CHAPTER – II

Total synthesis of (-) Cleistenolide
INTRODUCTION

6-Substituted-5,6-dihydro-2H-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.

\[
\begin{align*}
\text{1.5,6-dihydropyran-2-one} \\
\text{(+)Boronolide (2)}
\end{align*}
\]

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.\(^4\)

\[
\begin{align*}
2. & \ R = R' = OAc \ (\text{+)Boronolide}) \\
3. & \ R = R' = H \ (\text{+)Deacetylboronolide}) \\
4. & \ R = H, \ R' = OAc \ \text{Acetylboronolide}
\end{align*}
\]
**Tarchonanthus lactone (5)**

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

![Tarchonanthus lactone](image1)

**Cryptocarya diacetate**

![Cryptocarya diacetate](image2)

**Cryptocarya triacetate**

**Passifloricin A (8)**

Polyketide-type α-pyrone passifloricin A 8, 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.

![Passifloricin](image3)

**Kurzilactone (9)**

Kurzilactone 9, 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}.

![Kurzilactone](image4)
Massoialactone (10) and Argentilactone (11)

Massoialactone 10 was 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 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.

\[
\text{10. (R)-Massoialactone} \quad \text{11. (R)-Argentilactone}
\]

Strictifolione (12)

Strictifolione 12 was isolated from Cryptocarya stricifolia and has shown to display antifungal activity.

\[
\text{12. (+)-Strictifoline}
\]

(-)-Ratjadone (13)

In 1994, the polyketide ratjadone 13 was isolated from cultures of Sorangium cellulosum strain Soce360. Ratjadone displays potent in vitro antifungal activity with MIC values in the range from 0.004 to 0.6µg/mL for Mucor hiemalis, Phytophthora 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.
Fostriecin (14)

Fostriecin 14 was isolated in 1983 from Streptomyces pulveraceus.\(^{14}\) This compound displays potent *in vitro* activity against a broad range of cancer cell lines and its inhibitory activity against protein serine/threonine phosphatases.

\[
\text{HO-}\begin{array}{c}
\text{HO-} \\
\text{HO-}
\end{array}
\text{OH-} \\
\text{HO-}
\]

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.\(^{15}\)

\[
\text{HO-} \\
\text{HO-} \\
\text{HO-}
\]

15. Callystatin A

Spicigerolide (16)

\(\alpha,\beta\)-unsaturated \(\delta\)-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 \(\alpha,\beta\)-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 \(\mu\)g/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.\(^{20}\)
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, (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-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.

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.\(^{22}\)
Stereoselective synthesis of (-)-Cleistenolide

Lactone rings are a structural feature of many natural products. Many naturally occurring lactones, particularly \( \alpha, \beta \)-unsaturated lactones that are Michael acceptors, display interesting pharmacologic properties. 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. Among the different kinds of cyclic compounds obtainable by RCM, unsaturated lactones of various ring sizes are achievable from \( \alpha, \omega \)-diolefinic esters using first and/or second-generation Grubbs’ catalysts. More specifically, the preparation of \( \alpha, \beta \)-unsaturated \( \gamma \)-lactones through RCM of allyl and homoallyl acrylate have been reported using second-generation (II) Grubbs’ catalysts. 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.

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,\textsuperscript{37} in which a considerable number of new compounds, having interesting chemical structures and important biological activities, have been isolated from this family.\textsuperscript{38} Recently, the first total synthesis of cleistenolide 21 was published by Schmidt and co-workers\textsuperscript{39} in 18\% overall yield, by applying a ring-closing metathesis (RCM) protocol to prepare the key building block, an $\alpha,\beta$-unsaturated lactone.\textsuperscript{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.\textsuperscript{41} The cheap and commercially easy availability high enantiomeric purity and equivalence of double unit of C\textsubscript{3}-chiral building block because of C\textsubscript{2}-symmetry were the strong incentives to start from D-mannitol. Initially, we have outline the previous synthetic approaches of compound 21

