Synthetic Strategies Towards the Sex Pheromone of Trogoderma Species

G. Nageswara Rao[a,*], B. Jagan Mohan Reddy[b] and N. Thrimurtulu[b,c]

[a]*School of Chemistry, Andhra University, Visakhapatnam, India*

[b]*Department of Organic Chemistry, Adikavi Nannaya University, Rajahmundry, India*

[c]*Department of Chemistry, Georgia State University, Atlanta, USA*

Abstract: Z-14-methyl-8-hexadecenal and its E-isomer were identified as the essential female secreted sex pheromones of trogoderma species of insects. Since the discloser of its structure in 1969, (*Z*)-(-)-14-methyl-8-hexadecen-l-ol and methyl (*E*)-(-)-14-methyl-8-hexadecenoate as the sex pheromones have been the subject of intense study by the synthetic organic community. Several strategies have been developed for the total synthesis of these exciting pheromone molecules and they are discussed in detail.

Keywords: sex pheromones, trogoderma, total synthesis.

INTRODUCTION

Trogoderma species of insects are notorious pests of stored product. Beetles that belong to *Trogoderma* genus create havoc in rice storage. It certainly requires a non-pesticidal management strategy to protect the stored grains, such as the application of insect pheromones. In 1969 Rodin *et al.* [1] isolated (*Z*)-(-)-14-methyl-8-hexadecen-l-ol and methyl (*E*)-(-)-14-methyl-8-hexadecenoate (Figure **1**) as the sex pheromone blend of the female dermestid beetle (*Trogoderma inclusum)* by extracting whole body of insects. In 1976 Cross *et al.* [2] isolated the genuine sex pheromone systems of *Trogoderma inclusum*, *Trogoderma variabile* and *Trogoderma glabrum.* They identified it as (*Z*)-14-methyl-8-hexadecenal in both *T. inclusum* and *T. variabile* but the corresponding (*E*)–isomer in *T. glabrum*. However, both the isomers were found in *T. granarium* in a *Z:E* ratio of 92:8.

Earlier Approaches to the Synthesis of Trogodermal

1) Mori's First Approach

Mori [3] reported a synthetic scheme (Scheme **1**) based on Isopentane (**11**) and 2-(non-8-yn-1-yloxy)tetrahydro-2H-pyran (**14**). Isopentane (**11**) was converted into *(2S)*-**12** by treatment with phosphorus tribromide. The Grignard reagent derived from *(2S)*-**12** was coupled with ally1 bromide to give an olefin *(5S)*-**13**. The olefin *(5S)*-**13** on hydroboration with B_2H_6 followed by bromination yielded a bromide *(5S)*-**14**. Lithium salt of 2-(non-8-yn-1-yloxy) tetrahydro-2H-pyran was coupled with bromo compound *(5S)*-**14** in the presence of HMPA to produce alkyne *(14S)*-**16**. Deprotection of the Tetrahydropyranyl group with *p*-TSA in MeOH gives alcohol *(14S)*-**17.** Catalytic partial hydrogenation of alcohol *(14S)*-**17** with Lindlar's catalyst containing quinoline gave Z-isomer of Trogodermol *(14S)*-**2**. Jones oxidation of *(14S)*-**2** with CrO_3 produced corresponding acid which was converted into methyl ester *(14S)*-**10** by treatment with diazomethane.

2) Mori's Second Approach

Mori [4] achieved the synthesis of *R*,*S* enantiomers of Z-isomer from a common starting material *R*-Citronellol *(3R)*-**19**. Citronellol was converted into tosylate (*3R*)-**20**. The corresponding tosylate (*3R*)-**20** was oxidized with *m*-CPBA to give an epoxide (*3R*)-**22.** This was cleaved with HIO_4 to give an aldehyde (*3R*)-**23**. Reduction of (**23**) with LAH yielded (*S*)-(+)-4-methylhexan-l-ol which upon tosylation with tosylchloride in pyridine gave tosylate(*4s*)-**24**. The corresponding tosylate (*4s*)-**24** was treated with LiBr to give a bromide (*4s*)-**25**. The Grignard reagent derived from (*4s*)-**25** was coupled with ally1 bromide to give an olefin *(7S)*-**26**.

Citronellol was converted into acetate (*3R*)-**21**. The corresponding acetate (*3R*)-**21** was oxidized with *m*-CPBA to give an epoxide (*3R*)-**27**. This was treated with selenophenol followed by hydrogen peroxide to give a crude alcohol (*3R*)-**28** which upon acetylation with acetic anhydride in pyridine gave (*3R*)-**29**. **T**he olefinic alcohol was oxidized with *m*-CPBA to give an epoxide (*3S*)-**30** and cleaved with HIO_4 to give an aldehyde (*3R*)-**31**. The Wolff-Kishner reduction of

*Address correspondence to this author at the School of Chemistry, Andhra University, Visakhapatnam, India; Tel: +918912567607;
E-mail: gollapallinr@yahoo.com

