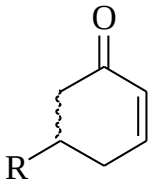
CHAPTER – II

Total synthesis of (-) Cleistenolide

INTRODUCTION

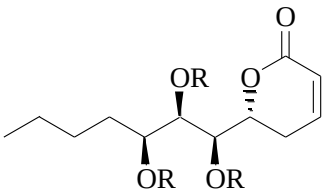
6-Substituted-5,6-dihydro-2*H*-pyran-2-ones (α,β-unsaturated-δ-lactones) **1**[1] are important structural subunits in many biologically important natural products. These units are important for a wide variety of biological activities, such as insect growth inhibition and insect antifeedent, antifungal, and antitumor properties. The pyrone units are widely distributed in all parts of plants (*Lamiaceae*, *Piperaceae*, *Lauraceae*, and *Annonaceae* families) including leaves, stems, flowers, and fruits. Various kinds of substitutions have been found at the C-6 position of the ring such as polyacetoxy alkane, polyhydroxy alkane, a combination of both, or even a simple alkane. Biological activity of these types of molecules, their structural complexities, and the challenge to synthesize them in optically pure form made them an attractive target for many total syntheses. Some of these natural products isolation and biological activities are discussed in below.



1.5,6-dihydropyran-2-one

(+)-Boronolide (2)

The (+)-boronolide was isolated from the bark and branches of *Tetradenia fruticosa* and from the leaves of *Tetradenia barbera*,[2] which have been used as local folk medicine in Madagascar and southern Africa. (+)-Deacetylboronolide and (+)-dideacetylboronolide were obtained from *Tetradenia riparia*, [3] a central African species widely used as a tribal medicine. Medicinal properties of boronolides have been exploited for a long time in crude form. Zulu used roots of these plants as an emetic, and infusion of leaves has been reported to be effective against malaria.[4]



2

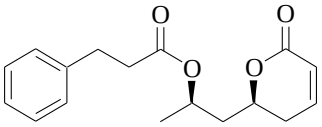
2. R = R' = OAc **(+)-Boronolide**

3. R = R' = H **(+)-Deacetylboronolide**

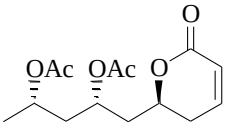
4. R = H, R' = OAc **Acetylboronolide**

Tarchonanthuslactone (5)

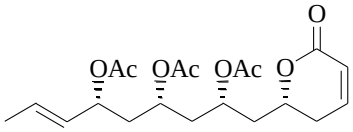
The simplest compound isolated with the syn-1,3-diol/5,6-dihydropyran-2-one, motif is the dihydrocaffeic ester, tarchonanthuslactone **5**.[5] Some more complex examples of these structures are cryptocarya diacetate **6** and cryptocarya triacetate **7**. Tarchonanthuslactone **6** was isolated by Bohlmann from *Tarchonanthustrilobus compositae*. Hsu *et al*., have reported that tarchonanthuslactone lowers plasma glucose in diabetic rats.[6]



5. Tarchonanthus lactone



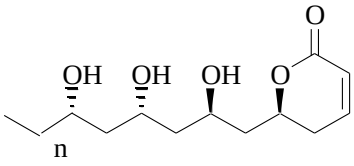
6. Cryptocarya diacetate



7. Cryptocarya triacetate

Passifloricin A (8)

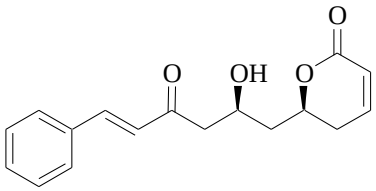
Polyketide-type α-pyrone passifloricin A **8**,[7] was isolated from the resin of *Passiflora foetida var, hispida,* a species from the family *Passifloraceae* that grows in tropical zones of America and was found to be active in the *Artemia salina* test. Passifloricin was found to be active in the Artemia salina test.



8. Passifloricin n = 14

Kurzilactone (9)

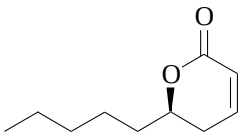
Kurzilactone **9**,[8] a new α,β-unsaturated-δ-lactone, that has been isolated from the leaves of *Cryptocarya kurzii*. The structure of kurzilactone was determined by spectroscopic methods. Kurzilactone exhibits marked cytotoxicity against KB cells with IC_{50} = 1 μg ml^{-1}.



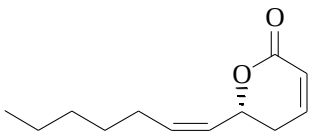
9. Kurzilactone

Massoialactone (10) and Argentilactone (11)

Massoialactone **10**[10] first isolated from the bark oil of *Cryptocarya massoia* by *Abe* in 1937. This lactone has been used for many centuries as a constituent of native medicines. In 1977, *Ruveda* and co-workers reported the isolation of argentilactone **11**[9] from *Aristolochia argentina* (*Aristolochiaceae*). Later, this natural pyranone was also isolated from *Chorisia crispflora* and *Annona haematantha*. Argentilactone **10** was shown to have antileishmanial and cytotoxic activities.



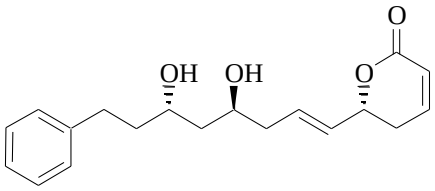
10. (*R*)-Massoialactone



11. (*R*)-Argentilactone

Strictifolione (12)

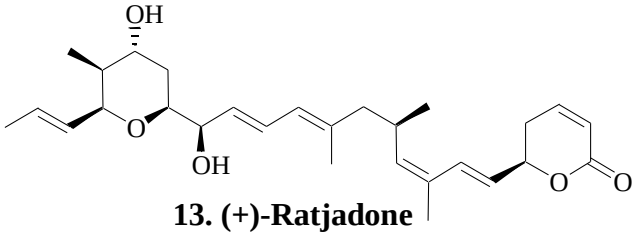
Strictifolione **12**[11] was isolated from *Criptocarya stricifolia* and has shown to display antifungal activity.



12. (+)-Strictifoline

(-)-Ratjadone (13)

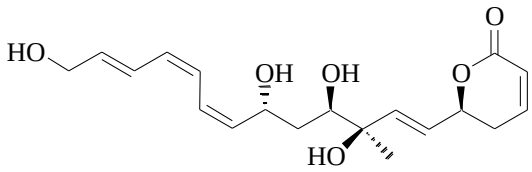
In 1994, the polyketide ratjadone **13** was isolated from cultures of *Sorangium cellulosum* strain Soce360.[12] Ratjadone displays potent in vitro antifungal activity with MIC values in the range from 0.004 to 0.6μg/mL for Mucor hiemalis, Phythophthora drechsleri, Ceratocystis ulmi, and Monilia brunnea. Additionally, significant cytotoxicity in mammalian L929 cell lines (IC_{50} = 0.05 ng/mL) and HeLa cell line KB3.1 (IC_{50} = 0.04 ng/mL) has been demonstrated.[13]



13. (+)-Ratjadone

Fostriecin (14)

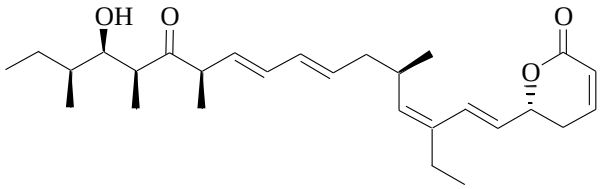
Fostriecin **14** was isolated in 1983 from *Streptomyces pulveraceus*.[14] This compound displays potent *in vitro* activiy against a broad range of cancer cell lines and its inhibitory activity against protein serine/threonine phosphatases.



14. Fostriecin

(-)-Callystatin A (15)

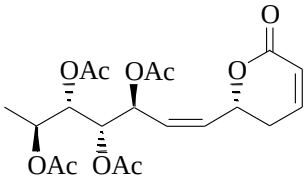
(-)-Callystatin A **15** is a polyketide-based natural product isolated in 1997 by *Kobayashi et al* from the marine sponge *Callyspongia truncata*. It exhibits remarkable cytotoxicity with an IC_{50} value of 10pg/mL against KB cell lines and 20 pg/mL against L1210 cells.[15]



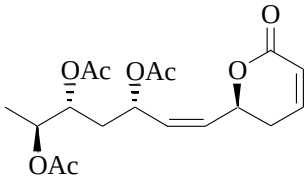
15. Callystatin A

Spicigerolide (16)

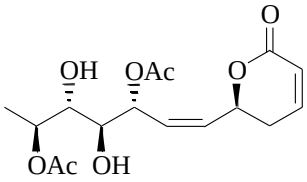
α,β-unsaturated δ-lactones (+)-spicigerolide **16**,[16] (+)-hyptolide **17**,[17] (-)-synrotolide **18**[18] and (+)-anamarine **19**[19] have been isolated from several *Hyptis* species and other botanically related genera. These compounds contain a polyoxygenated chain connected with an α,β-unsaturated six memberted lactone and have been found to show a range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity, etc. (+)-spicigerolide, for instance, has been found to exhibit cytotoxicity with ED_{50} =1.5 μg/mL in the human nasopharyngeal carcinoma (KB) assay system. Other structurally similar lactones 'synrolide', 'hypotolide' and 'anamarine' from *Hyptis* and taxonomically related species have been found to be antimicrobial.[20]



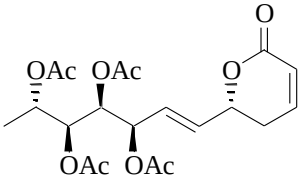
16. (-)-Spicigerolide



17. Hypotolide

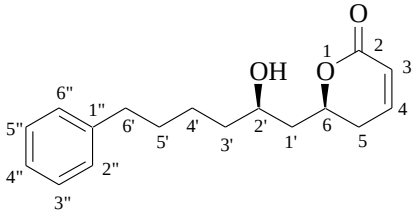


18. (-)-Synrotolide



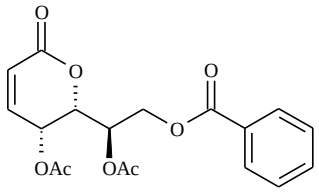
19. (+)-Anamarine

Hostettman et al was isolated an α,β-unsaturated lactone in 2001 from *Ravensara crassifolia* DANGUY (Lauraceae) (syn. *Cryptocarya crassifolia* Baker), is a tree growing up to 18-20m long in the eastern region of Madagascar. The genus Ravensara is considered as endemic to Madagascar. In a series of preliminary screenings, (6*S*)-5,6-dihydro-6-[(2*R*)-2-hdroxy-6-phenylhexyl]-2*H*-pyran-2-one (**20**)[21], was isolated from above natural source displayed antifungal activity against the phytopathogenic fungus *Cladosporium cucumerinum* in a bioautographic TLC assay.

