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Total synthesis of (*S*)-Zearalenone and Zeranol and development of Amberlyst-15® promoted reactions

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ABSTRACT

This work review is structured in three different parts. The first part includes total synthesis of 14-membered macrolides (*S*)-zearalenone and zeralenone through the application of Diels-Alder reaction, Jacobsen kinetic resolution, Mitsunobu coupling, Ring-closing metathesis, and hydrogenation as key steps. The second part discusses a convenient and metal-free protocol for the preparation of α,β-unsaturated ketones from alkynes and aldehydes using Amberlyst-15®. The third part describes the preparation of β-butynyloxy enones through the 2:1 coupling of homopropargyl alcohol and aldehydes using Amberlyst-15® as a heterogeneous solid acid.

Keywords: Macrolide, (S)-Zearalenone, Zeranol, Ion-exchange resin, Conjugated ketones, β-Alkoxy conjugated enones

Section A: Total Synthesis of (*S*)-Zearalenone and Zeranol

The β-resorcylic macrolides are a class of naturally occurring 12- and 14-membered macrolides.[1-6] (*S*)-Zearalenone is a 14-membered macrolactone of this type that exhibits anabolic, estrogenic, uterotropic, and antibacterial activity.[7-9] Zearalenone was first isolated from the mycelium of the fungus *Gibberella zeae* (*Fusarium graminearum*) growing as a mould on corn.[10] Zeranol also belongs to this class of macrolide and is closely related to (*S*)-zearalenone (Figure 1). Zeranol is a non-steroidal estrogen agonist and animal growth-promoting agent and is under clinical trials as a potential treatment for menopausal and post-menopausal syndrome.[11]

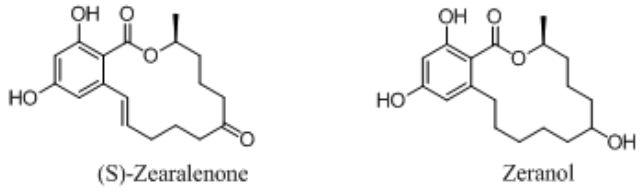
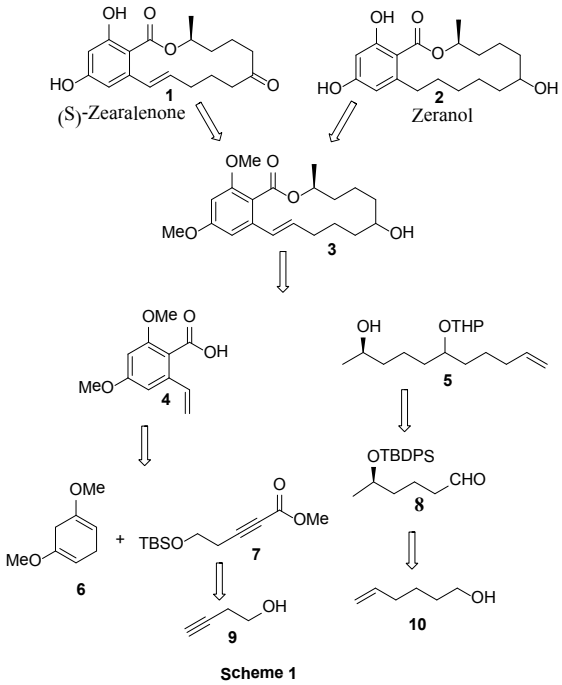


Figure 1. Chemical Structure of (s) – Zearalenone and Zeranol

Retrosynthetic Analysis

In our retrosynthetic analysis (Scheme 1), we envisaged that the target molecules **1** and **2** could be synthesized from a common intermediate **3**, which, in turn, could be obtained from Mitsunobu and RCM reaction of aromatic acid **4** and alcohol **5**. Aromatic acid **4** was to be obtained from Diels–Alder reaction of diene **6** and dienophile **7**. Fragments **5** and **7** could be derived from commercially available 5-hexene-1-ol and homopropargyl alcohol, respectively.