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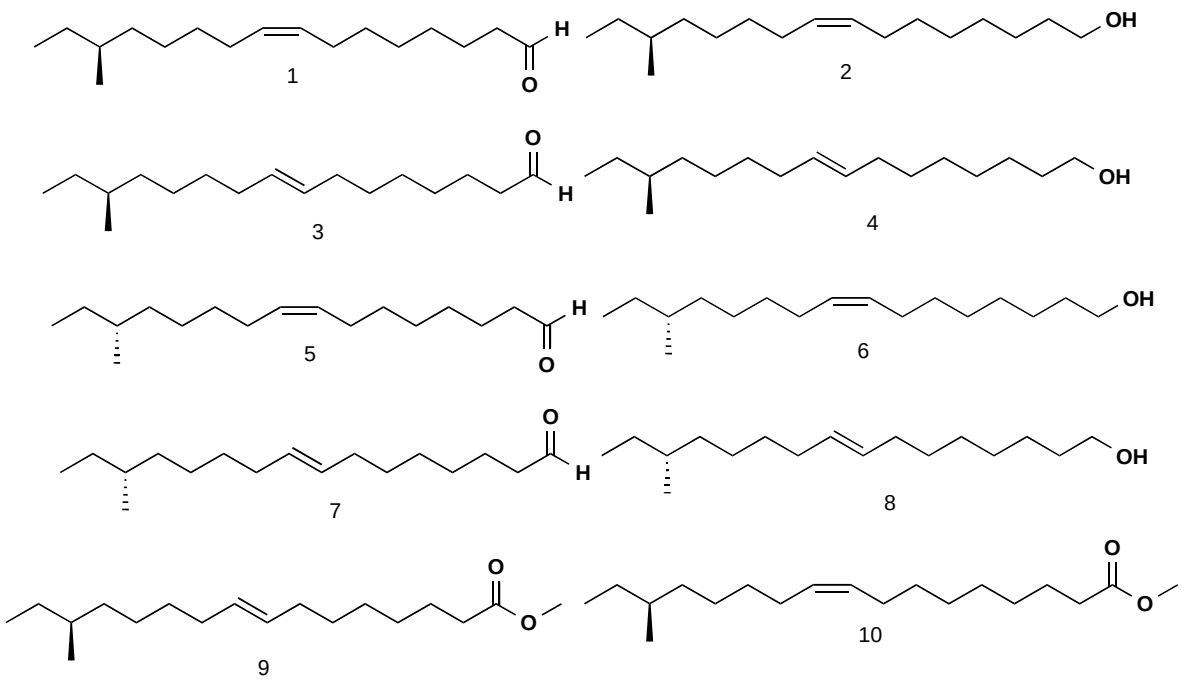
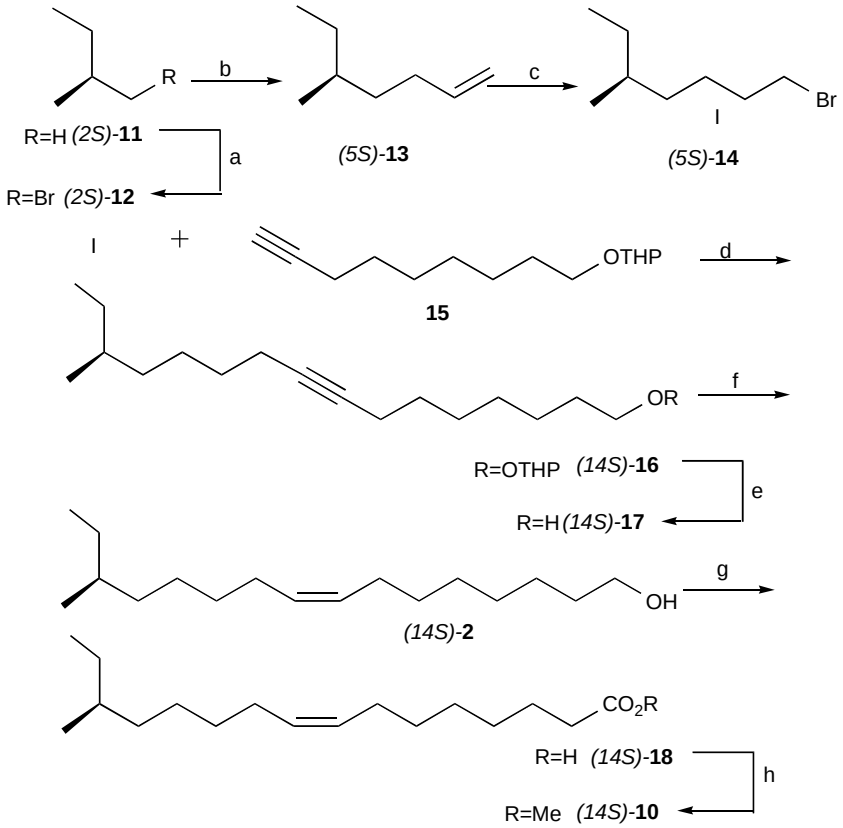
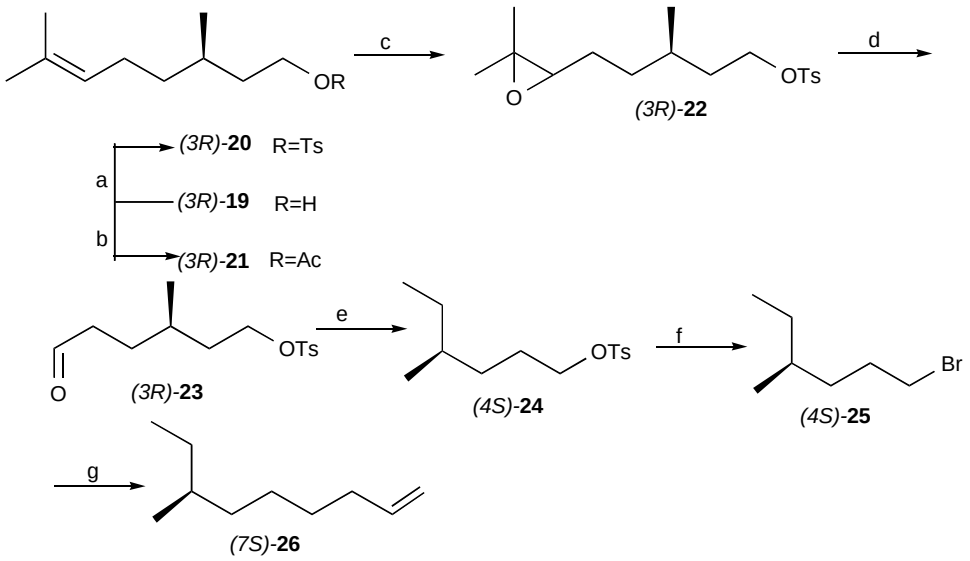


