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REGULAR ARTICLE

# Sequential ring-closing enyne metathesis and intramolecular Diels–Alder reaction: an approach to the synthesis of the core structure of galiellalactone

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**Abstract.** Development of a route for the synthesis of the core structure of galiellalactone is described. The key step involves a ring-closing enyne metathesis of an allyl propargyl ether to produce a dihydro furano diene with a latent dienophile. The dienophile, when generated from this latent functionality, underwent an *in situ* intramolecular Diels–Alder reaction to produce the tricyclic skeleton present in galiellalactone.

**Keywords.** Catalysis; Diels–Alder reaction; enyne metathesis; natural product.

## 1. Introduction

Galiellalactone **1** is a fungal metabolite isolated from cultures of the ascomycete *Galiella rufa*.[1] Galiellalactone is found to be associated with various biological activities projecting it as a potent anticancer agent. The proposed biosynthesis[2] (Scheme 1) involves an enzymatic hydroxylation of desoxygaliellalactone **2** which in turn is obtained through an intramolecular Diels–Alder reaction of pregaliellalactone **3a**.

Galiellalactone has become an attractive target for synthesis[3–7] due to its intriguing structure and important biological activities. The reported approaches involve the synthesis of the biosynthetic intermediate desoxygaliellalactone **2**. Since chemical hydroxylation at the bridgehead carbon was difficult, an enzymatic hydroxylation of **2** was used for the synthesis of **1**.[5,7] Thus, all the reported approaches to galiellalactone were focussed on the synthesis of desoxygaliellalactone **2**. The key step in the synthesis of **2** relied on an inverse electron demand intramolecular Diels–Alder (IMDA) reaction of pregaliellalactone **3a**. This cycloaddition required harsh reaction condition such as high temperature and high pressure and proceeded to afford **2** in moderate yield. We thought that structural modification of the intramolecular Diels–Alder substrate **3a** to **3b** having an electron-withdrawing group (EWG) in the dienophilic moiety would make the cycloaddition more facile. This modification would also allow access not only to **2** but to its structural analogues for eventual transformation to galiellalactone and its analogues. Ring-closing enyne metathesis[8–11] (RCEYM) of the propargylate **4** in principle would provide the precursor **3b**. Thus a tandem RCEYM-IMDA reaction[12,13] of an appropriately designed substrate is expected to provide **2**. Herein we describe the results of our preliminary investigation.

## 2. Experimental[14]

### 2.1 *Synthesis of the carbinol* ***6***

Vinyl magnesium bromide (3 mL, 2.9 mmol, 1 M in THF) was added to a solution of the known aldehyde **5**[15] (599 mg, 2.65 mmol) in anhydrous THF (10 mL) at 0 °C. The reaction mixture was left to come to rt slowly with constant stirring for 12 h. It was then quenched by saturated aqueous $NH_4Cl$ solution (1 mL). The precipitated solid was allowed to settle down. The precipitate was filtered out. The filtrate was concentrated. The residual mass was purified through

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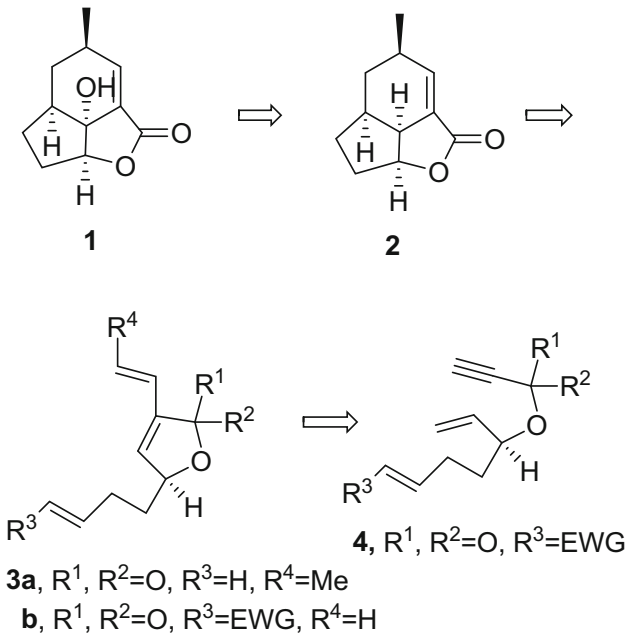