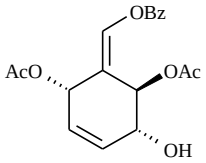


20. (6*S*)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one

In 2007, *Nkunya et al*.[22] discovered two novel constituents, (-)-cleistenolide **21** and (-)-cleistodienol **22** from the *Annonaceae*, *Cleistochlamys kirkii Oliver*, a plant species found in Tanzania and Mozambique. Extracts made from this plant are used in traditional medicine as a remedy for treatment of wound infections, rheumatism, and tuberculosis.[23] Cleistenolide also reportedly exhibits in vitro antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, and antifungal activity against Candida albicans.[22]



21. (-)-Cleistenolide

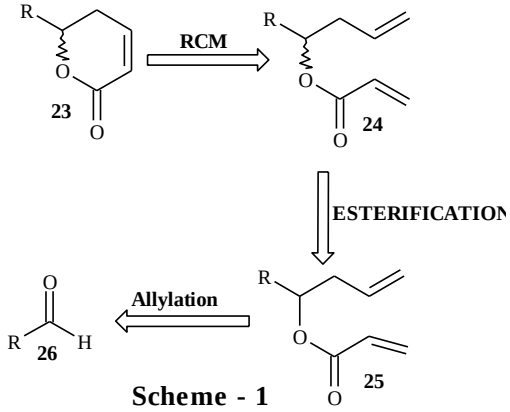


22. (-)-Cleistodienol

Stereoselective synthesis of -(-) Cleistenolide

Lactone rings are a structural feature of many natural products [24-27]. Many naturally occurring lactones, particularly α, β−unsaturated lactones that are Michael acceptors, display interesting pharmacologic properties[24]. The olefin metathesis reaction has become a powerful tool in organic synthesis. One of its most successful applications is the ring closing metathesis reaction (RCM) which affords cyclic compounds from diolefinic precursors[28-33]. Among the different kinds of cyclic compounds obtainable by RCM, unsaturated lactones of various ring sizes are achievable from α,ω−diolefinic esters using first and/or second-generation *Grubbs's* catalysts. More specifically, the preparation of α,β unsaturated γ-lactones through RCM of allyl and homoallyl acrylate have been reported using second-generation (II) *Grubbs'* catalysts[34-36]. So that by observing above data the brief discussion is that several aliphatic and aromatic lactones and two dimers were synthesized using the sequence: allylation - esterification - metathesis. The structure-activity relationship showed the importance of the aliphatic side chain to enhance the biological activity and to obtain lower cytotoxicity. It was also observed that a decrease in the size of the lactone ring increases the selectivity index.

Retrosynthetic analysis of the lactone targets.



Scheme - 1

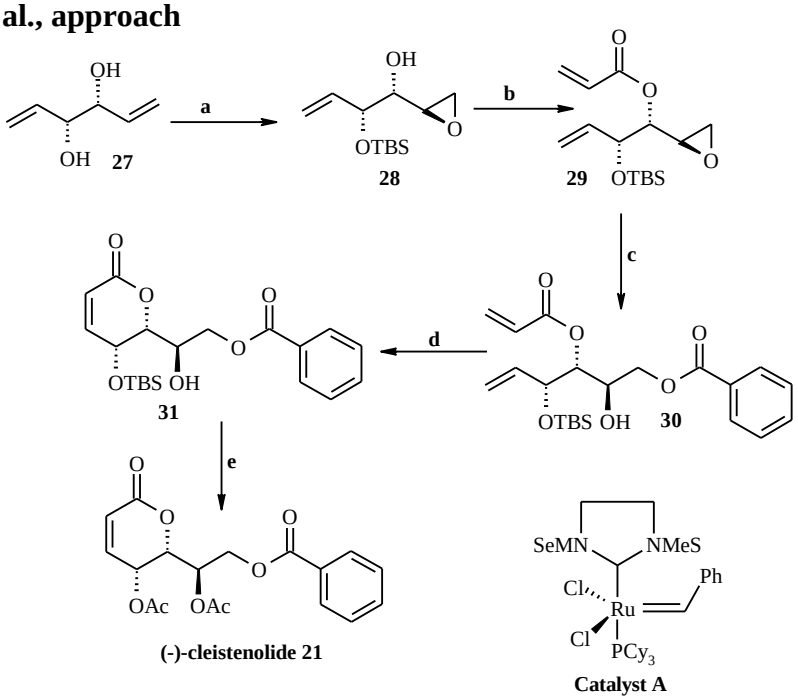
Natural products and their semi synthetic derivatives are traditionally important drugs, drug candidates, or lead structures for novel drugs. The family *Annonaceae* includes over

2000 species,[37] in which a considerable number of new compounds,having interesting chemical structures and an important biological activities, have been isolated from this family.[38] Recently, the first total synthesis of cleistenolide **21** was published by Schmidt and co-workers[39] in 18% overall yield, by applying a ring-closing metathesis (RCM) protocol to prepare the key building block, an α,β-unsaturated lactone.[40]

Owing to the importance of this cleistenolide styrylactones regarding antimicrobial activity basic we encouraged to stereo selective synthesis of (-)-cleistenolide **21** starting from commercially available D-mannitol. In direct reciprocation of retro synthetic analysis, we commenced our synthesis from D-mannitol.[41] The cheap and commercially easy availability high enantiomeric purity and equivalence of double unit of C_3-chiral building block because of C_2- symmetry were the strong incentives to start from D-mannitol. Initially, we have outline the previous synthetic approaches of compound **21**

PREVIOUS SYNTHETIC APPROACHES

Schmidt et al., approach

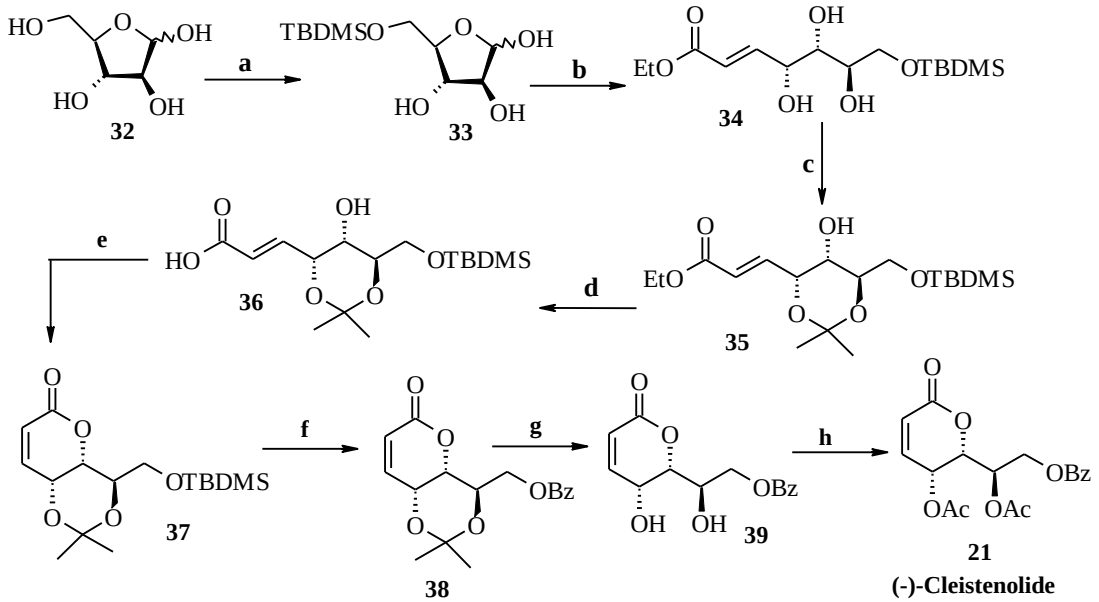


Scheme – 2

Reagents and conditions : (a)(i)TBSCl,imidazole,CH_2Cl_2,20^0C,87% (ii) $Ti(OPr^i)_4$,L(+)-DET.Bu^tOOH,CH_2Cl_2,-30^0C, 84% (b)Acroloylchloride, Pri_2NEt,CH_2Cl_2, 0^0C,92% (c) Benzoicacid,Pri_2NEt,20^0C,53% (d) A (10mol%),phenol (50 mol%),toluene,70^0C,75% (e) TBAF, then Ac_2O,THF,20^0C,66%

Schmidt et al.[39] has achieved the first stereo selective synthesis of **21** in linear steps. The main features of this scheme are asymmetric epoxidation and ring closing met*athesis* (Scheme-2). The synthesis starts with 1,5-hexadiene-3,4-diol **27**. Diol **27** was mono protected as its tributyl silyl ether **27a,** which was subjected to *sharpless* epoxidatation to give β-epoxide **28**. In epoxide **28** the hydroxyl group was protected with acryloylchloride in presence of N-ethyldiisopropylamine in DCM at 0^0C to give compound **29**. In compound **29**, the opening of epoxide with benzoicacid in presence of N-ethyldiisopropylamine at 20^0C to give compound **30** which is ready to undergo RCM reaction. Compound **30** was subjected to ring closing metathesis with *Grubbs 2nd generation* catalyst[42-44] to give α,β-unsaturated sixmembered lactone **31**. Synthesis required desilylation of **31** and acetylation of the two secondary alcohols. Conversion of Compound **31** to compound **21** i.e (-)-cleistenolide involves a one-flask reaction in THF by addition of TBAF and subsequently of acetic acid anhydride. Thus the (-)-cleistenolide **21** was obtained as a single regioselective stereoisomer in 66% yield.