\textbf{PREVIOUS SYNTHETIC APPROACHES}

\textbf{Schmidt et al., approach}

\textbf{Scheme – 2}

\textbf{Reagents and conditions} : (a)(i)TBSCl, imidazole, CH\textsubscript{2}Cl\textsubscript{2}, 20\degree C, 87\% (ii) Ti(OPr\textsubscript{i})\textsubscript{4}, L(+)-DET, Bu\text{''}OOH, CH\textsubscript{2}Cl\textsubscript{2}, -30\degree C, 84\% (b) Acroloyl chloride, Pri\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, 0\degree C, 92\% (c) Benzoic acid, Pri\textsubscript{2}NEt, 20\degree C, 53\% (d) A (10mol\%), phenol (50 mol\%), toluene, 70\degree C, 75\% (e) TBAF, then Ac\textsubscript{2}O, THF, 20\degree C, 66\%
Schmidt et al.\textsuperscript{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 metathesis (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 epoxidation to give β-epoxide 28. In epoxide 28 the hydroxyl group was protected with acryloyl chloride in presence of N-ethyl diisopropylamine in DCM at 0°C to give compound 29. In compound 29, the opening of epoxide with benzoic acid in presence of N-ethyl diisopropylamine at 20°C to give compound 30 which is ready to undergo RCM reaction. Compound 30 was subjected to ring closing metathesis with Grubbs 2nd generation catalyst\textsuperscript{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.

\textbf{Scheme - 3}

\textbf{Reagents and Conditions:} (a)TBDMSCI, DMAP, Pyridine,0°C to rt,92% (b) Ph₃P=CHCO₂Et, Dioxane, 70°C, 89% (c) Me₂C(OMe)₂, ppts, dcm, 0°C to rt, 87% (d) LiOH, THF/H₂O,rt (e) 2,4,6-trichlorobenzoyl chloride, pyridine,0°C to rt (f) TBAF,THF, then Bz₂O,rt,84% (g) PdCl₂(CH₃CN)₂,CH₃CN/H₂O,65°C (h) Ac₂O,Py,rt,91%
Cai et al.,\textsuperscript{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\textdegree{}C regioselectively afforded the 5-O-silyl aldehyde 33 in 92\% yield. Wittig olefination of aldehyde 33 with ethyl (triphenylphosphoranylidene) acetate in dioxane at 70\textdegree{}C furnished the \(\alpha,\beta\)-unsaturated ester 34 in 89\% yield. Treatment of an ester 34 with 2 equiv of Me\(_2\)C(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\(_2\)O afforded the corresponding acid 36 in quantitative yield. Intramolecular esterification of acid 36 under modified Yamaguchi conditions\textsuperscript{46} afforded key precursor 37 in 90\% yield. The key precursor 37 was converted to compound 38 by using TBAF and Bz\(_2\)O 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\textdegree{}C, furnished diol 39. Acetylation, with Ac\(_2\)O in pyridine, completed the synthesis of (-)-cleistenolide 21 in 91\% yield over the final two steps.

Venkateswarlu et al., approach

Venkateswarlu et al.,\textsuperscript{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 \(\alpha\)-hydroxy ester 41 using the literature procedure.\textsuperscript{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 \textit{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°C, 30 min (ii) Vinyl magnesium bromide, 0°C to rt, 3 h, 73% (c) IBX, DMSO, rt, 3 h; 96% (d) K-Selectride, -78°C, 6 h, 91% (e) PMB/Br, NaH, THF, rt, 1 h, 84% (f) TBAF, THF, rt, 2 h, 96% (g) Acryloyl chloride, Et$_3$N, DMAP, rt, 4 h, 86%; (h) DOWEX-50 (H$^+$), MeOH, rt, 6 h, 95% (i) Pyridine, BzCl followed by Ac$_2$O, DCM, 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$_2$O, pyridine, DCM, rt, 2h, 89%.