**Scheme 1.** Biosynthesis based synthetic plan.

column chromatography (20% EA/PE) as the eluent to afford the carbinol **6** (531 mg, 79%) as a light yellow oil as 1:1 inseparable diastereomeric mixture; $^1$H NMR (300 MHz, $CDCl_3$) (of the mixture of diastereoisomers) $\delta$ 5.90–5.78 (1H, m), 5.28–5.03 (2H, m), 4.25–4.07 (2H, m), 3.99–3.92 (1H, m), 3.64–3.55 (1H, m), 2.78 (s) and 2.66 (s) (total 1H), 1.90–1.72 (1H, m), 1.62–1.50 (9H, m), 1.49–1.47 (1H, m), 1.46–1.36 (4H, m), 0.96–0.89 (3H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) (of the mixture) $\delta$ 141.8, 141.3, 114.6, 114.2, 109.4 (X 2), 77.7, 77.5, 72.0, 70.5, 66.4, 66.3, 39.1, 37.9, 36.8, 36.7, 36.2 (X 2), 34.9, 34.7, 25.3 (X 2), 24.3, 24.1, 24.0, 23.9, 23.3 (X 2), 11.6, 11.4; HRMS (ESI) m/z Calcd for $C_{15}H_{26}O_3Na$ $(M+Na)^+$, 277.1780; found, 277.1782.

## 2.2 *Synthesis of the en-yne derivative **8***

To a suspension of NaH (190 mg, 3.9 mmol) (50% suspension in oil) in THF (10 mL) cooled at 0 °C, a solution of the hydroxyl compound **6** (500 mg, 2.0 mmol) in THF (10 mL) was added dropwise. The reaction mixture was allowed to stir for additional 30 min. HMPA (0.7 mL, 3.93 mmol) was slowly added at this temperature and kept stirring for 15 min. Propargyl bromide (0.4 mL, 4.33 mmol) was added at the same temperature and was stirred for additional 20 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ (1 mL) and the organic layer was separated. The aqueous layer was extracted with $Et_2O$ (3 X 20 mL). The combined organic layer was washed with brine (5 mL) and dried and evaporated under reduced pressure. The residual mass was purified through column chromatography (10% EA/PE) to afford the en-yne derivative **8** (542 mg, 94%) as an oil (inseparable 1:1 diastereomeric mixture). $^1$H NMR (of the mixture of diastereoisomers) (300 MHz) $\delta$ 5.63–5.50 (1H, m), 5.24–5.18 (2H, m), 4.17–3.95 (5H, m), 3.58–3.51 (1H, m), 2.38–2.34 (1H, m), 1.54–1.44 (12H, m), 1.35 (3H, s), 0.91–0.89 (3H, m); $^{13}$C NMR (75 MHz) (of the mixture) $\delta$ 138.1, 137.8, 118.6, 118.2, 109.0, 108.9, 80.2 (X 2), 78.4, 77.8 (X 2), 77.4, 74.0, 73.9, 67.3, 67.2, 55.1 (X 2), 38.7, 38.1, 36.4 (X 2), 35.4, 35.1, 35.0, 34.9, 25.3 (X 2), 24.1 (X 2), 24.0 (X 2), 23.2, 23.0, 10.9, 10.6; HRMS (ESI) m/z Calcd for $C_{18}H_{29}O_3$ $(M+H)^+$ 293.2117, found 293.2118.