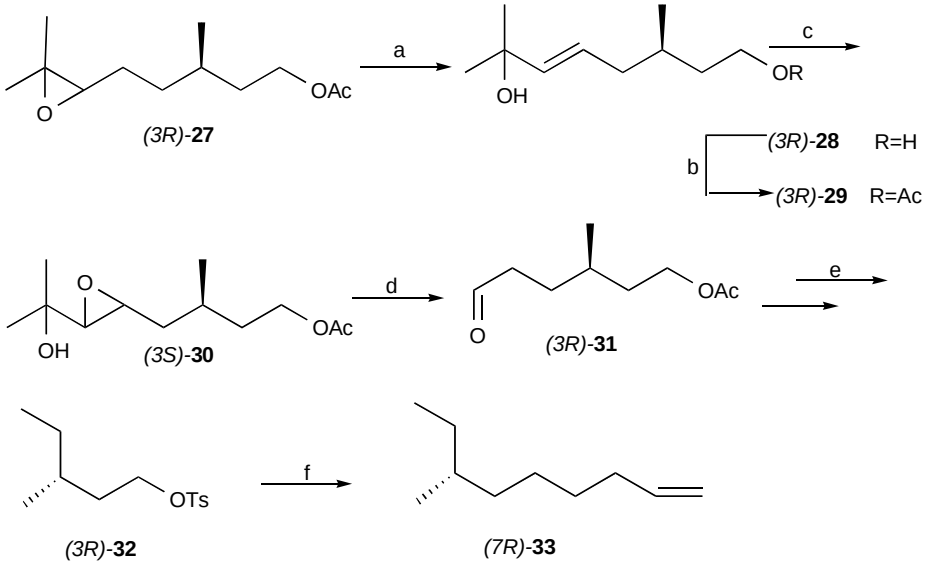
Figure 1: Structures of sex pheromones of trogoderma species.



Scheme 1: *Reagents and conditions:* a) PBr_3, neat, -15 ^oC- rt. b) Mg, Et_2O,16 h,C_3H_5Br. c) B_2H_6, THF, 2h,0 ^oC. d) n-BuLi, THF, HMPA, 1h, 10 ^oC to 20 ^oC. e) MeOH, *P*-TsOH, 60^oC, 1h. f) 5% $Pd/BaSO_4$, quinoline, MeOH, H_2, rt, 1/2 h. g) CrO_3, Et_2O.



Scheme 2: *Reagents and conditions:* a) TsCl, dry p**y**ridine, 0^{o}C to 5^{o}C, 2h. b) Ac_2o, dry pyridine, 3h, 94%. c) *m*-CPBA,CH_2Cl_2, 2h. d) $HIO_4.2H_2O$, THF, 1h. e) i) LAH, Et_2O,12h. ii) TsCl, dry pyridine,0 ^{o}C to 5^{o}C, 2h. f) LiBr, acetone, 12h. g) Mg, Et_2O, 2h.



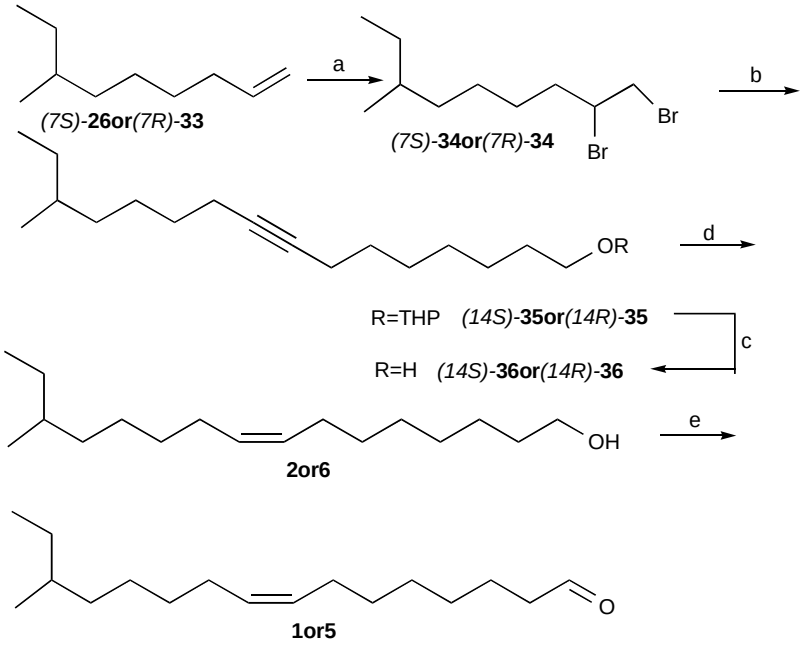
Scheme 3: *Reagents and conditions:* a) $C_6H_5SeSe_6H_5$, $NaBH_4$, EtOH, 2 h, THF, H_2O_2.b) Ac_2O, dry p**y**ridine, 3 h. c) *m*-CPBA, CH_2Cl_2, 2 h d) $HIO_4.2H_2O$,THF, 1 h e) i) $N_2H_4.H_2O$, diethylene glycol, neat,-15 ^{o}C- rt ii) TsCl, dry p**y**ridine, 0 ^{o}C to 5^{o}C, 2 h, f) Li_2CuCl_4, Mg, Et_2O, but-3-enyl bromide.