The reduction of 44 was next attempted with K-Selectride$^{49}$ under suitable reaction conditions (-78°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 benzylation 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\(_4\)Cl (cat), 6 h, 90% (b) DIPEA, MOMCl, DCM, 0°C, 2 h, 92% (c) (i) OsO\(_4\) (0.5 mol %), NMO, acetone–H\(_2\)O, 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°C to rt, 2 h, 88% (f) TBAF, THF, 0°C to rt, 85% (g) (i) IBX, DMSO/CH\(_2\)Cl\(_2\), 90%, rt, 3 h (ii) (CF\(_3\)CH\(_2\))\(_2\)P(O)CH\(_2\)-CO\(_2\)CH\(_3\), NaH, THF, 75% (h) CeCl\(_3\).7H\(_2\)O, CH\(_3\)CN, reflux, 12 h, 65% (i) TiCl\(_4\), CH\(_2\)Cl\(_2\), 0°C to rt, 30 min, 75% (j) (i) BzCl, Et\(_3\)N, DMAP, 4 h, 92% (ii) Ac\(_2\)O, Et\(_3\)N, DMAP, 24 h, 88%.
Subba Reddy et al.\textsuperscript{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.\textsuperscript{51} The zinc-mediated allylation of compound 53 in aqueous medium under Luche\textquotesingle s\textsuperscript{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\textquotesingle s base afforded MOM ether 55 in 92% yields. Dihydroxylation of compound 55 with OsO\textsubscript{4}/NMO system followed by sodium periodate oxidation resulted in aldehyde 56. Subsequent, α-amino-oxylation\textsuperscript{53} of compound 56 with nitrosobenzene in the presence of D-proline at -10\textdegree C, followed by the treatment with NaBH\textsubscript{4} in MeOH gave the crude aminooxy alcohol. Treatment of aminooxy alcohol with 30 mol % CuSO\textsubscript{4}.5H\textsubscript{2}O afforded the chiral diol\textsuperscript{54} 57 in 70% overall yield with 95% yield. Monosilylation of diol 57 was achieved by using TBSCI 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\textsubscript{2}Cl\textsubscript{2} gave the aldehyde, which was subjected directly to a homologation under Still–Gennari conditions\textsuperscript{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\textsubscript{3}.7H\textsubscript{2}O in CH\textsubscript{3}CN at reflux conditions.\textsuperscript{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\textsubscript{4} in dichloromethane at 0\textdegree C 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.,\textsuperscript{57} started the synthesis of \((-\)-cleistenolide 21) from commercially available \(\text{D}(+)-\text{mannitol}\). The diol 63 is readily accessible from tri-O-isopropylidene-D-(+)-mannitol,\textsuperscript{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.\textsuperscript{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\(_2\)Cl\(_2\), -78°C–20°C, 4 h, 83% (b) TBDPS–Cl, imidazole, CH\(_2\)Cl\(_2\), 0°C to rt, 86% (c) CuCl\(_2\).2H\(_2\)O, CH\(_3\)CN, 0°C, 45 min, 99% (d) PPh\(_3\)-imidazole-iodine, toluene, 110°C, 4 h, 84% (e) PPTS (cat)/MeOH, rt, 86% (f) TBS–OTf (1 equiv), 2,6-lutidine, CH\(_2\)Cl\(_2\), -78°C, 85% (g) acryloyl chloride, DIPEA, CH\(_2\)Cl\(_2\), 0°C to rt, 81% (h) 5 mol% Grubb’s 2nd generation catalyst, toluene, 110°C, 68% (i) TBAF, THF then Ac\(_2\)O, 62%.
The diacetonide 65 underwent selective hydrolysis of the terminal acetonide using an equivalent amount of \( \text{CuCl}_2 \cdot 2\text{H}_2\text{O} \) at 0°C to generate the diol 66 in quantitative yield.\(^{60}\) Diol 66 was converted to terminal olefin 67 by the reaction with \( \text{Ph}_3\text{P} \)-imidazole-iodine in toluene and gave 84% yield.\(^{61}\) Thus, acetonide cleavage of 67 by PPTS/MeOH (or) \( \text{CuCl}_2 \cdot 2\text{H}_2\text{O} \) 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°C selectively gave allylic silyl ether 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 \( \delta \)-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 \( \alpha \)-pyrone 21, from (R)-2,3-O-isopropylidene glyceraldehyde. Wittig reaction, ring closing metathesis (RCM) and one pot acetylation and benzylation of compound 21 are the key steps 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).

![Scheme - 7 : Retrosynthetic analysis of (-)-Cleistenolide](image-url)
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,\(^6^3\) which was further reacted with benzoxyl chloride in the presence of Et\(_3\)N in CH\(_2\)Cl\(_2\) to afford 1,2,5,6-diisopropylidene-3, 4-dibenzoyl derivative 74 in 91% yield \(^6^4\) as shown in (Scheme – 8).

