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T. Subramanian [a] , R. Padmakumar [a] & Sujata V. Bhat [a]

[a] Department of Chemistry , Indian Institute of Technology , Bombay, India
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CONVENIENT SYNTHESIS OF 1,3,6-TRIENE SYSTEMS THROUGH ALKYLATION OF 3-METHYL-3-SULFOLENE.

T.Subramanian, R.Padmakumar and Sujata V. Bhat *

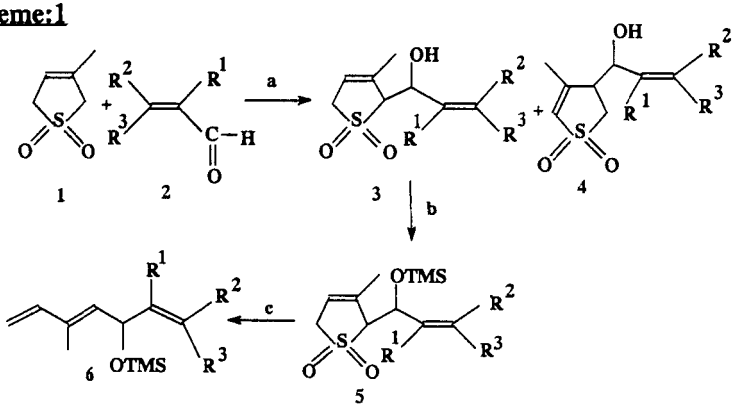
Department of Chemistry, Indian Institute of Technology, Bombay, India.

Abstract: Various 1,3,6-triene systems have been synthesised through alkylation of 3-methyl-3-sulfolene with conjugated aldehydes followed by silylation and subsequent desulfonylation. A new route to synthesis of (+/-)-α-chamigrene, isofokienol and 5-hydroxy-α-farnesene has been described.

The conjugated dienes are versatile building blocks in the synthesis of natural products especially as a component of Diels-Alder reactions[1]. Moreover, wide varieties of biological activities are associated with conjugated diene systems, the prominent among them are the insect sex pheromones[2], organoleptic and antifungal properties. In recent years large number of methods for synthesising conjugated dienes have been reported. Among others, the methods utilising modified Wittig reagents[3], palladium[4], boron reagents[5] and thermal opening of 3-sulfolenes[6] have received considerable interest.

The utility of 3-sulfolenes as anionic and cationic butadienyl equivalents in organic synthesis has drawn increasing attention. The reaction of 3-sulfolene with alkyl halides or aldehydes followed by thermal desulfonylation provides a facile stereoselective method for synthesising (E), (E,Z) and (E,E) conjugated dienes[7].

Scheme:1



Reagents: a) LiHMDS, THF,- 90 C b) TMSCl, Pyridine, Ether c) Pyridine, Reflux, 1h.

We report herein our studies on the synthesis of 1,3,6-trienes having hydroxy group in the 5-position through the alkylation of 3-sulfolene with few terpenic conjugated aldehydes, protection of hydroxyl group by treatment with trimethylsilyl chloride and subsequent desulfonylation in refluxing pyridine.

The alkylation of 3-methyl-3-sulfolene with conjugated aldehydes was achieved in the presence of lithium hexamethyl disilazane (LiHMDS) in THF at -90°C to give α-adducts (major) and γ-adducts (minor). The resultant α-adducts were converted into trimethylsilyl derivatives by treatment with trimethylsilyl chloride in the presence of pyridine . These silyl derivatives were heated in refluxing pyridine for 1 hr to get 1,3,6-trienes (Scheme 1,Table 1).

Similarly α-cyclocitral (7) was condensed with 3-methyl-3-sulfolene to get adduct 8 wihich was desulfonylated to yield tetraene **10** , the advanced intermediate to (+)- α - Chamigrene .(Scheme2).

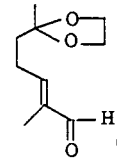
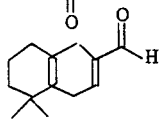
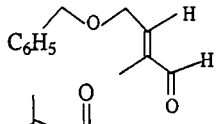
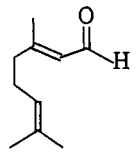
Thus we have achieved the synthesis of terpenic hydroxy trienes particularly (E,E)-5-hydroxy-α-farnesene [8], isofokienol and a tetraene which is an intermediate in the total synthesis of (+/-)-α- chamigrene [9].