aldehyde with $N_2H_4.H_2O$ followed by tosylation with tosylchloride in pyridine gave tosylate (*3R*)-**32**. The corresponding tosylate (*4s*)-**24** was coupled in the presence of Li_2CuCl_4, with a Grignard reagent prepared from but-3-enyl bromide to give an olefin *(7R)*-**33**.

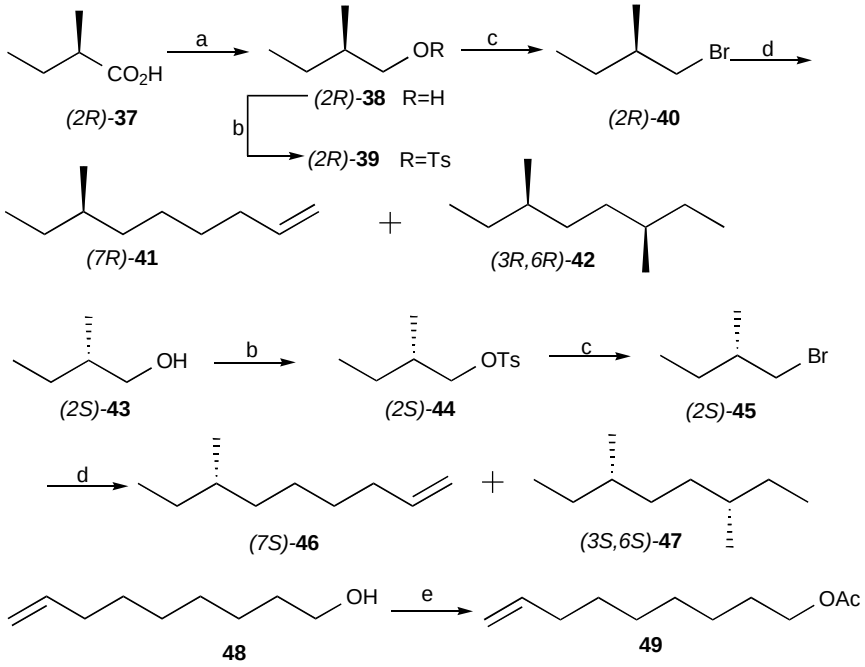
The olefin *(7S)*-**26** or *(7R)*-**33** was converted into *(7S)*-**34** or *(7R)*-**34** by treatment with bromine in DCM. Dihydrobromination of *(7S)*-**34** or *(7R)*-**34** with $NaNH_2$ in liq.NH_3 gave acetylenes, which in THF were treated with n-BuLi and the resulting carbanion was alkylated with 1-tetrahydropyranyloxy-7-iodoheptane in HMPA. Deprotection of the tetrahydropyranyl group with *p*-TSA in MeOH gave alcohol *(14S)*-**36** or *(14R)*-**36.** Catalytic partial hydrogenation of alcohol *(14S)*-**36** or *(14R)*-**36** by Lindlar's catalyst containing quinoline gave Trogodermol **2** or **6**. Oxidation of **2** and **6** with $CrO_3.C_5H_5NHCl$ yielded Trogodermal **1** or **5**.

3) Mori's Third Approach

Mori [5] achieved the synthesis of *R,S* enantiomers of E-isomer from (R)-2-methylbutanoic acid and (S)-2-methylbutanoic acid *via* cross metathesis. Reduction of *R,S* enantiomers of *E*-isomer of 2-methylbutanoic acid with LAH afforded *(2R)*-**38** and*(2s)*-**43** followed by



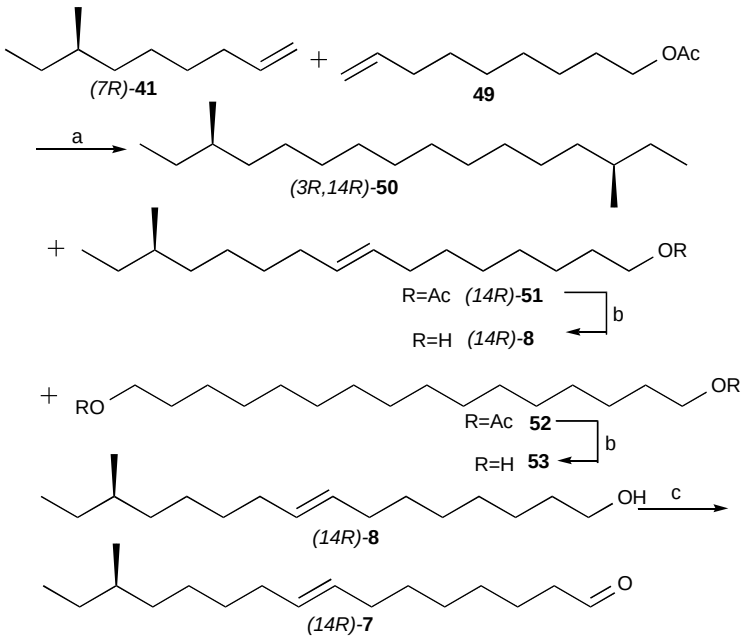
Scheme 4: *Reagents and conditions*: a) Br_2, CH_2Cl_2. b) i) $NaNH_2$, Na, liq NH_3,Et_2O, –33 °C, 4 h. ii) *n*-BuLi, THF, 1-tetrahydropyranyloxy-7-iodoheptane, HMPA, 30 min, -40 °C to 25 °C. c) *P*-TsOH, MeOH, 60 °C, 1h. d) 5% Pd/$BaSO_4$, quinoline, MeOH, H_2, rt, 40 min. e) $CrO_3.C_5H_5N.HCl$.