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

Compound 74 was treated with orthoperiodic acid (H\(_5\)IO\(_6\)) followed by NaHCO\(_3\) in Et\(_2\)O at room temperature to yield the corresponding aldehyde.\(^6^5\) 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 K₂CO₃/MeOH to afford diol 76 in 91% yields. The formation of compound 75 was established by its ¹H 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 ¹³C-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 ¹H 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 ¹³C-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).

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 CH₂Cl₂-DMF (1:1) at −78°C to obtain the compound 77 as a colorless liquid in 90% yield. The monoprotected triethylsilyl ether 77 was reacted with acryloyl chloride in the presence of Et₃N to give the corresponding acrylate ester 78 in 84% yield. (Scheme-10). The formation of compound 77 was confirmed by its ¹H 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 ¹³C-NMR spectrum (Fig.2.11) shows the signals at δ 6.72 (3 C), 4.88 (3 C) is an indicative of monoprotected triethylsilyl ether 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 ¹H and ¹³C NMR spectral data. The ¹H 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 ¹³C 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 \(\alpha,\beta\)-unsaturated ester corresponding acrylate ester 78 in 84\% yield.(Scheme - 10)

![Diagram](attachment:image.png)

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 \(^1\)H NMR (Fig. 2.18) signals at \(\delta\) 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 \(\delta\) 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 \(^1\)H and \(^{13}\)C NMR spectral data. Its \(^1\)H NMR (Fig. 2.22) signals at \(\delta\) 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 \(\delta\) 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 \(\delta\) 170.3, 169.75, 167.37, 166.47

![Diagram](attachment:image.png)

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 1H NMR spectrum (Fig.2.26) of C-3 and C-4 olefinic 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 13C 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 at m/z 385 [(M⁺+Na)] further its HRMS calculated for C₁₈H₁₈O₈Na 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):

![Chemical Structure Image](image-url)
To a stirred solution of diol 73 (5 g, 19.08 mmol) and Et₃N (7.96 mL, 57.24 mmol) in dry CH₂Cl₂ (30 mL) was added benzoyl chloride (4.87 mL, 41.96 mmol) at 0°C under a nitrogen atmosphere. After completion of the reaction, the reaction mixture was diluted with water (20 mL), extracted with dichloromethane (3 x 15 mL), washed with brine (2 x 10 mL). Organic solution was dried over anh. Na₂SO₄ and concentrated under reduced pressure and the crude residue was purified by Column chromatography (EtOAc/n-hexane 10:90) to afford 74 (8.1 g, 91%) as a white solid.

**M.P.** : 82–85 °C

**[α]²⁵°** : -113.9 (c 3.4, CHCl₃)

**IR (KBr)** : ν (cm⁻¹) 3433, 3062, 2991, 2896, 1727, 1600, 1453, 1378, 1206, 1112, 1067

**¹H-NMR (300 MHz, CDCl₃)** : δ 8.02 (t, J = 6.7 Hz, 4 H), 7.53 (t, J = 6.7 Hz, 2 H), 7.41 (t, J = 7.5 Hz, 4 H), 5.48 (d, J = 5.2 Hz, 1 H), 4.88 (q, J = 6.0 Hz, 1 H), 4.37 (q, J = 6.0 Hz, 2 H), 4.11 (dd, J = 5.2, 11.3 Hz, 1 H), 3.96 (q, J = 9.0 Hz, 2 H), 3.70 (q, J = 6.7 Hz, 1 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.31 (s, 3 H).

**¹³C-NMR (75 MHz, CDCl₃)** : δ 165.5, 165.4, 133.12 (2 C), 129.8 (2 C), 129.6 (4 C), 128.3 (4 C), 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-diyldibenzoate (75) :

To a solution of diester 74 (5 g, 10.6 mmol) in dry Et₂O (45 mL), was added H₅IO₆ (3.32 g, 14.56 mmol) at 0°C and the reaction mixture was stirred for 6 h at room
temperature. After completion of the reaction, the mixture was neutralized with NaHCO₃ (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°C) solution of Ph₃PCH₂Br (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°C) for 2 h. After completion of reaction as monitored by TLC, the mixture was quenched with addition of saturated NH₄Cl solution (20 mL) and extracted into EtOAc (3x15 mL). The combined extract was washed with brine, dried (Na₂SO₄), 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. : 70-72°C
[α]²⁵_D : + 35.3 (c =1.5, CHCl₃)
IR (KBr) : 2915, 2855, 1695, 1602, 1256, 1067, 710
¹H-NMR (300 MHz, CDCl₃) : 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).

