaction contents then poured in cold

water in a separating funnel and extracted with dichloromethane. The solvent layer was washed with water (3 x 20 mL) to neutral pH. The chloroform layer was dried over anhydrous calcium chloride and concentrated under reduced pressure to get 6-acetoxy-2-methyl-2-heptene oxide **5** (1.76 g, 95 %) as colourless oil. IR (KBr) cm^{-1}: 1243, 1377, 1658, 1737, 2929, 2977, 3145, ^{1}HNMR, δ: 1.09 (*d*, *J* = 6.5 Hz, 3H, C*H*$_3$CHO); 1.19 (s, 3H, C*H*$_3$CO); 1.24 (s, 3H, C*H*$_3$CO); 1.44-1.65 (m, 4H, 2 x C*H*$_2$'s); 1.96 (s, 3H, C*H*$_3$CO); 2.64 (t, *J* = 5.8 Hz, 1H, CH$_2$C*H*O); 4.80-4.89 (m, 1H, C*H*OAc); ^{13}CNMR, δ: 16.9, 18.9, 20.3, 23.3, 23.7, 31.6, 57.3, 62.3, 69.6, 169.7; ESI-MS (*m/z*): 186(M^+).

***Syn*- and *anti*-2-(1-hydroxy-1-methylethyl)-5-methyltetrahydrofuran (1): ($C_8H_{16}O_2$)**

To a mixture of 6-acetoxy-2-methyl-2-heptene oxide **5** (1.86 g, 10 mmol) in water (20 mL) was added 10 % aqueous NaOH solution (2 mL) and the reaction mixture was allowed to stirr for 1-2 hrs. After the completion of the reaction as indicated by TLC, the product was extracted from water with CH_2Cl_2. The organic layer was dried over anhydrous calcium chloride and concentrated under reduced pressure to get s*yn*- and *anti*-2-(1-hydroxy-1-methylethyl)-5-methyltetrahydrofuran **1** (1.29 g, 90%) (*anti*:*syn*: 56:44) as colourless liquid. The *syn*/*anti* ratio of the two diastereoisomers was calculated on the basis of ^{1}HNMR and ^{13}CNMR.

***Syn*-2-(1-hydroxy-1-methylethyl)-5-methyltetrahydrofuran (1): ($C_8H_{16}O_2$)**

IR (KBr)cm^{-1}: 800, 1022, 1092, 1261, 1404, 1459, 1651, 2855, 2926, 2960, 3164, 3378; ^{1}HNMR, δ: 1.05 (s, 3H, C*H*$_3$COH), 1.15-1.20 (m, 6H, C*H*$_3$COH & C*H*$_3$CHO), 1.52-2.23 (m, 4H, 2 x C*H*$_2$'s), 3.62 (t, *J* = 7.1 Hz, 1H, CH$_2$C*H*O), 3.75-4.32 (m, 1H, CH$_3$C*H*O); ^{13}CNMR, δ: 21.6, 24.4, 26.4, 27.6, 33.6, 71.2, 75.9, 86.4; ESI-MS (*m/z*): 144(M^+).

***Anti*-2-(1-hydroxy-1-methylethyl)-5-methyltetrahydrofuran (1): ($C_8H_{16}O_2$)**

IR (KBr)cm^{-1}: 800, 1022, 1092, 1261, 1404, 1459, 1651, 2855, 2926, 2960, 3164, 3378; ^{1}HNMR, δ: 1.05 (s, 3H, C*H*$_3$OH), 1.15-1.20 (m, 6H, C*H*$_3$OH & C*H*$_3$CHO), 1.47-2.20 (m, 4H, 2 x C*H*$_2$'s), 3.76 (dd, *J* = 8.9, 6.6 Hz, 1H, CH$_2$C*H*O), 3.75-4.32 (m, 1H, CH$_3$C*H*O); ^{13}CNMR, δ: 21.7, 24.7, 26.4, 27.7, 34.9, 72.2, 76.7, 85.8; ESI-MS (*m/z*): 144(M^+).

References

[1] Karlson, P.; Luscher, M. *Nature* **1959**, *183*, 55-56.

[2]Zarbin, P. H. G.; Jose, A. F. P.; Villar, J. A. F. P.; Arlene G.; Correa, A. G. *J. Braz. Chem. Soc.* **2007**, *18*, 6, 1100-1124 and references cited therein.

[3] Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron Letters* **1987**, *28*, 6613-6617.

[4] Tang, S.; Kennedy, R. M. *Tetrahedron Letters* **1992**, *33*, 5299-5302.

[5] Steinreiber, A.; Edegger, K.; Mayer, S. F.; Faber, K. *Tetrahedron:Asymmetry*, **2001,** *12*, 2067-2071.

[6]A.) J. Rodriguez, J. P. Dulcere. *Synthesis* **1993**, *12*, 1177. B) S. C. Taneja, V.K. Sethi, S. Andotra, S. Koul and G.N. Qazi, USP 6,692,944, **2004**; C) S.C. Taneja, V.K. Sethi, S. Andotra, S. Koul and G..N. Qazi, *Synth. Commun.* **2005**, *35*, 2297.