Scheme 5: *Reagents and conditions*: a) LAH, Et_2O. b) TsCl, dry p**y**ridine, 86%. c) LiBr, DMF, 63%. d) Mg, THF, $H_2C{=}CH(CH_2)_3OTs$, Li_2CuCl_4, 56%. e) Ac_2O, dry p**y**ridine.

tosylation with tosylchloride to give*(2R)*-**39** and *(2s)*-**44.** Tosylates were treated with lithium bromide in DMF to give (R)-2-methylbutyl bromide *(2R)*-**40** and *(2s)*-**45**. 4-Pentenyl tosylate in THF was coupled in the presence of Li_2CuCl_4, with a Grignard reagent prepared from *(2R)*-**40** and *(2s)*-**45** to give an olefin *(7R)*-**41** and *(7s)*-**46.** In this reaction self-coupling of *(2R)*-**40** and *(2s)*-**45** to form **10%** of *(3R,6R)*-**42** and *(3S,6S)*-**47**. Acetylation of non-8-en-1-ol with acetic anhydride in pyridine gave **49**.

Cross-metathesis between 7-methyl-1-nonene*(7R)*-**41** and 8-nonenyl acetate **49** was achieved by using Grubbs' first generation catalyst to give a mixture of

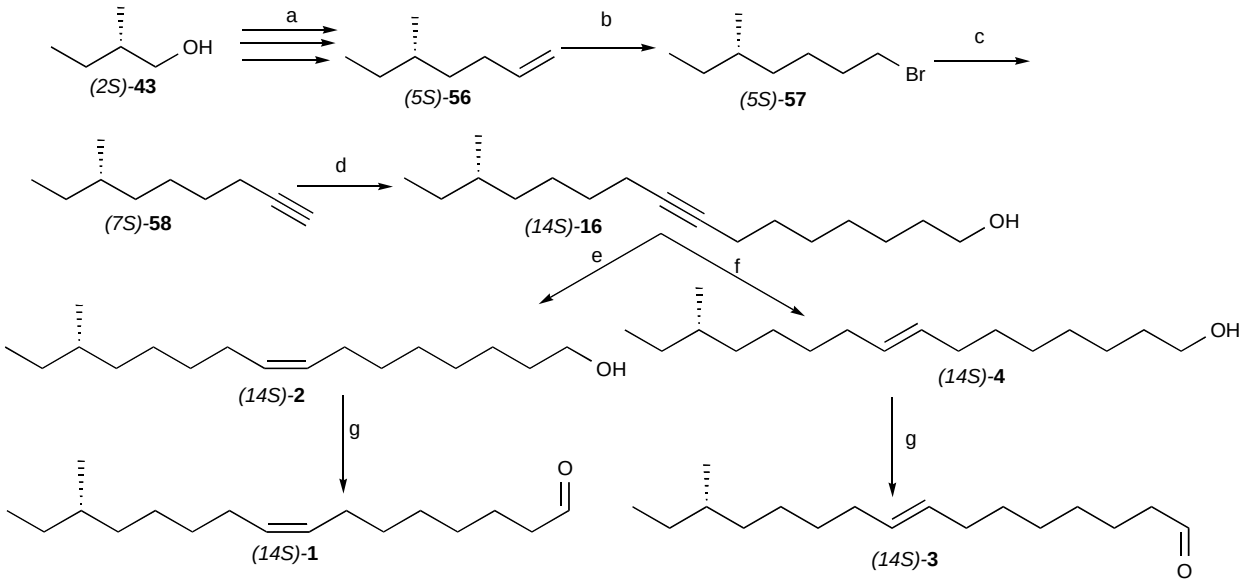


Scheme 6: *Reagents and conditions*: a) Grubbs (I) catalyst, reflux, 6h, 56%. b) aq.NaOH, MeOH, 62%. c) PCC, SiO_2, CH_2Cl_2.

(3R,14R)-**50,** and **51**. The acetate **51** on hydrolysis with sodium hydroxide gave Trogodermol *(14R)*-**8**. Oxidation of *(14R)*-**8** with pyridinium chlorochromate (PCC) furnished the desired aldehyde *(14R)*-**7**. Same pathway was reported for the synthesis of Trogodermol *(14S)*-**4** and aldehyde *(14S)*-**3** from 7-methyl-1-nonene *(7S)*-**41** and 8-nonenyl acetate **49**.