Cai et al., approach.



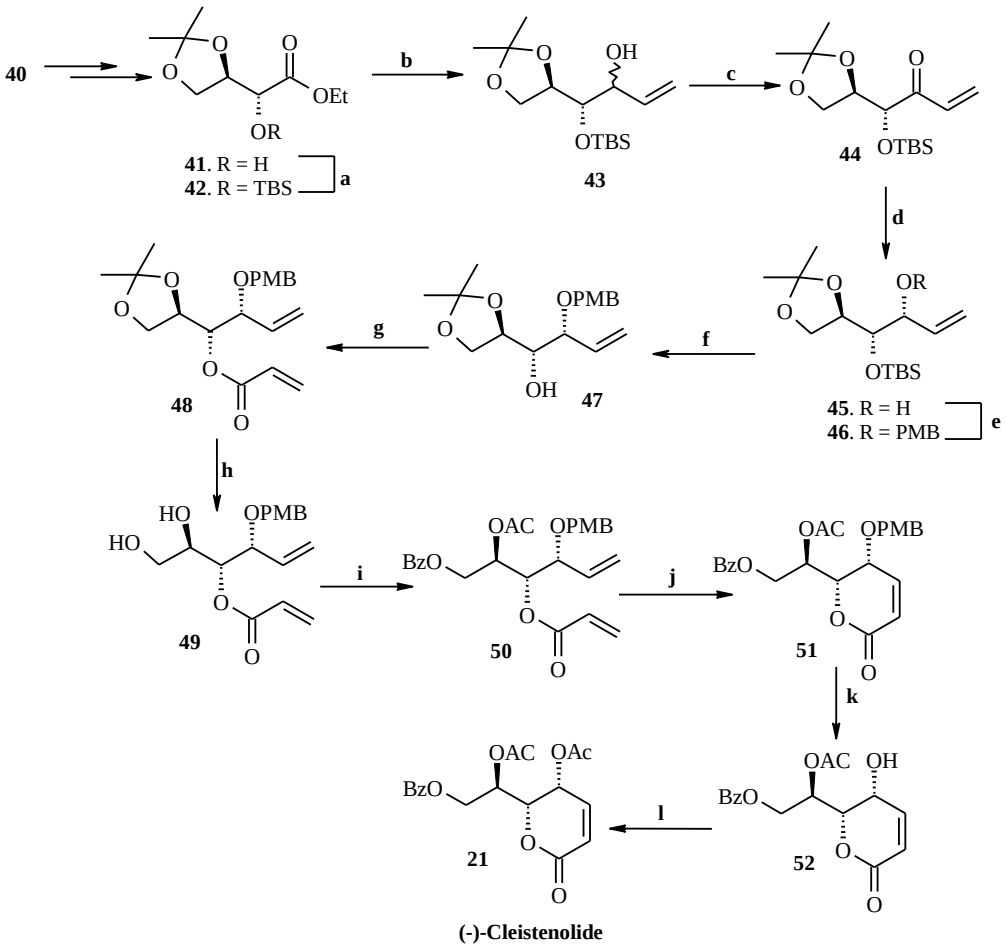
Scheme - 3

Reagents and Conditions: (a)TBDMSCl, DMAP, Pyridine,0^0C to rt,92% (b) $Ph_3P{=}CHCO_2Et$, Dioxane, 70^0C, 89% (c) $Me_2C(OMe)_2$, ppts, dcm, 0^0C to rt, 87% (d) LiOH, THF/H_2O,rt (e) 2,4,6-trichlorobenzoyl chloride,pyridine,0^0C to rt (f) TBAF,THF, then Bz_2O,rt,84% (g) $PdCl_2(CH_3CN)_2$,CH_3CN/H_20,65^0C (h) Ac_2O,Py,rt,91%

Cai et al., [45] has achieved the synthesis of **21** began with the known compound D(-) arabinose (Scheme - 3). Treatment of D-arabinose **32** with TBDMSCl in pyridine at 0^0C regioselectively afforded the 5-O-silyl aldehyde **33** in 92% yield. *Wittig* olefination of aldehyde **33** with ethyl (triphenylphosphoranylidene) acetate in dioxane at 70^0C furnished the α,β-unsaturated ester **34** in 89% yield. Treatment of an ester **34** with 2 equiv of $Me_2C(OMe)_2$ in the presence of a catalytic amount of PPTS at room temperature successfully afforded 1,3-trans-acetal, compound **35**, in 87% yield. Removal of ester protection from compound **35** with LiOH in THF/H_2O afforded the corresponding acid **36** in quantitative yield. Intramolecular esterification of acid **36** under modified *Yamaguchi* conditions[46] afforded key precursor **37** in 90% yield. The key precursor **37** was converted to compound **38** by using TBAF and Bz_2O in THF, the one-pot desilylation and benzoylation of **37** proceeded smoothly affording compound **38** in high yield (84%). Removal of isopropylidene group from **38**, with bis(acetonitrile)dichloropalladium(II) at 65^0C, furnished diol **39**. Acetylation, with Ac_2O in pyridine, completed the synthesis of (-)-cleistenolide **21** in 91%yield over the final two steps.

Venkateswarlu et al., approach

Venkateswarlu et al., [47] has achieved the total synthesis of *cleistenolide* **21** (Scheme-4)**.** Compound **21** was started from commercially available sugar D-(-)-isoascorbic acid **40**. Initially D-isoascorbic acid **40** was converted into α-hydroxy ester **41** using the literature procedure.[48] The hydroxyl group in compound **41** was protected with TBS group followed by the reduction with DIBAL-H to afford the aldehyde, which was subjected to *Grignard reaction* with vinylmagnesiumbromide to afford the required allyl alcohol **43** in 73% yield. For the requirement of 1,2-*syn* selectivity in compound **45** at chiral centers C_3 and C_4, the allylic alcohol **43** was first oxidized to allylic ketone **44** with IBX followed by selective reduction.



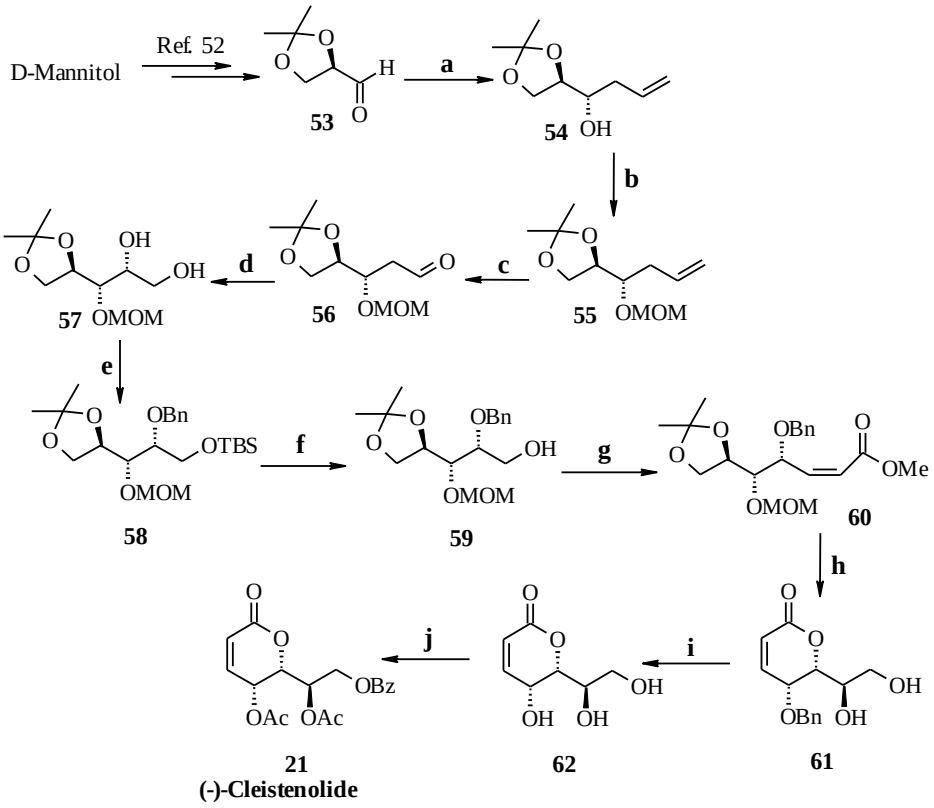
Scheme - 4

Reagents and conditions: (a) TBDMSCl, imidazole, DCM, 2 h, rt, 94% (b) (i) DIBAL-H, DCM, -78^{0}C, 30 min (ii) Vinyl magnesium bromide, 0^{0}C to rt, 3 h, 73% (c) IBX, DMSO, rt, 3 h; 96% (d) *K-Selectride*, -78^{0}C, 6 h, 91% (e) PMB/Br, NaH, THF, rt, 1 h, 84% (f) TBAF, THF, rt, 2 h, 96% (g) Acryloyl chloride, Et_3N, DMAP, rt, 4 h, 86%.; (h) DOWEX-50 (H^+), MeOH, rt, 6 h, 95% (i) Pyridine, BzCl followed by Ac_2O, DCM, 0^{0}C to rt, 12 h, 85% (j) *Grubbs second generation catalyst*, (5 mol %), DCM (0.01 mol/L), reflux, 12 h, 69% (k) DDQ, Phosphate buffer solution: DCM (9:1), rt, 2 h, 88%; (l) Ac_2O, pyridine, DCM, rt, 2h, 89%.

The reduction of **44** was next attempted with *K-Selectride*[49] under suitable reaction conditions (-78^{0}C, 6 h) to afford selectively diastereomeric alcohol **45** (>95:5) in isolated 91% yield. The allylic alcohol in **45** was protected with PMB group and removal of TBS protection using TBAF selectively afforded corresponding alcohol **47** in 96% yields. The secondary alcohol in compound **47** was subjected to acrylation to obtain the intermediate diene **48** in considerable yield (86%). The isopropylidene group was deprotected in

compound **48** by using DOWEX-50 (H^+) in MeOH to afford compound **49** in 95% yield. Further the one-pot synthetic strategy for benzoylation and acetylation by the sequential addition of pyridine and benzoyl chloride to compound **49** in dichloromethane followed by acetic anhydride to obtain the tri ester **50** in 85% yield. Now the tri ester was subjected to ring closing metathesis (RCM) by using *Grubbs second generation* catalyst to yield dihydropyranone derivative **51** in 69% yield. The *p*-methoxy benzyl group in **51** was deprotected with DDQ to afford compound **52**, which was further on acetylation delivered the natural product, (-)-cleistenolide **21** in 89% yield as a colorless solid.