Scheme 1. Retrosynthetic Analysis

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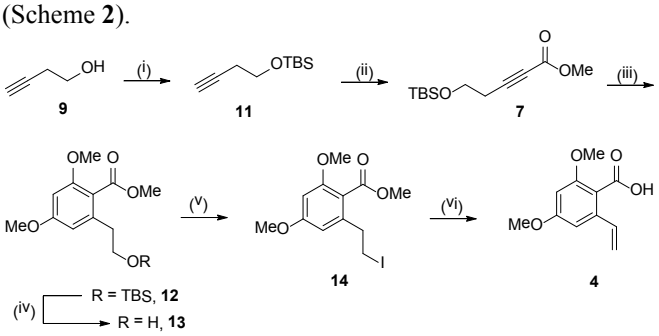
Highlights

- A convergent total synthesis of 14-membered macrolides (*S*)-zearalenone and zeranol has been achieved through application of the Diels–Alder reaction, Jacobsen kinetic resolution, Mitsunobu coupling, Ring-closing metathesis, and hydrogenation as key steps.
- We have described a simple, convenient and metal-free protocol for the preparation of α,β-unsaturated ketones from alkynes and aldehydes using Amberlyst-15® as a novel promoter.
- We have developed a novel and efficient approach for the preparation of β-butynyloxy enones through the 2:1 coupling of homopropargyl alcohol and aldehydes using Amberlyst-15® as a heterogeneous solid acid.

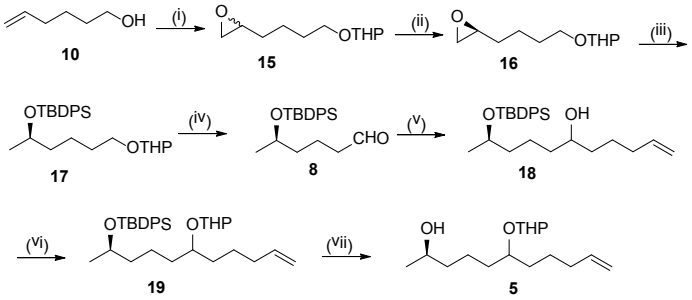
Results and Discussions:

Dienophile **7** was prepared from homopropargyl alcohol **9**, which was protected as the *tert*-butyldimethylsilyl (TBS) ether **12** with *tert*-butyldimethylsilyl chloride in the presence of imidazole and a catalytic amount of 4-(*N*,*N*-dimethylamino) pyridine (DMAP) in dichloromethane. Treatment with *n*-butyllithium and reaction with methyl chloroformate ($ClCO_2Me$) afforded **7** in 80% yield. The Diels–Alder reaction[12-13] between diene **6** and acetylenic dienophile **7** in a sealed tube at 180 °C for 48 hours in the presence of a catalytic amount of *N*,*N*-dimethylaniline gave the aromatic product **12** (40% yield). Silyl ether deprotection with HF·Py in acetonitrile afforded **13**, further iodination with triphenylphosphine and iodine in a mixture of acetonitrile and diethyl ether (1:2), yielded iodo compound **14** in 85% yield. Compound **15**, upon treatment with potassium *tert*-butoxide, afforded olefin, and hydrolysis of the ester ($LiOH·H_2O$ in $MeOH–H_2O$) furnished acid **4** in 80% yield over two steps (Scheme **2**).



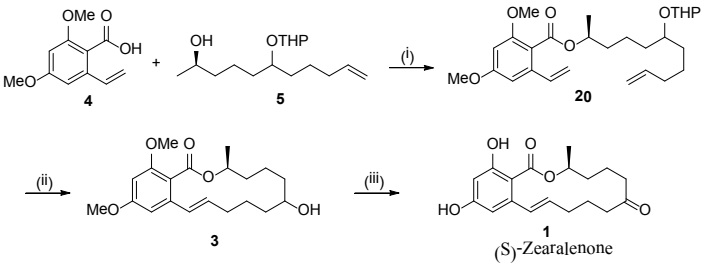
Scheme 2: ***Reagents and Conditions*****:** (i) TBSCl, DMAP, CH_2Cl_2, r.t, 95%; (ii) *n*-BuLi, $ClCO_2Me$ THF, -78 °C, 80%; (iii) **6**, Neat, N,N-Dimethyl aniline (Cat), 180 °C, 2 days, 40%; (iv) HF-Py, CH_3CN, r.t, 90%; (v) I_2, CH_3CN, Et_2O, r.t, 95%; (vi) a) ^{t}BuOK, THF, r.t, 90%; b) LiOH-H_2O, MeOH, H_2O (3:1), reflux, 85%.