4) Rossi Approach

Rossi and Carpita [6] reported a synthetic route from (*S*)-2-methyl-1-butanol *(2S)*-**43** and 1-tetrahydropyranyloxy-7-iodoheptane. (*S*)-2-methyl-1-butanol (neat) was converted to bromo compound by treatment with phosphorus tribromide. The Grignard reagent derived from bromo compound was coupled with ally1 bromide to give an olefin *(5S)*-**56**, which on hydroboration with B_2H_6 followed by bromination yielded a bromide *(5S)*-**57.** Treatment of a DMSO solution of *(5S)*-**57** with a DMSO solution of lithium acetylide-ethylenediamine complex gave (S)-7-methyl-l-nonine *(5S)*-**58.** 1-tetrahydropyranyloxy-7-iodoheptane was coupled with triple bond compound *(5S)*-**58**



Scheme 7: *Reagents and conditions*: a) i) PBr_3,neat,-15 ^oC- rt. ii) Mg, Et_2O,16 h,C_3H_5Br. b) i)B_2H_6,THF, 7h,0 ^oC to rt. ii) Br_2, 1 h,-10 ^oC . c) LiC≡CH.EDTA, DMSO, 0-5^oC, 24 h. d) *n*-BuLi, THF, 1-tetrahydropyranyloxy-7-iodoheptane, HMPA, 30 min, -40 °C to 25^oC. e) 5%Pd/$BaSO_4$, quinoline, MeOH, H_2, rt, 20 min. f) diglyme, LAH, THF, 140 ^oC, 48 h, 94%. g) PCC, Et_2O.

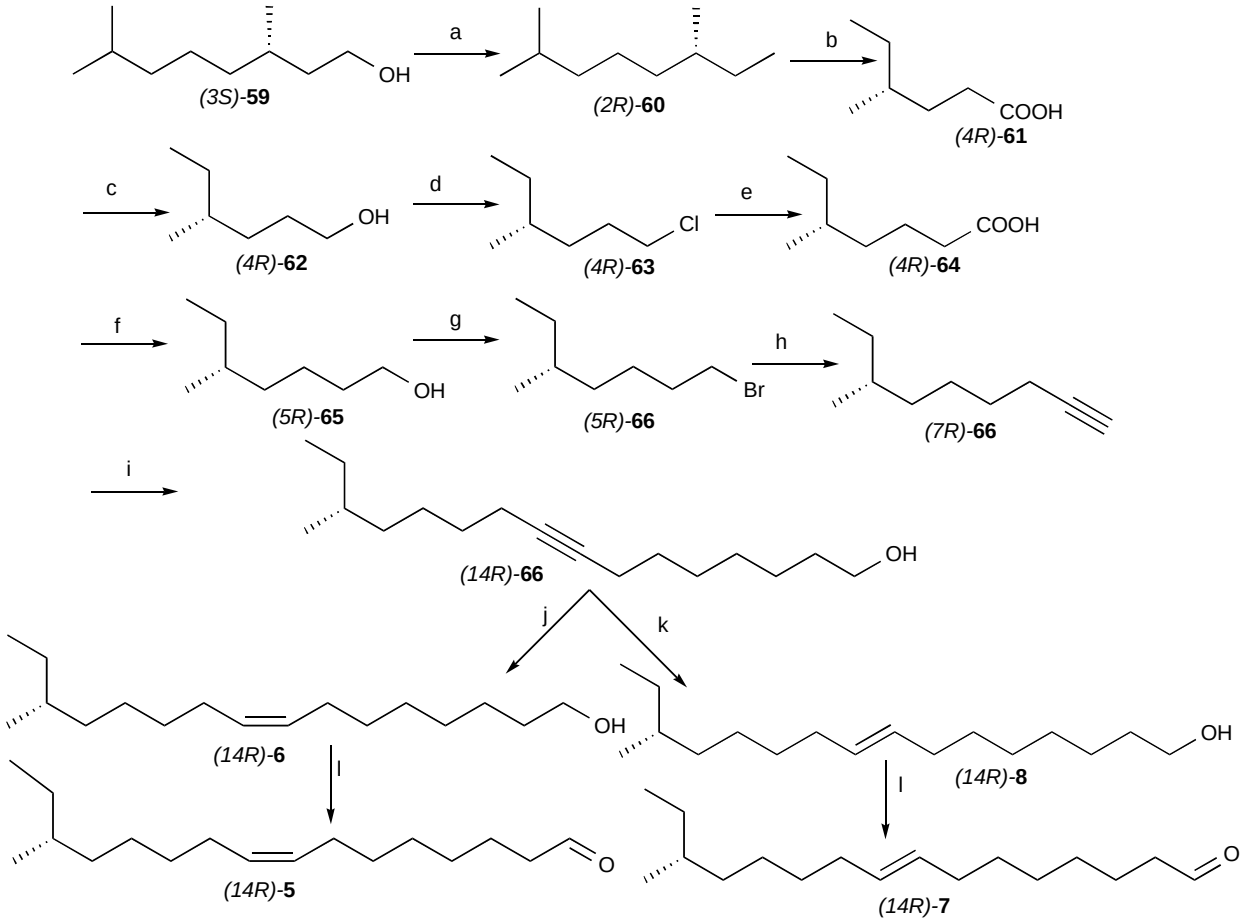
in the presence of *n*-BuLi and HMPA to produce (*14S)*-**16**. Catalytic partial hydrogenation of alcohol *(14S)*-**16** with Lindlar's catalyst [6] containing quinoline gave *Z*-isomer of Trogodermol *(14S)*-**2** which on further oxidation with PCC gave *Z*-Trogodermal *(14S)*-**1**. Similarly trans hydrogenation of alcohol (*14S)*-**16** with diglyme, LAH, afforded the *E*-isomer of Trogodermol (*14S)*-**4** which on further oxidation with PCC afforded the E-Trogodermal*(14S)*-**3**.