## 2.3 *RCEYM of the en-yne derivative **8***

The en-yne derivative **8** (100 mg, 0.34 mmol) in deoxygenated toluene (15 mL) was treated with Grubbs' 2nd generation catalyst G-II (15 mg, 0.017 mmol) under ethylene atmosphere at room temperature for 14 h. Toluene was removed under vacuum and the residual mass was purified by column chromatography (10% EA/PE) to afford the dihydrofuran derivatives **9** (78 mg, 94%) as a liquid as an inseparable 1:1 diastereoisomeric mixture; $^1$H NMR (300 MHz) (for the mixture of diastereoisomers) $\delta$ 7.38–7.20 & 6.53–6.44 (1H, m), 5.76–5.73 (1H, m), 5.17–5.13 (1H, m), 5.00–4.94 (2H, m), 4.83–4.65 (2H, m), 4.20–3.96 (2H, m), 3.60–3.55 (1H, m), 1.59–1.50 (12H, m), 1.44–1.38 (3H,m), 0.95–0.90 (3H, m); $^{13}$C NMR (75 MHz) (of the mixture) $\delta$ 138.6 (X 2), 129.7 (X 2), 129.0, 128.9, 116.4 (X 2), 109.2, 109.1, 85.0, 84.8, 77.9 (X 2), 73.6, 73.4, 67.3 (X 2), 39.7, 39.0, 36.4 (X 2), 35.8, 35.7, 35.2, 35.1, 25.4 (X 2), 24.1 (X 2), 24.0 (X 2), 23.5, 23.4, 11.1, 10.9; HRMS (ESI) m/z Calcd for $C_{18}H_{28}O_3Na$ $(M+Na)^+$ 315.1936, found 315.1935.

## 2.4 *Synthesis of the dien-yne derivative **12***

Following the procedure similar to that for synthesis of the en-yne derivative **8**, the known[16] divinyl carbinol **11** (1.66 g, 5.92 mmol), on treatment with NaH (1.71 g, 35.55 mmol), HMPA (5.2 mL, 29.62 mmol) and propargyl bromide (2.7 mL, 35.55 mmol), was converted after column chromatography (10% EA/PE) to the dien-yne derivative **12** (1.55 g, 83%); $[\alpha]_D^{25}$ − 2.07 (c 1.6, $CHCl_3$); $^1$H NMR (300 MHz) $\delta$ 5.86–5.75 (2H, m), 5.31–5.24 (4H, m), 4.12 (1H, q, $J$ = 6 Hz), 4.04–3.89 (3H, m), 3.56 (1H, t, $J$ = 7.8 Hz), 2.34 (1H, t, $J$ = 2.4 Hz), 1.71–1.66 (2H, m), 1.58–1.50 (10H, m), 1.36–1.23 (3H, m), 0.86 (3H, t, $J$ = 2.4 Hz); $^{13}$C NMR (75 MHz) $\delta$ 139.5, 139.4, 116.7, 116.5, 109.0, 81.8, 81.3, 77.3, 73.1, 66.8, 51.7, 38.8, 36.8, 36.4, 34.9, 25.4, 24.5, 24.1, 24.0, 11.0; HRMS (ESI) m/z Calcd for $C_{20}H_{30}O_3Na$ $[M + Na]^+$ 341.2093, found 341.2096.

## 2.5 *RCEYM of the dien-yne **12***

Following the procedure described above for ring closing enyne metathesis of the en-yne **8**, metathesis of the dien-yne

**12** (300 mg, 0.94 mmol) in toluene using G-II (40 mg, 0.047 mmol) gave the dihydro furan derivatives **13** and **14** (216 mg, 73%) as an inseparable 1:1 diastereomeric mixture; $^1$H NMR (300 MHz) (of the diastereomeric mixture) $\delta$ 7.36–7.23 and 6.52–6.41 (1H, m), 5.91–5.81 (1H, m), 5.65–5.64 (1H, m), 5.24–4.94 (4H, m), 4.74–4.72 (1H, m), 4.10–3.89 (3H, m), 3.61–3.51 (1H, m), 1.63–1.54 (12H, m), 1.36–1.31 (3H, m), 0.91–0.84 (3H, m); $^{13}$C NMR (75 MHz) $\delta$ 141.4, 141.1, 138.1, 137.9, 130.5, 130.4, 129.7, 129.6, 116.5, 116.4, 112.7, 112.4, 109.0, 108.9, 93.0, 92.8, 77.9, 77.6, 73.5, 73.3, 67.3, 66.8, 38.7, 38.3, 37.8, 37.7, 36.5, 36.4, 35.0, 34.9, 25.4 (X 2), 24.8, 24.6, 24.1 (X 2), 24.0 (X 2), 11.2, 10.9; HRMS (ESI) m/z Calcd for $C_{20}H_{31}O_3$ $[M + H]^+$, 319.2273; found, 319.2274.