Subba Reddy et al., approach

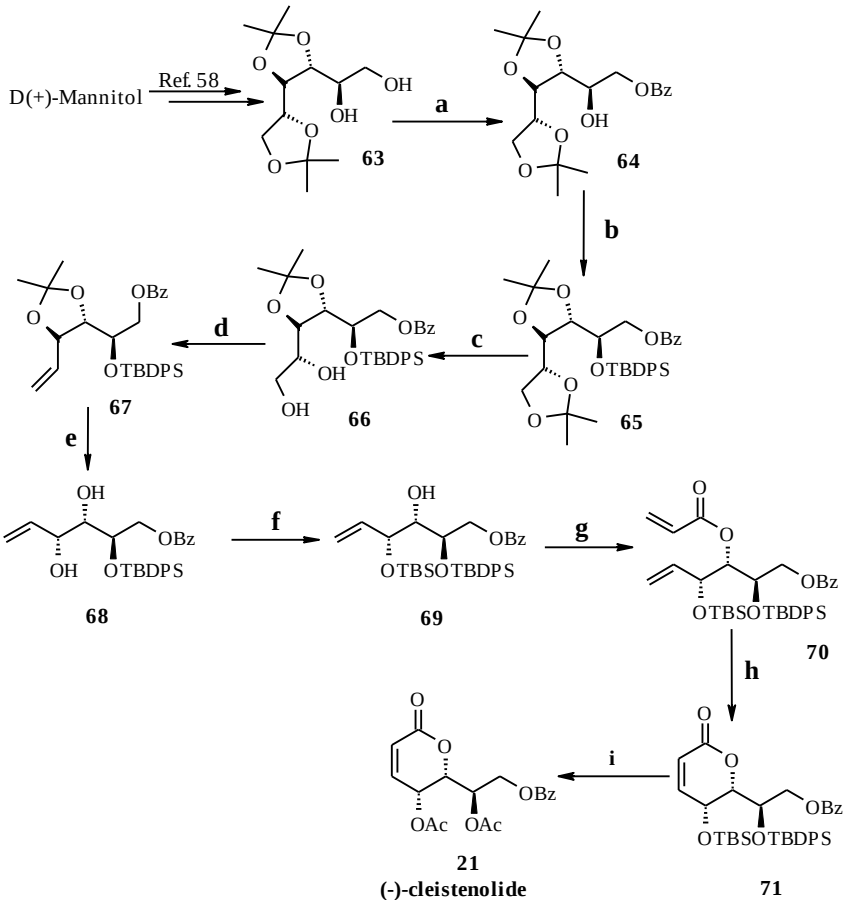


Scheme - 5

Reagents and conditions: (a) Zn, allyl bromide, THF, saturated solution of NH_4Cl (cat), 6 h, 90% (b) DIPEA, MOMCl, DCM, 0^0C, 2 h, 92% (c) (i) OsO_4 (0.5 mol %), NMO, acetone–H_2O, rt, 4 h; (ii) $NaIO_4$, rt, 2 h, 92% (d) (i) D-Proline, nitrosobenzene, DMSO (ii) $NaBH_4$, MeOH, 0.5 h, 70% (over two steps) (e) (i) TBSCl, imidazole, DCM, 1 h, 91% (ii) BnBr, NaH, TBAI, THF, 0^0C to rt, 2 h, 88% (f) TBAF, THF, 0^0C to rt, 85% (g) (i) IBX, DMSO/CH_2Cl_2, 90%, rt, 3 h (ii) $(CF_3CH_2O)_2P(O)CH_2$-CO_2CH_3, NaH, THF, 75% (h) $CeCl_3.7H_2O$, CH_3CN, reflux, 12 h, 65% (i) $TiCl_4$, CH_2Cl_2, 0^0C to rt, 30 min, 75% (j) (i) BzCl, Et_3N, DMAP, 4 h, 92% (ii) Ac_2O, Et_3N, DMAP, 24 h, 88%.

Subba Reddy et al.[50] started the synthesis of (-)-cleistenolide **21** began from the commercially available D-mannitol.(Scheme - 5) Initially, D-mannitol was converted into *(R)*-glyceraldehyde 1,2-acetonide **53** using a known protocol.[51] The zinc-mediated allylation of compound **53** in aqueous medium under *Luche's*[52]conditions gave the anti-homoallylic alcohol **54** in a highly diastereoselective manner (*syn/anti* = 5:95%). Protection of the resulting alcohol **54** with MOMCl in the presence of *Hunig's* base afforded MOM ether **55** in 92% yields. Dihydroxylation of compound **55** with OsO_4/NMO system followed by sodium periodate oxidation resulted in aldehyde **56**. Subsequent, α-amino-oxylation[53] of compound **56** with nitrosobenzene in the presence of D-proline at -10^0C, followed by the treatment with $NaBH_4$ in MeOH gave the crude aminooxy alcohol. Treatment of aminooxy alcohol with 30 mol % $CuSO_4.5H_2O$ afforded the chiral diol[54] **57** in 70% overall yield with 95% yield. Monosilylation of diol **57** was achieved by using TBSCl and imidazole. The resulting primary TBDMS ether was treated with benzyl bromide and NaH in THF, to furnish the benzyl ether **58**. Desilylation of compound **58** with TBAF resulted in the formation of primary alcohol **59** in 88% yields. Oxidation of **59** using IBX in DMSO/CH_2Cl_2 gave the aldehyde, which was subjected directly to a homologation under *Still–Gennari* conditions [55] to give (Z)-unsaturated ester, **60** in 75% yield with excellent stereoselectivity. Interestingly, the deprotection of acetonide and MOM ether followed by lactonisation of **60** were achieved in one-pot using $CeCl_3.7H_2O$ in CH_3CN at reflux conditions.[56] On the other hand, treatment of **60** with *p*-TSA in methanol under acidic conditions gave the undesired product. Debenzylation of lactone **61** was achieved by $TiCl_4$ in dichloromethane at 0^0C to give the triol **62**. Finally, primary alcohol of compound **62** was protected by benzoylchloride followed by the acetylation of secondary alcohols gave the natural product (-)-cleistenolide **21** in 88% yield.

Meshram et al., approach



Scheme 6

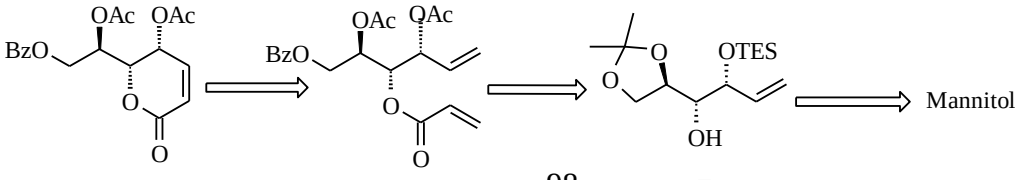
Meshram et al.,[57] started the synthesis of (-)-cleistenolide **21** from commercially available D-(+)-mannitol. The diol **63** is readily accessible from tri-O-isopropylidene-D-(+)-manitol, [58] with the terminal acetonides acting as surrogates for the generation of olefin. Monobenzoylation of diol **63** by using benzoyl chloride and DMAP in pyridine gave **64** in good yield.[59] The hydroxy group of compound **64** was protected with TBDPS–Cl to give silyl ether **65** with 86% yields.

Reagents and conditions: (a) Pyridine, benzoyl chloride, DMAP, CH_2Cl_2, -78^{0}C–20 ^{0}C, 4 h, 83% (b) TBDPS–Cl, imidazole, CH_2Cl_2, 0^{0}C to rt, 86% (c) $CuCl_2.2H_2O$, CH_3CN, 0^{0}C, 45 min, 99% (d) PPh_3-imidazole-iodine, toluene, 110^{0}C, 4h, 84% (e) PPTS (cat)/MeOH, rt, 86% (or) $CuCl_2$.2H2O, CH_3CN, rt, 20h, 84% (f) TBS–OTf (1 equiv), 2,6-lutidine, CH_2Cl_2, -78^{0}C, 85% (g) acryloyl chloride, DIPEA, CH_2Cl_2, 0^{0}C to rt, 81% (h) 5 mol % Grubb's 2nd generation catalyst, toluene,110^{0}C, 68% (i) TBAF, THF then Ac_2O, 62%.

The diacetonide **65** underwent selective hydrolysis of the terminal acetonide using an equivalent amount of $CuCl_2.2H_2O$ at 0^0C to generate the diol **66** in quantitative yield.[60] Diol **66** was converted to terminal olefin **67** by the reaction with Ph_3P-imidazole-iodine in toluene and gave 84% yield.[61] Thus, acetonide cleavage of **67** by PPTS/MeOH (or) $CuCl_2.2H_2O$ at room temperature produced the diol **68** in 44% yield.[59] Compound **68** on treatment with 1 equiv. of TBS–OTf, 2,6-lutidine DCM, -78^0C selectively gave allylic silylether **69**, in 85% yield. Esterification of **69** with acryloyl chloride led to the formation of **70** in 81% yields. Ring-closing metathesis of **70** proceeded well with 5 mol % of *Grubbs* catalyst. In dilute reaction conditions, the six-membered ring δ-lactone **71** was isolated in 68% yield.[57, 62] One-flask reaction in THF by the addition of TBAF and subsequent addition of acetic anhydride results in desilylation of **71** and also on acetylation of the two secondary alcohols, results in synthesis of (-)-cleistenolide **21** was obtained as a single regio and stereoisomer in a yield of 62%.