5) Rossi and Niccoli Approach

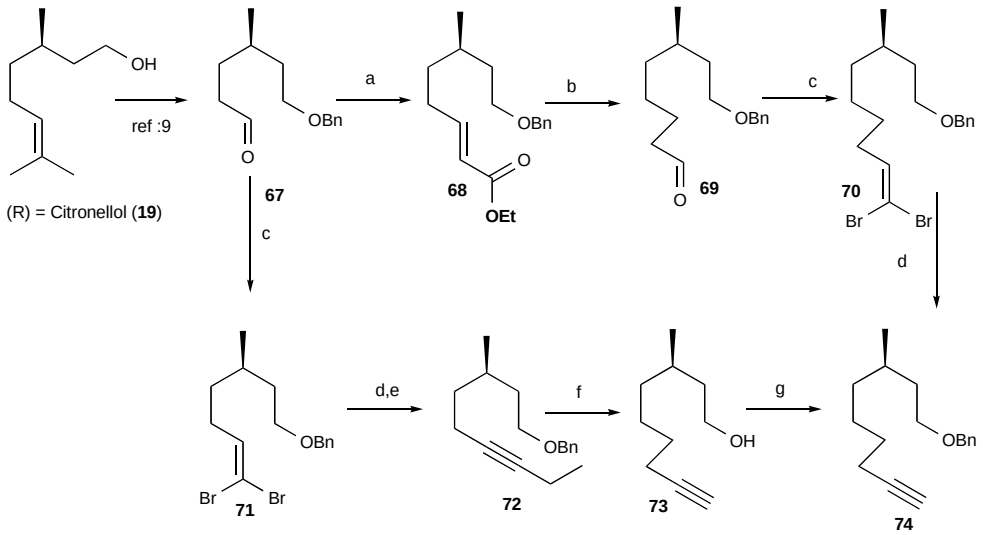
Rossi and Niccoli [7] achieved the synthesis of R enantiomer of Z and E isomers from a common starting material S-Citronellol *(3R)*-**59**. S-Citronellol was converted into (*2R*)-**60** by the treatment with CH_3SO_2Cl. This was treated with hydrogen peroxide to give (*4R*)-**61** followed by reduction with LAH yielded (*R*)-4-methylhexanoic acid (*4R*)-**62**. Treatment of (*4R*)-**62** with thionyl chloride and pyridine gave (*4R*)-**63** which was converted into the corresponding Grignard reagent and subsequently reacted with solid carbon dioxide to give (*4R*)-**64**. Reduction of (*R*)-5-methylheptanoic acid with LAH afforded *(5R)*-**65**. (*R*)-5-methylheptan-1-ol (neat) was converted into bromo compound *(5R)*-**66** by treatment with phosphorus tribromide. Treatment of *(5R)*-**66** with a DMSO solution of lithium acetylideethylenediamine complex gave (R)-7-methylnon-1-yne *(7R)*-**66**. 1-chloro-7-tetrahydropyranyloxyheptane was coupled with triple bond compound *(7R)*-**66** in the presence of *n*-BuLi and HMPA to produce (*14R)*-**66**. Catalytic partial hydrogenation of alcohol *(14R)*-**66** with Lindlar's catalyst [6] containing quinoline gave Z-isomer of Trogodermol *(14R)*-**6** which further oxidation with PCC gave Z-Trogodermal *(14R)*-**5**. Similarly trans hydrogenation of alcohol (*14R)*-**66** with diglyme, LAH, afforded the E-isomer of Trogodermol (*14R)*-**8** which on further oxidation with PCC afforded the E-Trogodermal *(14R)*-**7**.

6) Yadav Approach

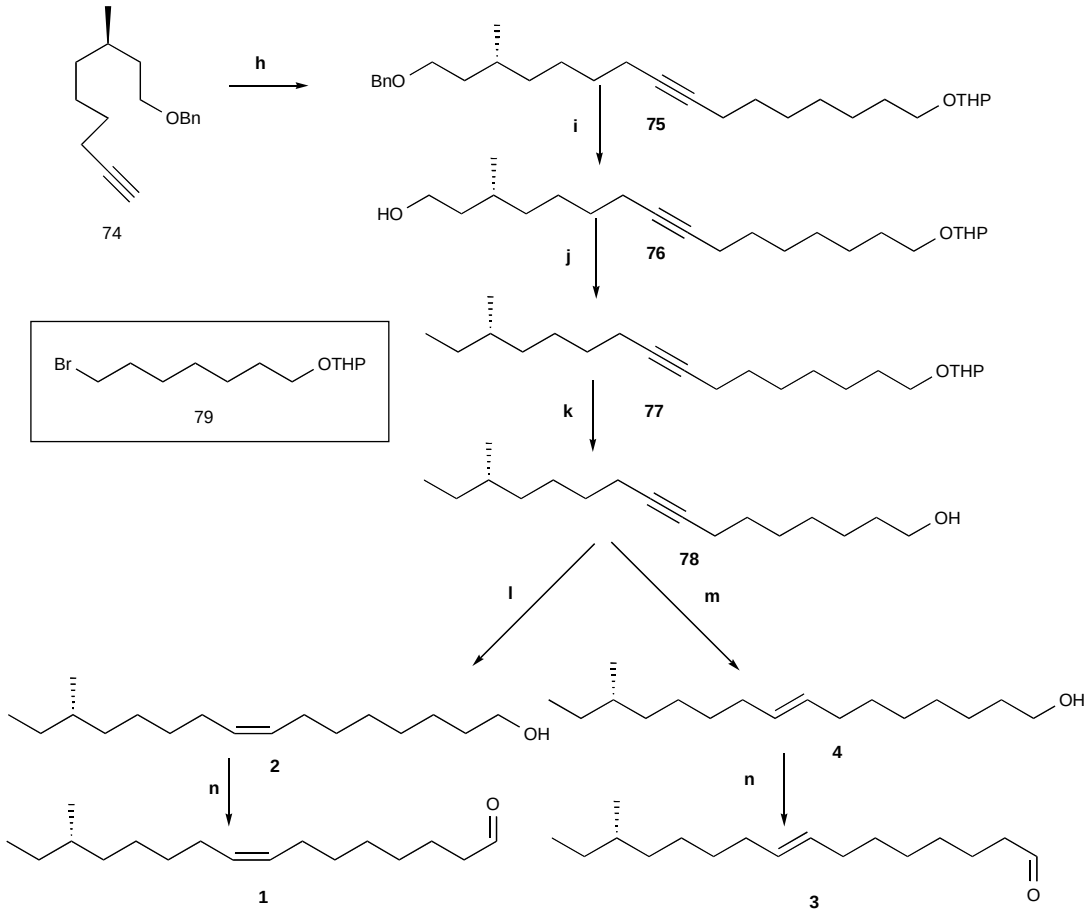
Yadav [8] achieved the practical approach of both *E*- and *Z*-Isomers of optically pure (*S*)-14-