Experimental[10]

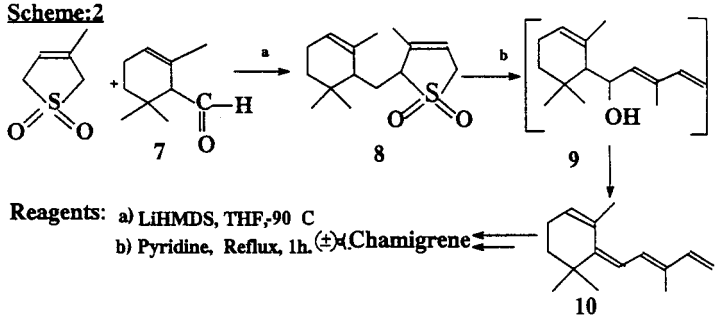
General procedure of condensation of aldehyde with 3-methyl-3-sulfolene:

To a mixture of 3-methyl-3-sulfolene (1) (2.64g, 2 mmoles) and aldehyde (2) (2 mmoles) in THF, was added dropwise the solution of LiHMDS (2 mmloes) in THF at -

Table1 : Alkylation of 3- methyl - 3 - sulfolene

No.	Aldehyde	Products Yield (%)	
		3	4
1		72 (3a)	15 (4a)
2		63 (3b)	12 (4b)
3		78 (3c)	0
4		73 (3d)	0

Scheme:2



Reagents: a) LiHMDS, THF,-90 C
b) Pyridine, Reflux, 1h. (±)-Chamigrene

90°C. The reaction mixture was stirred at the same temperature for 30 minutes. Then, the reaction mixture was gradually warmed upto 0°C and quenched with aqueous saturated NH_4Cl solution. After evaporating the solvent (THF) in vacuo, the residue was extracted repeatedly with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was subjected to column chromatography over silica gel to give the adducts.3 and 4. (Yield 73- 87%,Table 1).

3a: IR (Neat) ν_{max} 3463,2971,1629,1168,1231,1060 cm^{-1} ^1H NMR (300 MHz ,$CDCl_3$) δ 5.8 (1H, bs),5.5 (1H, m) 4.28 (1H, d, J=7.3 Hz), 3.75-3.85 (7H,m), 2.54 (2H ,t, J=7.3 Hz), 2.33 (2H m), 2.15 (3H, s) 1.84 ((3H, s), 1.75 (3H, s), 1.78 (3H, s),1.34 (3H, s)

4a: IR (Neat) ν_{max} 3468, 2975, 1634, 1445, 1231, 1110 cm^{-1} ^1H NMR (300MHz, $CDCl_3$) δ :6.4 (1H, bs) 5.6 (1H, m) 4.4 (1H ,bs) 3.95 (4H, bs) 3.95 (4Hm),3.2 -3.35 (2H, m) 3.1 (1H, dd, J=12.0, 7.7Hz) 2.04 (3H, s), 1.7 (2H, bt), 1.32 (3H, s)

3b: IR (Neat) ν_{max} 3490, 1630, 1616, 1480, 1320, 1180, 1020 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$), δ 5.6 (1H, bs), 5.4 (1H, m), 4.3 (1H, d, J=7.5 Hz), 3.6 -3.8 (3H, m), 2.7-2.8 (2H, m), ,1.9 (2H, t J=6.2 Hz), 1.75 (3H, s), 1.7 (3H, s), 1.6 (1H, m), 1.5 (3H, s), 1.45 (2H, m), 0.94 (3H, s), 0.93 (3H, s)

4b: IR (Neat) ν_{max} 3510, 2950, 1640, 1610, 1610, 1410, 1320, 1320, 1310,1280,1150, cm^{-1} ^1H NMR (300 MHz, $CDCl_3$) δ 6.4 (1H, bs), 5.4 (1H, bt), 4.4 (1H , bs), 3.2-3.35 (2H, m), 3.1 (1H, dd, J=12., 7.7 Hz), 2.78 (2H, bs,), 2.08 (3H, s), 2.04 (3H, s), 1.95 (2 H, bt), 1.6 (2H, m), 0.96 (3H, s), 0.94 (3H, s)

3C: IR (Neat): ν_{max} 3500, 3050, 1625, 1500, 1380, 1320, 1200,·cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.8 (2H, m), 4.51 (2H, s), 4.12 (2H, d, J=6.2 Hz), 3.75 (4H, m), 1.86 (3H, m), 1.76 (3H, s),

3d: IR (Neat): ν_{max} 3450, 2960, 1460, 1314, 1258, 1072. cm $^{-1}$.^1H NMR (300 MHz,$CDCl_3$) δ 5.8 (1H, bs), 5.5 (1H, d, J=7.5Hz), 5.1 (2H, m), 3.7-3.8 (3H, m), 2.1 (4H, m), 1.9 (3H, s), 1.7 (3H, d), 1.6 (3H, s).