The synthesis of compound **5** was started from the 5-hexene-1-ol **10**, which was protected with 2,3-dihydro-2H-pyran, and then oxidized to corresponding epoxide **15**. The solvent free hydrolytic kinetic resolution[14] of **15** with 0.3 mol% (*S,S*)-salen-Co(III)(OAc) complex furnished chiral epoxide **16** in 93% ee (determined by chiral HPLC). Reductive opening of epoxide **16** using LAH afforded alcohol in excellent yield.



Scheme 3: ***Reagents and Conditions*****:** (i) a) DHP, PPTS, CH_2Cl_2, r.t, 95%; b) *m*-CPBA, CH_2Cl_2, r.t, 90%; (ii) a) (S,S) Jacobsen cat, CH_3COOH, H_2O, Toluene, 40%; (iii) a) $LiAlH_4$, THF, 0 °C to r.t, 90%; b) TBDPSCl, Imidazole, CH_2Cl_2, 90%; (iv) a) PPTS, C_2H_5OH, 94%; b) IBX, DMSO, CH_2Cl_2 89%; (v) a) 5-pentenyl bromide, Mg, THF, 0 °C to r.t, 80%; (vi) DHP, PPTS, CH_2Cl_2, 90%; (vii) TBAF, THF, 90%.

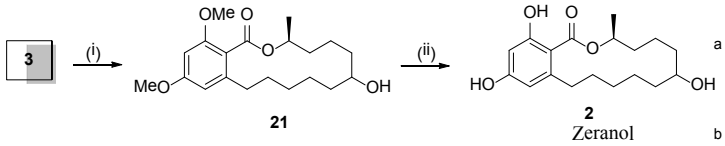
The resulting hydroxy group was oxidized with IBX to get the aldehyde **8**, which was further subjected to Grignard reaction with 5-pentenyl bromide, Mg in THF to get secondary alcohol **18** in 80% yield. The subsequent protection to its THP ether **19** and deprotection of TBDPS group gave the required alcohol **5** fragment in 90% yield (Scheme **3**). The next step was to couple both, the acid **4** and secondary alcohol **5** by employing Mitsunobu esterification reaction (Scheme **4**).



Scheme 4: ***Reagents and Conditions*****:** (i) DEAD, TPP, Et_2O, r.t, 90%; (ii) a) PPTS, C_2H_5OH, 85%; b) $(PCy)_3Cl_2Ru$=CHPh, Toluene, reflux, 80%; (iii) a) IBX, DMSO, CH_2Cl_2, r.t, 85%; b) AlI_3, TBAI, C_6H_6, 70%.

Accordingly, the acid **4** and alcohol **5** were treated with diethyl azodicarboxylate (DEAD) in Et_2O to afford the ester **20** in 90% yield with the appropriate stereogenic center. It was subjected to THP deprotection and olefin metathesis reaction using second generation Grubb's catalyst, $(PCy)_3Cl_2Ru$=CHPh for the formation of desired product *trans* macrolactone **3** in 80% yield. Macrolactone **3** was oxidized with IBX into ketone in 85% yield, which on subsequent demethylation with AlI_3, (*insitu* generated from Al powder and I_2, by refluxing in benzene for 1 h) and catalytic amount of TBAI, in benzene at 10°C for 1 h provided desired (S)-Zearalenone **1** in 70% yield. The ^{1}H NMR, ^{13}C NMR data and optical rotation of the

synthetic (S)-Zearalenone **1** were in agreement with that reported in the literature (Scheme **4**).[15] Reduction of the olefinic bond of compound **3** with Pd-C in C_2H_5OH at room temperature for 2 h under hydrogen gave **21** in 80% yield, which on subsequent demethylation with AlI_3 (*insitu* generated from Al powder and I_2, by refluxing in benzene for 1 h) and catalytic amount of TBAI, in benzene at 10 ^oC for 1 h provided Zeranol **2** in 70% yield and this analytical data were in good agreement with the reported data (Scheme **5**).[15]

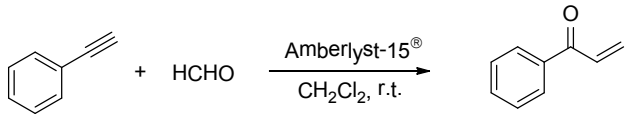


Scheme 5: ***Reagents and Conditions*****:** (i) Pd-C, H_2, C_2H_2OH, r.t, 80%; (ii) AlI_3, TBAI, C_6H_6, 70%.