PRESENT WORK

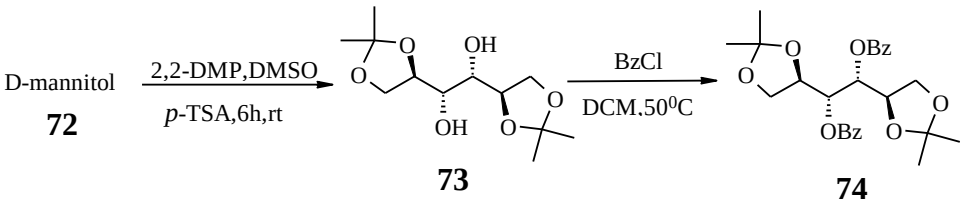
Here, we described an efficient stereo-selective synthesis of α-pyrone **21**, from (R)-2,3-O-isopropylidine glyceraldehyde. *Wittig* reaction, ring closing metathesis (RCM) and one pot acetylation and benzoylation of compound **21** are the keysteps involved in our synthesis. The retro-synthetic analysis for (-)-5-Acetoxy-6-(1-benzoyloxy-2-acetoxyethyl)-pyr-3-en-2-one **21** may be represented as shown in (Scheme – 7)**.**



2 **8** 98 **7**

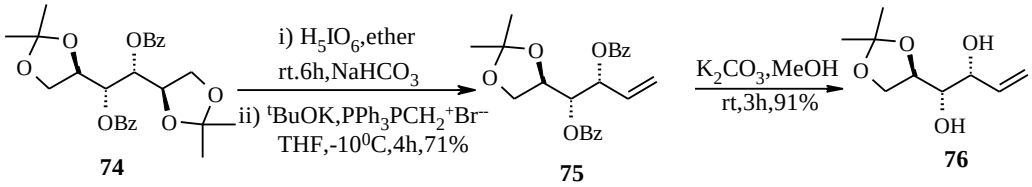
Scheme - 7 : Retrosynthetic analysis of (-)-Cleistenolide

Our synthetic approach starts from D-mannitol was reacted with 2,2-dimethoxypropane (2,2-DMP) in DMSO in the presence of *p*-toluenesulphonic acid (*p*-TSA) to afford the corresponding 1,2,5,6-diisopropylidene diol **73** as a white solid,[63] which was further reacted with benzoyl chloride in the presence of Et_3N in CH_2Cl_2 to afford 1,2,5,6-diisopropylidene-3, 4-dibenzoyl derivative **74** in 91% yield [64] as shown in (Scheme – 8).



Scheme - 8

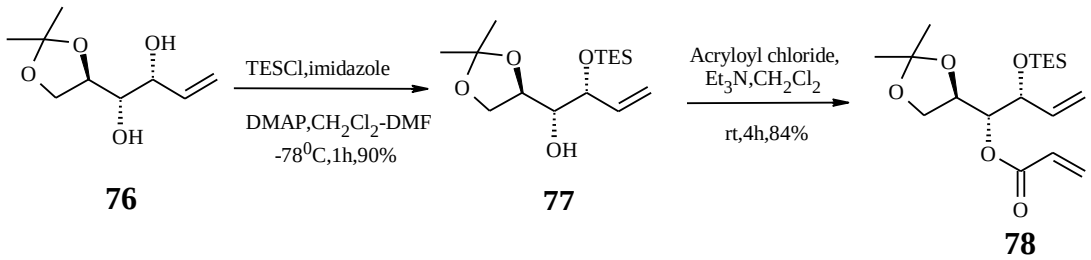
The formation of compound **74** was established by its ^1H NMR spectrum (Fig.2.01), which displayed signals due to benzoyl ester, at δ 7.42-8.20 (m, 10H). Further its ^{13}C NMR spectrum (Fig.2.02) showed the signal at δ 165.59 indicates the carbonyl carbon of benzoyl ester.



Scheme - 9

Compound **74** was treated with orthoperiodic acid (H_5IO_6) followed by $NaHCO_3$ in Et_2O at room temperature to yield the corresponding aldehyde.[65] The aldehyde was further

converted into the terminal alkene **75** using *Wittig* reaction with methyltriphenylphosphonium bromide salt in the presence of *tert*-BuOK. The dibenzoyl protecting groups in **75** were removed by reacting with K_2CO_3/MeOH to afford diol **76** in 91% yields.[67] (Scheme -9). The formation of compound **75** was established by its ^{1}H NMR spectrum (Fig.2.03),which displayed signals due to terminal bond at δ 5.83-5.97 (m, 2H) and 5.61-5.66 (m, 1H). Its ^{13}C-NMR spectrum (Fig.2.04) shows the olefinic signals at δ 133.20 and 118.95. Further the formation of compound **76** was established by devoid signals in its ^{1}H NMR spectrum (Fig.2.06) due to benzoyl moiety at δ 8.13 (d, *J* = 8.30 Hz, 4H) and 7.63 (t, *J* = 7.54 Hz, 2H) and 7.49 (t, *J* = 7.54 Hz, 4H) and its ^{13}C-NMR spectrum (Fig.2.07) shows the signals at δ 73.78 and 72.03 is an indicative of hydroxy attached carbons further the molecular ion at *m/z* 201 [(M^++Na)] (Fig.2.09)

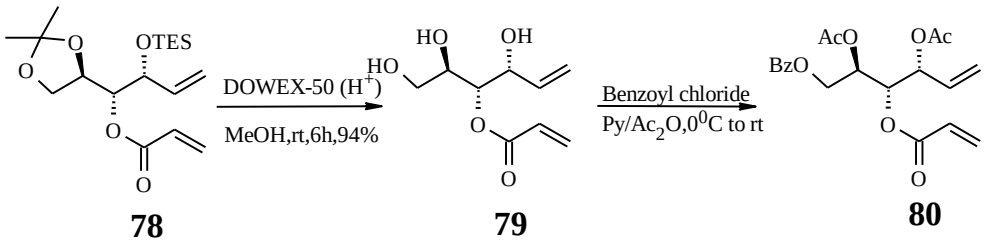


76 **77** **78**

Scheme - 10

The sterically less hindered allylic hydroxyl group in **76** was selectively protected as triethylsilyl ether by reacting **76** with triethylsilyl chloride (TESCl) and imidazole in CH_2Cl_2-DMF (1:1) at –78^{0}C to obtain the compound **77** as a colorless liquid in 90% yield.[66] The monoprotected triethylsilyl ether **77** was reacted with acryloyl chloride in the presence of Et_3N to give the corresponding acrylate ester **78** in 84% yield. (Scheme-10). The formation of compound **77** was confirmed by its ^{1}H NMR spectrum (Fig. 2.10) by conspicuous presence of signals at 0.96 (t, *J* = 7.93 Hz, 9H), 0.65 (q, *J* = 7.5, 15.48 Hz, 6H). Its ^{13}C-NMR spectrum (Fig.2.11) shows the signals at δ 6.72 (3 C), 4.88 (3 C) is an indicative of monoprotected triethylsilylether of compound **77**. Further its mass spectrum gave a peak at *m/z* 327 [(M^++Na)$^+$] (Fig. 2.12). Further the structure of acrylate ester **78** was established from its ^{1}H and ^{13}C NMR spectral data. The ^{1}H NMR spectrum (Fig.2.14) exhibited the distinctive peaks of acrylate ester at δ 6.47-6.41 (m, 1H), 6.19-6.07 (m, 2H). The ^{13}C NMR spectrum (Fig.2.15) showed a signal at δ 165.28 for ester carbonyl and the

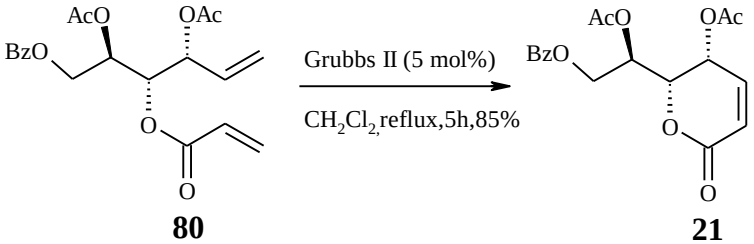
IR spectrum (Fig.2.17) shows absorption band at 1732 cm^{-1} to designate the α,β-unsaturated ester corresponding acrylate ester **78** in 84% yield.(Scheme - 10)



78 **79** **80**

Scheme - 11

Compound **78** was treated with DOWEX-50 (H^+) resin in methanol afforded the desired triol intermediate **79** in 94% yield. At this stage we introduced a new application like one pot synthetic strategy involves the sequential addition of benzoyl chloride in presence of pyridine followed by acetic anhydride to yield diene tetra ester **80** in 85% yield.(Scheme - 11). The formation of compound **79** was established by its ^1H NMR (Fig. 2.18) signals at δ 4.48-4.35 (m, 3 H), 4.02- 3.97 (m, 1 H), 3.32-3.06 (br,1H), 3.02-2.77 (br,1H), 2.03-1.75 (br,1H) due to hydroxy attached protons of triol and in its ^{13}C NMR (Fig. 2.19) devoid signals at δ 108.46, 26.31, 25.26, 6.69, 4.73 indicates absence of acetonide and TES protection resulting a triol and showed the molecular ion at m/z 225 [(M^++Na)] **(**Fig.2.20**)**. Further the structure of compound **80** was established from its ^1H and ^{13}C NMR spectral data. Its ^1H NMR (Fig. 2.22) signals at δ 8.02 (dd, *J* = 8.3, 1.51 , 2 H), 7.57 (t, *J* = 7.55, 1 H), 7.45 (t, *J* = 7.55, 2 H) due to benzoyloxy and the signal at δ 5.16-5.10 (m, 1 H), 4.69-4.61 (m, 1 H), 4.38-4.27 (m, 1 H), 2.10 (s, 3 H), 2.06 (s, 3 H) indicates the presence of diacetate of ester **80**. Its ^{13}C NMR (Fig. 2.23) spectrum shows signals of carbonyl carbon of ester functional groups at δ 170.3, 169.75, 167.37, 166.47