¹³C-NMR (125 MHz, CDCl₃) : 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) :

\[
\begin{align*}
&O \\
&O \\
&OH \\
&\text{HO} \\
&\text{HO}
\end{align*}
\]
To a cooled 0°C solution of diester alkene 75 (2.9 g, 7.43 mmol) in MeOH (20 mL) was added K₂CO₃ (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 Na₂SO₄ 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.

[α]²⁵° : +13.6 (c 1.7, CHCl₃)
IR (neat) : ν (cm⁻¹) 3419, 2986, 2926, 1643, 1376, 1065
¹H-NMR (300 MHz,CDCl₃) : 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, 1H), 3.93-4.16 (m, 3H), 3.59 (dd, J =3.3 Hz, 6.2 Hz, 1H), 2.84 (brs, 2H), 1.43 (s, 3H) 1.36 (s, 3H).
¹³C-NMR (100 MHz,CDCl₃) : 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 CH₂Cl₂-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 NH₄Cl 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 (Na₂SO₄), 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.

\[\alpha\]_D \ ^{25} : +2.5 (c 2.0, CHCl₃)

IR (neat) : \upsilon (cm⁻¹) 3426, 2954, 2880, 1647, 1374, 1063

\(^1\)H-NMR (500 MHz, CDCl₃) : \delta 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, CDCl₃) : \delta 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-(triethylyxyloxy)but-3-enyl acrylate (78):

To a cooled 0°C solution of 77 (1.25 g, 4.1 mmol) in CH₂Cl₂ (20 mL) was added Et₃N (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 CH₂Cl₂ (3x15 mL). The combined org. layer was washed with saturated NaHCO₃, brine, dried (Na₂SO₄), 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.
[α]_{D}^{25} : +30.8 (c 2.35, CHCl₃)
IR (neat) ν (cm⁻¹) : 2955, 2880, 1732, 1635, 1460, 1406, 1259, 1184, 1063

^1^H-NMR (300 MHz,CDCl₃) : 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).

^1^3^C-NMR (100 MHz,CDCl₃) : δ 165.28, 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].

(2R, 3S, 4R)-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.

[α]_{D}^{25} : +9.7 (c 0.65, CHCl₃)
IR (neat) ν (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, 1 H), 2.03-1.75 (brs, 1 H).

$^{13}$C-NMR (75MHz, CDCl$_3$) : δ 166.9, 137.2, 131.9, 127.7, 117.1, 117.0, 71.8, 70.7, 66.1.

ESI-MS : 225 [M$^+$ + Na]

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

![Chemical Structure](image)

To a cooled 0°C solution of triol 79 (0.6 g, 2.9 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (3x15 mL). The combined org. layer was washed with saturated NaHCO$_3$, water, brine, dried (Na$_2$SO$_4$), 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.

$[\alpha]^{25}$D : +25.6 (c 0.55, CHCl$_3$)

IR (neat) $\nu$ (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, 1 H), 7.45 (t, $J = 7.5$ Hz, 2 H), 6.52-6.40 (m, 1 H), 6.22-6.09 (m, 1 H), 5.95-
1H-NMR (500 MHz, CDCl₃) : 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 = 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).

13C-NMR (75 MHz, CDCl₃) : 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 CH₂Cl₂ (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°C
[α]D²⁵ : -142 (c 0.4, CHCl₃)
IR (KBr) : 2963, 1725, 1452, 1372, 1224, 1099, 1070
1H-NMR (500 MHz, CDCl₃) : 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 109
= 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\(_3\)CO, 3 H), 2.04 (s, CH\(_3\)CO, 3H).

\(^{13}\text{C-NMR}(75\text{MHz,CDCl}_3)\) : \( \delta \) 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]
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