In conclusion, we have synthesized (S)-Zearalenone through the Mitsunobu esterification and ring-closing metathesis of acid **4** and alcohol **5**. The stereochemistry in aliphatic fragment was established by Jacobsen resolution method. The aromatic acid **4** was prepared through Diels-Alder approach based strategy. This approach should be widely applicable to complex natural product synthesis.

Section B: One-pot synthesis of α,β-unsaturated ketones

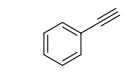
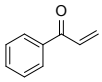
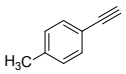
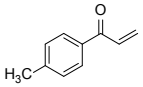
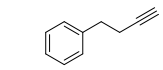
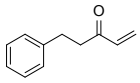
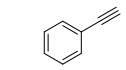
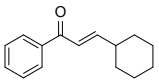
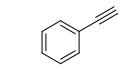
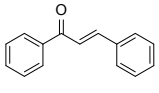
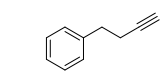
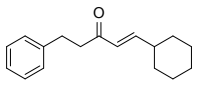
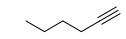
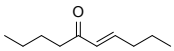
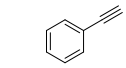
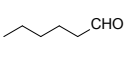
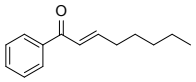
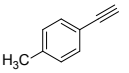
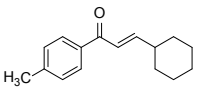
α,β-Unsaturated ketones have attracted increasing attention due to their numerous pharmacological properties such as anticancer activity, cytotoxicity, anti-inflammatory, analgesic, and antipyretic behavior.[16] Ion-exchange resins can make reaction processes simple, more convenient, economic, and environmentally benign which enable them to function as efficient catalysts for various transformations.[17-20] In continuation of our interest in the use of solid acid catalysts, herein, we report an efficient and metal-free method for the preparation of α,β-unsaturated ketones by means of coupling alkynes with aldehydes using a cheap and readily available cation exchange resin.



Scheme 6

Initially, we attempted the coupling of phenylacetylene **22a** with paraformaldehyde **23a** in the presence of Amberlyst-15®. The reaction was complete within 2.0 h and the product, 1-phenylprop-2-en-1-one **3a** was obtained in 86% yield (Scheme 6). Other terminal alkynes such as p-methylphenylacetylene and 4-phenylbut-1-yne were also coupled effectively with paraformaldehyde under similar conditions (Table **1**, entries b and c). These results provided the incentive for further study with various alkynes and aldehydes. Interestingly, several aldehydes such as cyclohexanecarboxaldehyde, n-hexanal, n-butyraldehyde, benzaldehyde, p-methoxy-benzaldehyde and thiophene-2-carboxaldehyde reacted well with alkynes under similar conditions to afford a wide range of conjugated enones (Table **1**, entries d–i). This method worked equally well with aliphatic, heterocyclic and aromatic aldehydes.

Table 1: Amberlyst-15® promoted coupling of aklynes with aldehydes

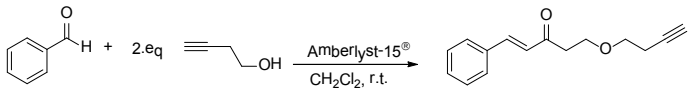
Entry	Alkyne **22**	Alkyne **23**	Product **24**	Time (h)	yield (%)
a				2.0	86
b				2.0	90
c				3.0	81
d				2.5	85
e				2.0	90
f				3.0	80
g				4.0	70
h				3.5	78
i				2.5	87

In summary, we have described a simple, convenient and metal-free protocol for the preparation of α,β-unsaturated ketones from alkynes and aldehydes using Amberlyst-15® as a novel promoter. In addition to its simplicity and mild reaction conditions, this method provides high yields of products in short reaction times with high selectivity. The use of an inexpensive and recyclable acid resin makes this method simple, convenient, and economically viable.