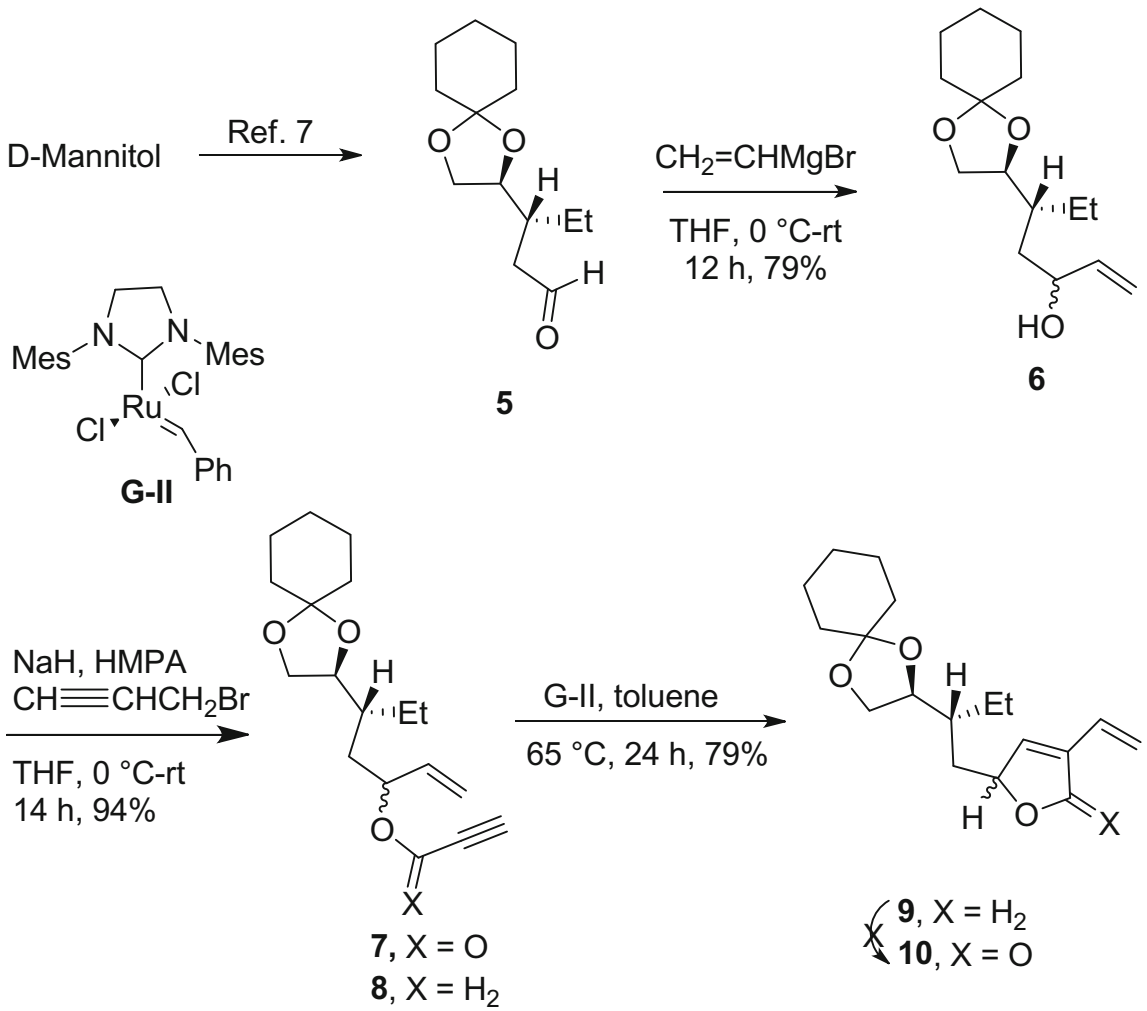
### 2.6 *Synthesis of the tricycle **21***