Scheme 8: *Reagents and conditions*: a) CH_3SO_2Cl, CH_2Cl_2, TEA, 2.5h, -10° C. b) 36% H_2O_2, 1.5h, 45°C. c) LAH, Et_2O, 18 h. d) SO_2Cl_2, pyridine,-10°C to 100°C. e) Mg, Et_2O, CO_2, 12h, rt. f) LAH, Et_2O. g) PBr_3, neat, 100°C- rt. h) LiC≡CH.EDTA, DMSO, 0-5°C, 24h, rt. i) *n*-BuLi, THF, 1-chloro-7-tetrahydropyranyloxy heptane, HMPA, 30 min, 0°C, 12h, rt. j) 5% Pd/$BaSO_4$, quinoline, MeOH, H_2, rt, 1h. l) PCC, CH_2Cl_2. k) diglyme, LAH, THF, 140 °C, 48h.



Scheme 9: *Reagents and Conditions*: a) $Ph_3P{=}CH\ CO_2Et$, CH_2Cl_2, 0-25 ^oC, 2 h, 80%; b) i) LAH, THF, 73%; ii) IBX, DMSO/DCM (1:3), 1 h, 90%; c). CBr_4, TPP, THF, 12 h, 90%; d) *n*-BuLi, THF, 0 ^oC, 90%; e) C_2H_5I, THF, -78 ^oC, 80%; f) i) Na, liq. NH_3, THF, -33 ^oC, 15min, 94%; ii) $NaNH_2$, $NH_2(CH_2)_3NH_2$, 6 h, 68%; g) NaH, BnBr, THF, 90%.



Scheme 10: *Reagents and Conditions*: h) Li/liq.NH_3, **79,** THF, -78 ^oC, 85%; i) Na/liq. NH_3, THF, -33 ^oC, 15 min, 94%; j) TsCl, Et_3N, DCM 0 ^oC -rt, 6 h, 95%; then $LiAlH_4$, THF, 0 ^oC-rt, 4 h, 95%; k) *p*-TSA, MeOH,1 h, 90%; l) Pd/$BaSO_4$, H_2, Quinoline, 6 h, 94%; m) Na/liq. NH_3, THF, -33 ^oC, 12 h, 94%; n) IBX, DMSO, 90%.

Methylhexadec-8-enal from (*R*)-Citronellol **19** in two ways. Accordingly, alkyne fragment **74** is derived from aldehyde **67** [9] which is prepared from *R*-Citronellol. **67** is converted into alkyne **74** by using C_2-Wittig salt in benzene, Corey–Fuchs [10] reaction, Zipper isomerization.

For the preparation of Trogodermal (**1** and **3)**, compound **74** is converted into corresponding alkynyllithium by using lithium in liquid ammonia and coupled with bromo compound **79** to produce alkyne **75**. Deprotection of benzyl group which upon tosylation followed by reduction with LAH has afforded the alkyne **77.** This is treated with *p*-TSA in MeOH to give primary alcohol **78.** Catalytic partial hydrogenation of **78** with Lindlar's catalyst gave Z-isomer of Trogodermol **2** which on further oxidation with IBX in DMSO/ CH_2Cl_2 (1:3) provided *Z*-Trogodermal **1.** Similarly trans reduction of **78** with sodium in liquid ammonia at -33 ^oC has afforded the *E*-isomer of Trogodermol **4** which on further oxidation with IBX in DMSO/ CH_2Cl_2 (1:3) has afforded the *E*-Trogodermal **3** (Scheme **10**).

CONCLUSION

In Summary, sequential coupling/reduction reactions have been developed, allowing the straight forward synthesis of interesting methyl center containing fragment. In addition, an asymmetric variant of the process has been developed which may be readily employed to access optically active chiral methyl center containing fragment.

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GLOSSARY

DCM = Di Chloro Methane

HMPA = Hexa Methyl Phosphor Amide

LAH = Lithium Aluminium Hydride

m-CPBA = meta Chloro Per Benzoic Acid

MeOH = Methanol

PCC = Pyridinium Chloro Chromate

THP = Tetrahydropyran

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