Synthesis of silyl derivatives 5

To a solution of adduct 3 (1mmole) in pyridine and ether (1:3,12ml) at 0°C was added dropwise trimethyl chlorosilane (1g, 1mmol) under argon atmosphere. The reaction mixture was stirred for 2 hr. and poured into ice cold water and extracted with ether. The

organic layer on concentration followed by column chromatography yielded silyl derivatives **5.** (Yield 70-75%).

5a IR (Neat) ν_{max} 2955, 1630, 1457, 1252, 1041, 898, 850 cm^{-1}.1 H NMR (300 MHz, $CDCl_3$) 5.7 (1H, bt), 5.5 (1H, bt, J=7.1 Hz), 4.4 (1H , d, J=7.1 Hz), 3.95 (4H, m), 3.7 (2H, m), 3.65 (1H, bs), 2.15 (2H, m), 1.85 (2H, bt).0.1 (9H, s)

Thermolysis of silyl derivatives 5.

A solution of silyl derivative **5** (1mmol) in pyridine (5ml) was refluxed for 1h. Pyridine was removed under vacuo and the residue was column chromatographed over silica gel to yield trienes **6.**(yield 68-75%).

6a:IR(Neat)ν_{max} 2955, 1629, 1370, 1252, 1041 ,898, .854 cm^{-1}. ^1H NMR (300Mz ,$CDCl_3$) 6.35 (1H, dd, J=11.3, 17.3Hz), 5.47 (1H, d, J=8.41 Hz), 5.42 (1H, t, J=7.32), 5.18 (1H, d, J=17.5) 5.0 (1H, J=11.3 Hz), 4.8 (1H, J=8.42 Hz), 3.96 (4H, ,m), 2.1 (2H,m), 1.76 (3H, s), 1.65 (2H, m), 1.32 (3H, s), 0. 1 (9H, s).

6b: IR (Neat) ν_{max} 2950, 1628 ,1280, 1108 cm^{-1} ^1H NMR (300 MHz ,$CDCl_3$) δ; 6.4 (1H, dd, J=17.3 , 11.3 Hz), 5.5 (1H, J=8.2 Hz), 5.35 (1H, t J=6.0 Hz) 5.2 (1H, d, J=17.3 Hz), 5.03 (1H, d, J=11.3 Hz) 4.9 (1H, d, J=8 Hz) 2.72 (2H, d, J= 6.0 Hz), 1.9 (2H, bt), 1.82 (3H, s), 1.65 (3H, s), 1.55 (3H, s), 1.5 (2H, m), 1.4 (2H, m), 0.96 (3H, s,), 0.94 (9H, s).

6c: IR (Neat) ν_{max}3500, 2960, 1629, 1450, 1055$_{cm}$-1 ^1H NMR (300 MHz,$CDCl_3$) 7.35 (5H, bs), 6.38 (1H, dd, J=17.3, 11.3, Hz), 5.49 (1H, t, J=6.4 Hz), 5.2 (1H, d , J=17.3 Hz), 4.51 (2H, s), 4.08 (2H, d, J=6.4 Hz), 1.82 (3H, s), 1.62 (3 H, s).

6d: IR (Neat); ν_{max} 2986, 2930, 1625, 1109, 992, 892 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ 6.5 (1H, dd, J=17.3, 11.3 Hz), 6.3 (1H, d, J=12.5), 6.1 (1H, d, J=11.3 Hz), 5-5.25 (4H, m), 2.2 (4H, m),1.88 (3H, s), 1.7 (3H, s), 1.62 (6H, s), 1.6 (3H, s) ,0.1 (9H, s).

8:IR (Neat), ν_{max} 3510, 2960, 1620, 1430, 1315, 1120 cm^{-1} ^1H NMR (60 MHz, $CDCl_3$), δ 5.85 (1H, bs), 5.2 (1H, bs), 4.1 (1H, s), 3.7 (3H, bs), 2.1 -2.3 (5H, m), 1.95 (3H, bs), 1.7 (3H, s), 1.1 (6H,m)

10: IR (Neat) ν_{max} 2980, 1630, 1430, 1340, 1280, 1120, 1080 cm^{-1}. ^{1} H NMR (60 MHz, $CDCl_3$), δ 6.3 (1H, dd, J= 17.5, 11 Hz), 5.5 (1H, d, J=11Hz), 5.1 (1H, d, J=17.5 Hz), 4.6 (1H, d, J=12Hz,), 4.5 (1H, bt), 1.7 (8H, bs), 1.5 (3H s), 1.0 (3H, s), 0.9 (3 H, bs).

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10. All compounds gave satisfactory microanalysis.

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