The mixture of the dienes **13** and **14** (210 mg, 0.66 mmol) was treated with AcOH (16 mL) and water (4 mL) at room temperature for 30 h. The solvent was removed under vacuum and the residue was purified by column chromatography (50% EA/PE) to afford the corresponding diols (126 mg, 81%): $^1$H NMR (of the mixture of diastereoisomers) (300 MHz) $\delta$ 7.38–7.22 and 6.50–6.37 (1H, m), 5.90–5.75 (1H, m), 5.65–5.58 (1H, m), 5.29–4.96 (4H, m), 4.89–4.68 (1H, m), 4.10–3.65 (3H, m), 3.60–3.43 (3H, m), 2.14–1.84 (1H, m), 1.72–1.66 (1H, m), 1.60–1.49 (1H, m), 1.37–1.23 (2H, m), 0.89–0.83 (3H, m); $^{13}$C NMR (of the mixture) (75 MHz) $\delta$ 140.7, 139.2, 138.7, 136.8, 130.7, 129.3, 129.2, 129.0, 117.2, 117.1 113.7, 112.7, 93.3 (X 2). 74.1, 73.7, 73.6, 73.5, 64.0, 63.9, 38.8, 38.7, 38.5, 37.8, 25.1, 24.9, 12.0, 11.9; HRMS (ESI) m/z Calcd for $C_{14}H_{23}O_3$ $[M + H]^+$, 239.1647; found, 239.1648. To a solution of these diols (120 mg, 0.50 mmol) in DCM (10 mL), silica supported sodium metaperiodate (1 mmol/g, 1.01 g, 1.01 mmol) was added and was allowed to stir for 30 min. The reaction mixture was filtered through a sintered glass funnel. The solid on the funnel was washed with $Et_2O$ (30 mL). The combined organic layer was washed with brine (3 mL) and dried. Evaporation of solvent under vacuo afforded the aldehyde **17** (110 mg) which without any purification and characterization was directly used for Wittig olefination. To a magnetically stirred suspension of NaH (60 mg, 1.25 mmol) (50% in oil) in THF (3 mL), dimethyl 2-oxopropylphosphonate (**18**) (0.18 mL, 1.25 mmol) was added. The reaction mixture was allowed to stir for 1 h. A solution of the crude aldehyde (110 mg) in THF (3 mL) was added to this mixture and stirred for 72 h. Saturated $NH_4Cl$ (2 mL) was added to quench the reaction. The reaction mixture was extracted with $Et_2O$ (3 X 20 mL). The combined organic layer was washed with brine (2 mL), dried and concentrated under reduced pressure. The residual mass was purified by column chromatography (20% EA/PE) to afford the tricyclic adduct **21** (50 mg, 41%) as oil (0.4g, $CHCl_3$); $[\alpha]_D^{25}$ +20.8; $^1$H NMR (300 MHz) $\delta$ 5.93 (1H, dd, $J$ = 10.5, 17.1 Hz), 5.65–5.64 (1H, m), 5.29 (1H, dd, $J$ = 1.8, 17.4 Hz), 5.01 (1H, dd, $J$ = 1.8, 10.8 Hz), 4.26–4.16 (2H, m), 2.57–2.51 (1H, m), 2.50–2.46 (1H, m), 2.34–2.30 (1H, m), 2.28–2.25 (1H, m), 2.23 (3H, m), 2.09–2.08 (1H, m), 2.03–1.97 (1H, m), 1.65–1.60 (1H, m), 1.58–1.46 (1H, m), 1.36–1.25 (1H, m), 1.13–1.01 (1H, m), 0.86 (3H, t, $J$ = 7.5 Hz); $^{13}$C NMR (75 MHz) $\delta$ 211.2, 142.0, 141.9, 115.7, 111.2, 91.0, 70.4, 50.2, 48.6, 44.7, 44.6, 44.1, 28.9, 25.5, 25.4, 12.6; HRMS (ESI) m/z Calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$, 269.1518; found, 269.1515.