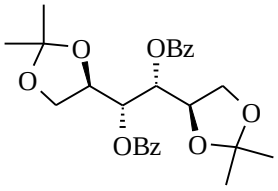
80 **21**

Scheme-12

The ring closure metathesis (RCM) of the diene tetra ester **80** has been successfully achieved to obtain the lacone **21** by using 5 mol% *Grubb's 2nd generation* catalyst in dichloro methane to afford the final target molecule of natural product (-)-cleistenolide **21** in 85% yield as a colorless solid (Scheme - 12). The formation of α, β-unsaturated six membered lactone **21** was established by the following data. Its ^{1}H NMR spectrum (Fig.2.26) of C-3 and C-4 olefinc protons resonated at δ 7.00 (dd, *J* = 9.6, 6.1 Hz, 1H), 6.29 (d, *J* = 9.7 Hz, 1H), further the H-5 of methin proton resonated at 5.52 (ddd, *J* = 9.5, 4.0, 2.3 *Hz*, 1H). The H-6 Proton observed at δ 5.42 (dd, *J* = 6.0, 2.5 *Hz*, 1H). In ^{13}C NMR (Fig.2.27) signal at δ 166.0, due to α, β-unsaturated δ-lactone. The IR spectrum showed absorbance at 1725 cm^{-1} further the mass spectrum (Fig.2.28) showing a molecular ion peak ar m/z 385 [(M^{+}+Na)] further its HRMS calculated for $C_{18}H_{18}O_8Na$ is 385. 1002, found 385.0992.confirms the formation of α,β-unsaturated six membered lactone **21.**

EXPERIMENTAL

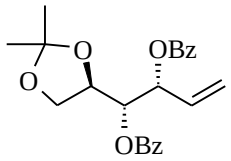
1,2-Bis (2,2-Dimethyl-1,3-dioxolan-4-)ethane-1,2-diyl dibenzoate (74):



To a stirred solution of diol **73** (5 g, 19.08 mmol) and Et_3N (7.96mL, 57.24mmol) in dry CH_2Cl_2 (30 mL) was added benzoyl chloride (4.87ml, 41.96mmol) at 0^oC under a nitrogen atmosphere. After completion of the reaction, the reaction mixture was diluted with water (20 mL), extracted with dichloromethane (3 x15 mL), washed with brine (2x 10 mL). Organic solution was dried over anh. Na_2SO_4 and concentrated under reduced pressure and the crude residue was purified by Column chromatography (EtOAc/n-hexane 10:90) to afford **74** (8.1g, 91%) as a white solid.

M.P.	**:**	82–85 ^oC
$[\alpha]^{25}_D$	**:**	-113.9 (*c* 3.4, $CHCl_3$)
IR(KBr)	**:**	υ(cm^{-1})3433, 3062, 2991, 2896, 1727, 1600, 1453, 1378,1206,1112,1067
^{1}H-NMR (300 MHz, $CDCl_3$)	**:**	δ 8.02 (t, *J* = 6.7 Hz, 4 H), 7.53 (t, *J* = 6.7 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 4 H), 5.48 (d, *J* = 5.2 Hz, 1H), 4.88 (q, *J* = 6.0 Hz, 1H), 4.37 (q, *J* = 6.0 Hz, 2H), 4.11 (dd, *J* = 5.2,11.3 Hz 1H), 3.96 (q, *J* = 9.0 Hz, 2H), 3.70 (q, *J* = 6.7 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3 H), 1.34 (s, 3H), 1.31 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$)	**:**	δ 165.5, 165.4 , 133.12 (2C), 129.8 (2C), 129.6(4C), 128.3 (4C), 108.9, 108.4, 74.5, 70.5,69.8, 66.2, 66.1, 62.1, 26.9, 26.5, 25.4, 25.0.
ESI-MS	**:**	493 [M^++ Na].

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-ene-1,2-diyl dibenzoate (75) :

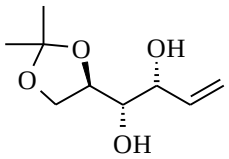


To a solution of diester **74** (5 g, 10.6 mmol) in dry Et_2O (45 mL), was added H_5IO_6 (3.32 g, 14.56 mmol) at 0^0C and the reaction mixture was stirred for 6 h at room

temperature. After completion of the reaction, the mixture was neutralized with $NaHCO_3$ (3.5 g), stirred for 30 min., filtered through a celite pad, and evaporated to give the crude aldehyde, which was used as such for the next reaction without purification. To a cooled (-10^oC) solution of Ph_3PCH_2Br (8.38 g, 21.2 mmol) in THF (30 mL) was added ^tBuOK (2.26 g, 20.1 mmol) portion wise and allowed to stir for 2 h at room temperature. To this reaction mixture a solution of aldehyde in dry THF (20 mL) was added slowly over 10 min. and stirred at the same temperature (-10^0C) for 2 h. After completion of reaction as monitored by TLC, the mixture was quenched with addition of saturated NH_4Cl solution (20 mL) and extracted into EtOAc (3x15 mL). The combined extract was washed with brine, dried (Na_2SO_4), concentrated, and the crude residue was purified by CC (EtOAc/n-hexane 5:95) to afford **75** (2.94 g, 71%) as colorless solid.

M.P.	**:**	$70\text{-}72^0C$
$\mathbf{[\alpha]^{25}_D}$	**:**	+ 35.3 (*c* =1.5, $CHCl_3$)
IR (KBr)	**:**	2915, 2855, 1695, 1602, 1256, 1067, 710
^{1}H-NMR (300 MHz, $CDCl_3$)	**:**	δ 8.13 (d, *J* = 8.3 Hz, 4 H), 7.63 (t, *J* = 7.5Hz, 2H), 7.49(t, *J* = 7.5Hz, 4 H), 5.83-5.97 (m, 2 H), 5.61-5.66 (m, 1 H), 5.23-5.45 (m, 2 H), 4.39-4.47 (m, 1H), 4.03-4.09 (m, 2 H), 1.34 (s, 3 H), 1.32 (s, 3H).
^{13}C-NMR (125 MHz, $CDCl_3$)	**:**	δ165.64, 165.21, 133.20, 132.14 (2C), 129.74 (2C), 129.68 (4C), 129.31(4C), 118.95, 109.61, 74.40, 73.49(2 C), 65.74, 26.45, 25.21.
ESI-MS	**:**	419 [M^+ + Na].

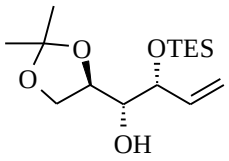
1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-ene-1,2-diol (76) :



To a cooled 0^{o}C solution of diester alkene **75** (2.9 g, 7.43 mmol) in MeOH (20 mL) was added K_2CO_3 (2.46 g, 17.8 mmol) and stirred for 3 h at room temperature. After completion of the reaction as monitored by TLC, the mixture was filtered and the solvent was removed under reduced pressure to afford the crude reaction mass which was diluted with water (10 mL) and extract into EtOAc (3x15 mL). The combined extract was washed with brine solution, dried with Na_2SO_4 and concentrated the final residue was purified by CC (EtOAc/n-hexane 30:70) to afford **76** (1.27 g, 91%) as a colorless oil.

$[\alpha]^{25}_{D}$	**:**	+13.6 (*c* 1.7, $CHCl_3$)
IR (neat)	**:**	υ (cm^{-1})3419, 2986, 2926, 1643, 1376, 1065
^{1}H-NMR (300 MHz,$CDCl_3$)	**:**	δ 5.88-6.01 (m, 1 H), 5.33-5.42 (m, 1H), 5.22-5.30 (m, 1H), 4.21-4.27 (m, 1 H), 3.93-4.16 (m, 3H), 3.59 (dd, *J* =3.3 Hz, 6.2 Hz, 1 H), 2.84 (brs, 2 H), 1.43 (s, 3 H) 1.36 (s, 3 H).
^{13}C-NMR (100 MHz ,$CDCl_3$)	**:**	δ 137.29, 116.77, 109.12, 75.47, 73.78, 72.03, 66.04,26.6, 25.19.
ESIMS	**:**	211 [M^+ + Na]

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(triethylsilyloxy)but-3-en-ol (77):

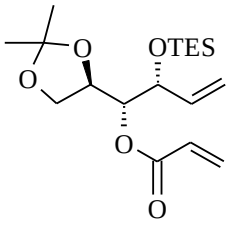


To a cooled (-78°C) solution of diol **76** (1.1 g, 5.84 mmol), imidazole (0.45 g, 6.7 mmol), and DMAP (35mg, 0.29 mmol) in CH_2Cl_2-DMF (20 mL) (1:1) was added TESCl (1.03 mL, 6.4 mmol) drop wise over 5 min. The mixture was stirred for 1 h at -78°C, warmed to ambient temperature, then quenched with addition of saturated NH_4Cl solution and diluted with EtOAc-hexanes (50:50). The layers were separated and the aqueous phase was extracted with 1:1 EtOAc -hexanes (3x10 mL). The combined extract was washed

with brine, dried (Na_2SO_4), concentrated, and the residue was purified by CC (EtOAc/n-hexane 10:90) to afford compound **77** (1.58 g, 90%) as a colorless liquid.

$[\alpha]^{25}_D$	**:**	+2.5 (*c* 2.0, $CHCl_3$)
IR (neat)	**:**	υ (cm^{-1})3426, 2954, 2880, 1647, 1374, 1063
^{1}H-NMR (500 MHz ,$CDCl_3$)	**:**	δ 5.98-5.84 (m, 1 H), 5.32-5.24 (m, 1 H), 5.20-5.14 (m, 1H), 4.38 (m, 1 H), 4.10-4.05 (t, *J* = 7.8 Hz, 1H), 3.99 (q, *J* = 6.8 Hz,14.7 Hz,1H), 3.95-3.90 (t, *J* = 7.8 Hz,1H), 3.36-3.30 (t, *J* = 7.8 Hz,1H),1.82-1.63 (brs, 1 H), 1.40 (s,3 H), 1.34 (s, 3 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 0.65 (q, *J* = 7.5 Hz, 15.4 Hz, 6 H).
^{13}C-NMR (100 MHz, $CDCl_3$)	**:**	δ 138.4, 115.7, 109.06, 75.5 ,75.27 , 72.68, 67.28, 26.77, 25.32, 6.72 (3 C), 4.88 (3 C).
ESIMS	**:**	325 [M^+ + Na]

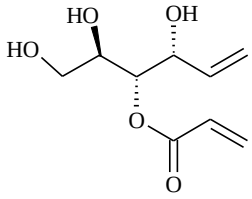
1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(triethylsilyloxy)but-3-enyl acrylate (78):



To a cooled 0^{o}C solution of **77** (1.25 g, 4.1 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.25 mL, 6.14 mmol) followed by acryloyl chloride (0.67 mL, 8.2 mmol) and stirred for 4 h at room temperature. After completion of the reaction as monitored by TLC, water (15 mL) was added and extracted into CH_2Cl_2 (3x15 mL). The combined org. layer was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), concentrated, and the residue was purified by Column Chromatography (EtOAc/n-hexane 08:92) to afford **78** (1.23 g, 84%) as a colorless liquid.