Section C: Synthesis of β-butynyloxy enones

The coupling of alkynes to aldehydes is an important transformation in organic synthesis. Although the addition of alkynylmetal reagents to aldehydes to produce propargyl alcohols has been extensively studied, [21-22] the reaction between alkynes and aldehydes to generate, α,β-unsaturated ketones has received less attention.[23] Herein, we report a novel and efficient protocol for the synthesis of β-butynyloxy enones from the 2:1 coupling of a homopropargyl alcohol and aldehydes using Amberlyst-15® as an inexpensive and recyclable heterogeneous solid acid catalyst. Initially, we attempted the coupling of benzaldehyde **25a** with 3-butyn-1-ol **26** in the presence of an acid resin. The reaction went to

completion within 2.5 h and the product, 5-(3-butynyloxy)-1-phenyl-(E)-1-penten-3-one **27a** was obtained in 86% yield (Scheme **7**).

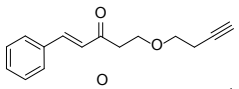
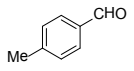
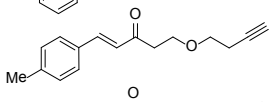
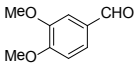
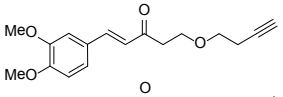
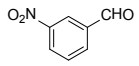
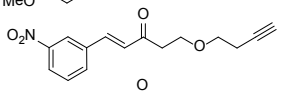
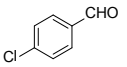
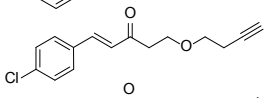
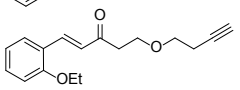
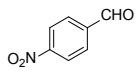
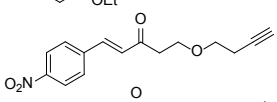
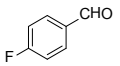
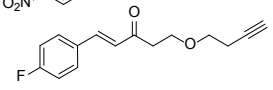
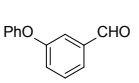
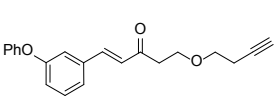
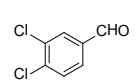
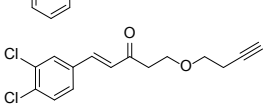


25a **26** **27a**

Scheme 7

Encouraged by the results obtained with benzaldehyde and 3-butyn-1-ol, we turned our attention to substituted aldehydes. Interestingly, a large number of substituted benzaldehydes such as the p-methyl-, 3,4-dichloro-, p-fluoro-,p-chloro-, o-ethoxy-, m-nitro-, 3,4-dimethoxy-, and m-phenoxy-derivatives reacted efficiently with 3-butyn-1-ol under similar conditions to afford a wide range of conjugated enones (entries b–j, Table **2**). This method is equally effective for both electron-rich as well as electron-deficient aromatic aldehydes. Sterically hindered 2-naphthaldehyde also gave the corresponding enone in 85% yield. In all cases, the reactions proceeded efficiently in high yields at ambient temperature under mild conditions.

Table 2: Synthesis of α,β-unsaturated ketones from aldehydes and homopropargyl alchol

Entry	Aldehyde **1**	Product **3**	Time (h)	Yield(%)
a			3.0	86
b			2.5	82
c			4.5	75
d			3.5	82
e			3.5	87
f			5.0	79
g			3.0	85
h			4.0	81
i			4.0	80
j			3.5	90

In summary, we have developed a novel and efficient approach for the preparation of β-butynyloxy enones through the 2:1 coupling of homopropargyl alcohol and aldehydes using Amberlyst-15® as a heterogeneous solid acid. The use of an inexpensive and recyclable acid resin makes this method simple, convenient and economically viable.

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Thesis Details

The thesis is the result of my Ph.D project carried out under the guidance of Dr. J. S. Yadav, F.N.A in Department of Organic chemistry at the Indian Institute of Chemical Technology (IICT), Hyderabad, India.