## 3. Results and Discussion

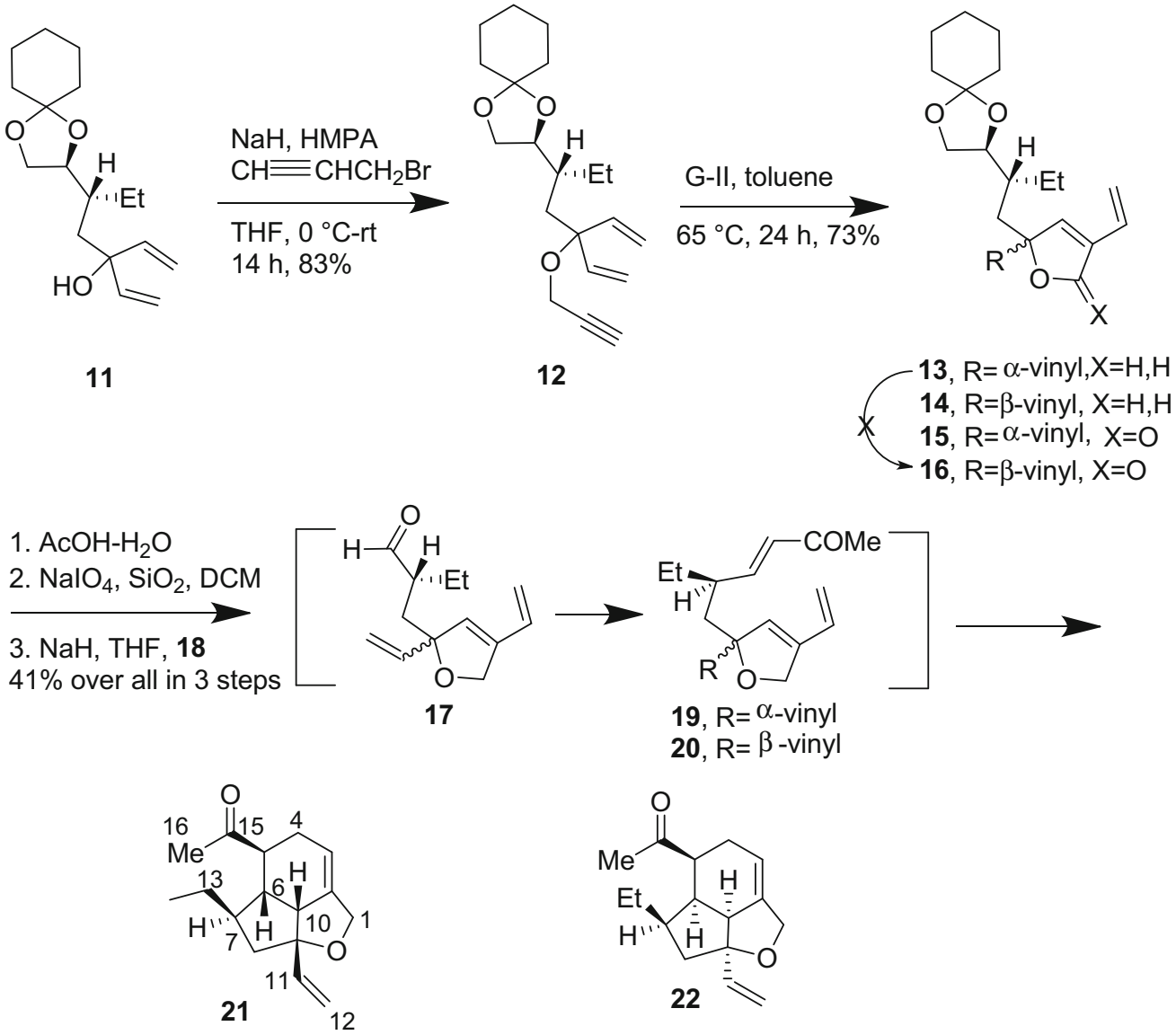
Based on the synthetic plan outlined in Scheme 1 we initially chose the synthesis of the diene **10** (Scheme 2). The ketal unit in the diene **10** can be elaborated to a dienophile at an appropriate stage. The diene **10** should, in principle, be available through RCEYM of the en-yne **8**. The enyne metathesis precursor **7** was attempted to prepare as follows. The aldehyde **5** was prepared from D-mannitol using a procedure developed earlier by us.[15] The aldehyde **5** on reaction with vinyl magnesium bromide afforded an inseparable 1:1 mixture of the carbinols **6** in 75% yield. Attempted coupling of these carbinols with propynoyl chloride under a variety of conditions to make the ester **7** led to an intractable mass. At this point, we decided to carry out the RCEYM of the propargyl ether **8** anticipating that the resulting dihydrofuran derivative **9** can be oxidised at a late stage to provide the butenolide **10**. The propargyl ether **8** was prepared as a mixture from the reaction of the carbinols **6** with NaH and propargyl bromide. RCEYM of the propargyl ether **8** with Grubbs' second generation catalyst (G II) in presence of ethylene went smoothly to produce an inseparable mixture (1:1) of the 2, 5-dihydro furan derivatives **9** in 79% yield. Allylic oxidation of **9** was expected to provide the butenolide**10**. However, attempted oxidation under a variety of conditions using PDC or PCC failed to provide the butenolide **10**. In an earlier occasion,[17] we have observed that oxidation of a 2, 5-dihydrofuran derivative with mono-substituent at the carbon centre next to the oxygen centre did not proceed while such oxidation went smoothly[16] when the carbon centre next to the oxygen centre of the dihydrofuran is quaternary. Based on this observation, synthesis of a dihydrofuran derivative with a quaternary carbon next to oxygen centre was planned.