$[\alpha]^{25}_{D}$	**:**	+30.8 (*c* 2.35, $CHCl_3$)
IR (neat) υ (cm^{-1})	**:**	2955, 2880, 1732, 1635, 1460, 1406, 1259, 1184, 1063
^{1}H-NMR (300 MHz ,$CDCl_3$)	**:**	δ 6.47-6.41 (m, 1 H), 6.19-6.07 (m, 2 H), 5.87-5.69 (m,2H), 5.31-5.25 (m,1H), 5.18-5.13 (m,2 H), 4.37-4.28 (m, 1 H), 3.99-3.82 (m, 2 H), 1.32 (s, 6 H) 0.94 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.5 Hz, 15.4 Hz, 6H).
^{13}C-NMR (100 MHz ,$CDCl_3$)	**:**	δ165.28, 136.89, 131.67, 128.15, 116.52, 108.46, 75.44, 73.95, 72.32, 65.47, 26.31, 25.26,6.69(3 C), 4.73(3 C)
ESI-MS	:	379 [M^+ + Na].

(2*R*, 3*S*, 4*R*)-1,2,4-tri Hydroxyl-hex-5-en-3-yl acrylate (79) :

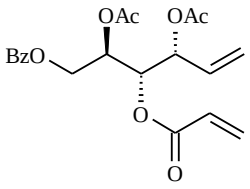


To a solution of diene **78** (1.2 g, 3.37 mmol) in MeOH (20 mL) was added DOWEX-50 H^+ resin (100 mg) and the mixture was allowed to stir for 6 h at room temperature. After completion of the reaction as monitored by TLC, the mixture was filtered and the filtrate was concentrated, and the crude residue was purified by CC (EtOAc/n-hexane 70:30) to afford triol **79** (0.64 g, 94 %) as a viscous liquid.

$[\alpha]^{25}_{D}$	**:**	+9.7 (*c* 0.65, $CHCl_3$)
IR (neat) υ (cm^{-1})	**:**	3448, 2956, 2884, 1735, 1630, 1461

^{1}H-NMR (500 MHz ,$CDCl_3$)	**:**	δ 6.55-6.44 (d, *J* = 17.3, 1 H), 6.23-6.09 (m, 1 H), 6.06-5.87 (m, 2 H), 5.44-5.38 (d, *J* = 17.1, 1 H), 5.31-5.27 (d, *J* =10.5, 1 H), 4.48-4.35 (m, 3 H), 4.02-3.97 (m, 1 H), 3.56-3.54 (m, 1 H), 3.32-3.06 (brs, 1 H), 3.02-2.77 (brs, 1H), 2.03-1.75 (brs, 1H).
^{13}C-NMR (75MHz,$CDCl_3$)	**:**	δ 166.9 ,137.2 , 131.9 , 127.7, 117.1 , 73.0, 71.8 , 70.7 , 66.1.
ESI-MS	**:**	225 [M^{+}+ Na]

3-(Acryloloxy)-1-(benzoyloxy)hex-5-ene-2,4-diyl diacetate (80):



To a cooled 0^{o}C solution of triol **79** (0.6 g, 2.9 mmol) in CH_2Cl_2 (15 mL) was added pyridine (1.43 mL, 17.4 mmol) followed by benzoyl chloride (0.36 mL, 3.04 mmol) and the mixture stirred at the same temperature for 3 h. To this mixture acetic anhydride (0.65 mL, 7 mmol) was added and stirred at room temperature for additional 4 h. After completion of the reaction, the reaction was diluted with water (10 mL) and extracted into CH_2Cl_2 (3x15 mL). The combined org. layer was washed with saturated $NaHCO_3$, water, brine, dried (Na_2SO_4), concentrated, and the crude residue was purified by CC (EtOAc/n-hexane 10:90) to afford a tetraester **80** (0.98 g, 85%) as a viscous liquid.

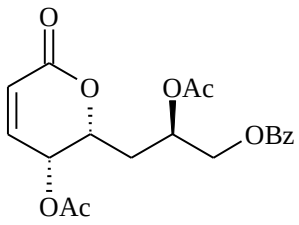
[α]^{25}D	**:**	+25.6 (*c* 0.55, $CHCl_3$)
IR (neat) υ (cm^{-1})	**:**	2963, 1725, 1452, 1372, 1224, 1099, 1070
^{1}H-NMR (500 MHz ,$CDCl_3$)	**:**	δ 8.02 (dd, *J* = 8.3, 1.51 , 2 H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.52-6.40(m,1H), 6.22-6.09 (m, 1H), 5.95-

5.87(m,1H),5.84-5.72 (m,1H), 5.70-5.59 (m,1H), 5.57-5.48 (m,1H), 5.38-5.24 (m, 2H), 5.16-5.10 (m, 1H), 4.69-4.61 (m, 1H), 4.38-4.27 (m, 1H), 2.10 (s, 3H), 2.06 (s, 3H).

^{13}C-NMR (75 MHz,$CDCl_3$) **:** δ 170.3, 169.75, 167.37, 166.47, 133.21, 132.51, 131.93, 131.52, 129.68 (2C), 128.40 (2C), 127.24, 119.16, 71.76, 70.69, 68.68, 62.25, 20.77(2 C).

ESI-MS **:** 413 [M^+ + Na].

Cleistenolide (21):



To a degassed solution of diene ester **80** (100 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (100 mL) was added *Grubbs* 2nd generation catalyst (10 mg, 0.012 mmol) and refluxed for 5 h. After completion of the reaction as monitored by TLC, the mixture was filtered and the solvent was evaporated to give crude product that was purified by CC (EtOAc/n-hexane 30:70) to afford required target molecule (-)-cleistenolide **21** (79 mg, 85%) as a colourless solid.

M.P. **:** 132-134^{0}C

$[\alpha]_D^{25}$ **:** -142 (*c* 0.4, $CHCl_3$)

IR (KBr) **:** 2963, 1725, 1452, 1372, 1224, 1099, 1070

^{1}H-NMR (500 MHz ,$CDCl_3$) **:** δ 8.02 (d, *J* = 7.7, 2 H); 7.57 (t, *J* = 7.5 Hz, 1H); 7.45 (t, *J* = 7.6 Hz, 2 H); 7.00 (dd, *J* = 9.6 Hz, 6.1 Hz,1H), 6.29 (d, *J* = 9.7 Hz, 1H), 5.52 (ddd, *J* = 9.5 Hz, 4.0 Hz, 2.3 Hz, 1H), 5.42 (dd, *J* = 6.0 Hz, 2.5 Hz, 1H), 4.93 (dd, *J*

		= 12.5 Hz, 2.0 Hz, 1H), 4.80 (dd, *J* = 9.6 Hz, 2.5 Hz,1H), 4.53 (dd, *J* = 12.5 Hz, 4.4 Hz, 1 H),2.09 (s, CH_3CO, 3 H), 2.04 (s, CH_3CO, 3H).
^{13}C-NMR(75MHz,$CDCl_3$)	**:**	δ 169.9, 169.5, 166.0, 161.1, 139.7, 133.3, 129.7, 129.7, 129.6(2C), 128.5(2C), 125.4, 75.5, 67.7,62.0,59.7,20.7,20.5.
ESI-MS	**:**	385 [M^++Na]

REFERENCES

1. a) Coleman, D. M. T.; Rivett, D. E .A. *Fortschr. Chem. Org. Naturst*. **1989**, *55*,1.(b)Ohloff.G.,*Fortschr.Chem.Org.Naturst*.**1978**,*35*,431.(c)Adityachaudhury, N.; Das, A. K. *J. Sci. Ind.l Res. (India)* **1979**, 38, 265. d) Siegel, S. M. *Phytochemistry* **1976**, *15*, 566.
2. France, N. C.; Polonsky, J. C. R. *Hebd. Seanes. Acad.l Sci., Ser*. C. **1971**, *273*, 439.
3. Coleman, D. M. T.; Rivett, D. E. A *Phytochemistry* **1987**, *26*, 3047.
4. Watt, J.M., Brandwijk, M.G. B. *The Medicinal and Poisonous Plants of Southern and Eastern Africa,* **1962** , p. 516.
5. a) Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677. (b) Andrianaivoravelona, J. O.; Sahpaz, S.; Terreaux, C.; Hostettmann, K.; Stoecki-Evans, H.; Rasolondramanitra, J. *Phytochemistry* **1999**, *52*, 265. (c) Echeverri, F.; Arango, V.; Quinones, W.; Tyorres, F.; Escobar, G.; Rosero, Y.; Archbolde, R. *Phytochemistry* **2001**, *56*, 881.
6. Hsu, F. L.; Chen, Y. C.; Cheng J. T. *Planta Med*. **2000**, *66*, 228.
7. Ecgeverri, F.; Arango, V.; Quinones, W.; Torres, F.; Escobar, G.; Rosero, Y.; Archbold, R. *Phytochemistry* **2001**, *56*, 881.
8. Fu, X. T.; Sevenet, A.; Hamid, A.; Hadi, F.; Remy and Pais, M. *Phytochemistry*, **1993**, *33*, 1272.
9. a) Priestap, H. A.; Bonafede, J. D.; Ruveda, E. A. *Phytochemistry* **1977**, *16*, 1579. (b) Priestap, H. A.; Van Baren, C. M.; Lira, P. D. L.; Coussio, J. D.; Bandoni, A. L. *Phytochemistry* **2003**, *63*, 221. (c) Matsuda, M.; Endo,Y.; Fushiya, S.; Endo, T.; Nozoe, S. *Heterocycles* **1994**, *38*,1229. d) Juliawaty, L. D.; Kitajima, M.; Takayama, H.; Achmad, S. A.; Aimi, N. *Chem Pharm, Bull*. **2000**, *48*, 1726.
10. Abe, S. *J. Chem. Soc. Jpn*. **1937**, *58*, 246.
11. Juliawaty, L.D.,Kitajima,M.,Takayama,H.,Achmad,S.A., Aimi, N. *Phytochemistry* **2000**, *54*, 989.
12. Schummer, D.; Gerth, K.; Reichenbach, H.; Hofle, G. *Liebigs Ann*. **1995**, p. 685.
13. Gerthl, K.; Schummer, D.; Hofle, G.; Irschik, H,; Reichenbach, H. *J. Antibiot*. **1995**, *48*, 973.

14. a) Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot*. **1983**, *36*, 1595. (b) Stamplwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601. c) Leopold, W. R.; Shillis, J. L.; Mertus, A. E.; Nelson, J. M.; Roberts, B. J.; Jackson, R. C. *Cancer Res*. **1997**, *44*, 1928.

15. (a) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett*. **1997**, *38*, 2859-2862. (b) Kalesse, M.; Christmann, M. *Synthesis*, **2002**, 981-1003.

16. Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-Garcia-Roja, C. M. *Tetrahedron* **2001**, *57*, 47.

17. Achmad, S. A.; Hoyer, T.; Kjaer, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand.* **1987**, *41(B)*, 599.

18. Coleman, M. T. D., English, R. B.; Rivett, D. E. A. *Phytochemistry* **1997**, *26*, 1497.

19. Allemany, A.; Marquez, C.; Pascual, C.; Valverde, S.; Martinez-Ripoll, M.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1979**, *20*, 3583.

20. Pereda-Miranda, R.; Hernandez, L.; Villavicencio, M. J.; Novelo, M.; Ibarra, P.; Chai, H.; Pezzuto, J. M. *J. Nat. Prod*. **1993**, *56*, 583.

21. Samwel, S.; Mdachi, S. J. M.; Nkunya, M. H. H.; Irungu, B. N.; Moshi, M. J.;Moulton, B.; Luisi, B. S. *Nat. Prod. Commun*. **2007**, *2*, 737–741.

22. Nkunya, M. H. H. *Pure. Appl. Chem*. **2005**, *77*, 1943–1955.

23. Verzar, R.; Petri, G. J. Ethnopharm. **1987**, *19*, 67–80.

24. Hoffmann, H.M.R.; Rabe, J. Synthesis and Biological Activity of α -Methylene-γ-butyrolactones. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94-110.

25. Negishi, E.; Kotora. M. *Tetrahedron* **1997**, *53*, 6707-6738.

26. Collins, I. *J. Chem. Soc. Perkin Trans. I* **1999**, 1377-1396.

27. Carter, N.B.; Nadany, A.E.; Sweeney, J.B. *J. Chem. Soc. Perkin Trans. I.* **2002**, *34*, 2324-2342.

28. Kirkland, T.A.; Grubbs, R.H. *J. Org. Chem.* **1997**, *62*, 7310-7318.

29. Bassetti, M.; D'Annibale, A. *Org. Lett.* **2005**, *7*, 1805-1808.

30. Schuster, M.; Blechert, S.A. *Angew. Chem. Int. Ed.* **1997**, *36*, 2036-2055.

31. Grubbs, R.H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450.

32. Fürstner, A.; Grela, K. *Angew. Chem. Int. Ed.*, **2000,** *39*, 1234-1236.

33. Armstrong, S.K. *J. Chem. Soc. Perkin Trans.* **1998**, *1*, 371-388.

34. Gosh, A.K.; Liu, C.A. *Chem. Commun*. **1999**, 1743-1744.

35. Cossy, J., Bauer, D., Bellosta, V. *Tetrahedron Lett*. **1999**, *40*, 4187-4188.

36. (a) amachandran, P.V., Reddy, M.V.R., Brown, H.C.*Tetrahedron Lett*. **2000**, 41, 583-586. (b). Carda, M.; Rodrıguez, S.; Gonzalez, F.; Castillo, E.; Villanueva, A.; Marco,J. A. *Eur. J. Org. Chem.*, **2002**, 15, 2649-2655.

37. Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod*. **1999**, *62*, 504–540.

38. (a) Nkunya, M.; Weenen, H.; Koyi, N.; Thijs, L.; Zwanenburg, B. *Phytochemistry*., **1987**, *26*, 2563–2565. (b) Weenen, H.; Nkunya, M.; Mgani, Q.; Achenbach, H.; Posthumus,M.;Waibel,R. J. Org. Chem. **1991**, *56*, 5865–5867. (c)Kamperdick, C.; Van, N. H.; Sung, T. V. *Phytochemistry*., **2002**, *61*, 991–994. (d) Li, C.; Lee, D., Graf, T. N.; Phifer, S. S., Nakanishi, Y., Riswan, S., Wani, M. C., Oberlies, N. H. *J. Nat. Prod.*, **2009**,*72*, 1949–1953.

39. Schmidt, B.; Kunz, O.; Biernat, A. *J. Org. Chem.*, **2010**, *75*, 2389–2394.

40. (a) De Fatima, A.; Pilli, R. A. *Tetrahedron Lett.* **2003**, *44*, 8721–8724. (b) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935–3941. (c) Curran, D. P.; Moura-Letts, G.; Pohlman, M. *Angew. Chem., Int. Ed.*, **2006**, *45*, 2423–2426. (d) Subhash, G.; Ch. Nageswara, R. *Tetrahedron Lett.* **2010**, *51*, 2052–2054.

41. Chanti Babu Dokuburra; Ashalatha Kankati; Bhujanga Rao Chitturi; Jon Paul Selvam Jondoss and Venkateswarlu Yenamandra, *Helvetica Chimica Acta*, **2011**. (Accepted, in Press)

42. Scholl, M.; Ding, S., Lee; C. W., Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

43. Dragutan, V.; Dragutan, I.; Delaude, L.; Demonceau, A. Coord. *Chem. Rev.* **2007**, *251*, 765–794.

44. Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.

45 Chao Cai; Jun Liu; Yuguo Du; Robert J. Linhardt; *J.Org.Chem*., **2010**, *75*, 5754–5756.

46. Ono, M.; Zhao, X. Y.; Shida, Y.; Akita, H. *Tetrahedron*, **2007**, *63*, 10140– 10148.

47. Chanti Babu Dokuburra ; Jon Paul Selavam Jondoss ; Kumar Reddy Dorigondla; Shekhar Vanam ; Venkateswarlu Yenamandra *Tetrahedron*., **2011**, *67*, 3815 -3819

48. Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni A. B.; Wu, D. C. J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.*, **1988**, *53*, 2598 - 2602.

49. Brown, C. A. *J. Am. Chem. Soc.*, **1973**, *95*, 4100 - 4102.

50. Subba Reddy B.V.; Phaneendra Reddy B,;Pandurangam T; Yadav J. S. *Tetrahedron Letters*, **2011**, *52*, 2306–2308.

51. Xu, Y., Prestwich, G. D. *J. Org. Chem.* **2002**, *67*, 7158.

52. (a) Petrier, C., Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910 (b) Einhorn, C.; Luche, J. L. *J. Organomet. Chem.* **1987**, *322*, 177.

53. (a) Yadav, J. S.; Reddy, U. V. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 5984 (b) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2005**, 127, 3697 (c) Zhong, G. *Angew. Chem., Int. Ed.*, **2003**, *42*, 4247.

54. (a) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem*., **2009**, *74*, 9531 (b) Rajiv, T. S.; Suresh, B. W. *Tetrahedron*., **2009**, *65*, 1599.

55. Still, W. C., Gennari, C. *Tetrahedron Lett.*, **1983**, *24*, 4405.

56. Sabitha, G.; Babu, R. S.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org.Lett.*, **2001**,*3*,1149.

57. Ramesh.P, Meshram H. M.; Tetrahedron Letters, **2011**, *52* , 2443–2445

58. Wiggins, L. F. *J. Chem. Soc.* **1946**, 13.

59. Chandrasekhar, M.; Kusum, L. C.; Singh, V. K.; *J. Org. Chem.* **2003**, *68*, 4039.

60. (a) Saravanan, P.; Chandrasekhar, M.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, 39, 3091; (b) Yadav, V. K.; Agrawal, D. *Chem. Commun.* **2007**, 5232.

61. Garegg, P. J.; Samuelsson, B. Synthesis 1979, 469.

62. Feurstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. J. Org. Chem. 2000, 65, 220; (b) Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. Chem. Commun. 2008, 6282; (c) Rost, D.; Porta, M.; Gessler, S.; Blechert, S. Tetrahedron Lett. 2008, 49, 5968. (d) Yadav, V. K.; Agrawal, D. Chem. Commun. 2007, 5232.

63. a) K. Yamauchi ; F. Uni ; S. Tabata ; M. Kinoshita, *J. Chem. Soc*., *Perkin Trans. 1*, **1986**, 765. b) D. Seebach; A. K. Beck; R. Imwinkelried; S. Roggo; A. Wonnacott,

Helv. Chim. Acta **1987**, *70*, 954; c) H. G. Choi; J. B. Son; D.S. Park; Y. J. Ham; J.M. Hah; T. Sim, *Tetrahedron Lett.* **2010**, *51*, 4942; d) G. V. M. Sharma; S.Mallesham; C. Chandra Mouli, *Tetrahedron*: *Asymmetry* **2009**, *20*, 2513.

64. Yadav J.S.; Mysorekar S.V.; Pawar S. M.; Gurjar M.K., *J. Carbohydr. Chem.* **1990**, *9*, 307.
65. W. Wu; Y. Wu, *J. Org. Chem.* **1993**, *58*, 3586.
66. Hicks J.D.; Huh C.W.; Legg A. D., Roush W. R., *Org. Lett.* **2007**, *9*, 5621.
67. Georges Y.; Allenbach Y.; Ariza X.; Campagne J -M.; Garcia J.; *J. Org. Chem.* **2004**, *69*, 7387.