Toward this end, the divinyl carbinol **11** was chosen anticipating that the angular vinyl group in the tricycle **21** (Scheme 3) to be obtained could be removed using a sequence involving oxidation to carboxylic acid and its decarboxylation. The reaction of the known divinyl




**Scheme 2.** Synthesis of the diene **9**.

carbinol[16] **11** with NaH-propargyl bromide gave the propargyl ether **12** in 83% yield. Metathesis of this compound in toluene with Grubbs' second generation catalyst in presence of ethylene afforded an inseparable 1:1 mixture of the dihydrofuran derivatives **13** and **14** in 73% yield. Attempted oxidation of the mixture of **13** and **14** failed to produce the butenolides **15** and **16**. Thus we decided to elaborate the ketal unit to construct the dienophile chain first and then oxidation of the resulting tetrahydrofuran derivative after Diels–Alder reaction. Deprotection of the ketal followed by periodate cleavage of the resulting vicinal diol led to the formation of the aldehyde **17**. The aldehyde **17** without characterization was then subjected to Wittig olefination with dimethyl 2-oxopropyl phosphonate (**18**) in the presence of NaH. Amazingly, out of the olefination products **19** and **20**, only **20** underwent spontaneous in situ IMDA reaction during olefination of the aldehyde **17** to afford the tricycle **21** in overall 41% yield in three steps. The gross structure of the tricyclic adduct **21** was established by $^{1}H$ and $^{13}C$ NMR spectra. The stereochemical assignment is based on analysis of 2D NMR spectra [HSQC, HMBC (Figure 1), COSY and ROESY (Figure 2)]. The compound **21** thus arose from IMDA reaction of the trienone **20**. The absence of the adduct **22**, expected to arise from the trienone **19** on IMDA, may be attributed as follows. Inspection of the structure **22** reveals that the C-7 ethyl and the C-5 COMe groups lie within the concave face leading to a highly strained structure. Thus the diastereoisomer **19** failed to undergo Diels–Alder reaction. During cycloaddition, it simply decomposed. However, attempted oxidation of the tetrahydrofuran unit in compound **21** to produce the lactone ring present in galiellalactone failed. The present investigation, although failed to provide the natural product, can be employed for the total synthesis of galiellalactone with the appropriately designed starting material.




**Scheme 3.** Synthesis of the tricycle **21**.

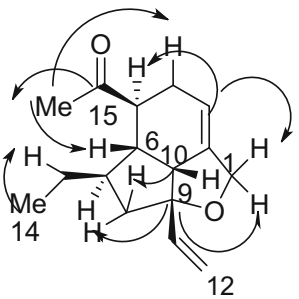


**Figure 1.** Significant HMBC(C→H) correlations of **21**.

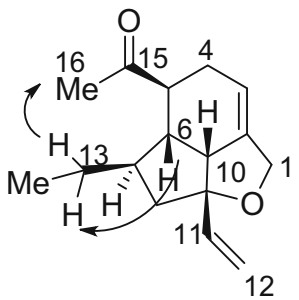


**Figure 2.** ROESY correlations of **21**.

## 4. Conclusions

We have developed a convenient route to access the core structure of the fungal metabolite galiellalactone. The synthetic sequence involves ring-closing enyne metathesis of an allyl propargyl ether derivative with a ketal containing side chain using second generation Grubbs catalyst to provide a substituted dihydrofurano diene. The ketal unit in the diene served as a latent dienophile. Transformation of the ketal to an α, β-unsaturated ketone led to facile in situ Diels–Alder reaction to afford the tricyclic core structure of galiellalactone.

## Supplementary Information (SI)

All additional information regarding the characterisation of the new compounds using $^{1}H$, $^{13}C$ NMR and 2D NMR spectra are given in the supplementary information available at www.ias.ac.in/chemsci.

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