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Lewis acid catalyzed Nazarov type cyclization for the synthesis of a substituted indane framework: total synthesis of (±)-mutisianthol†

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A new synthetic route has been developed for the synthesis of a substituted indane derivative using Lewis acid catalyzed modified Nazarov type cyclization, which was further applied in the total synthesis of mutisianthol and *epi*-mutisianthol in a nine step longest linear sequence.

The indane motif is an important cyclic component present in many natural products and drug candidates possessing interesting biological activities (Fig. 1).[1] It is also used as functional materials[2] and ligands for transition metal complexes, which are widely utilized in catalytic reactions such as catalytic olefin polymerization.[3]

In 1979, Bohlmann *et al.* reported the isolation of a phenolic sesquiterpene mutisianthol **1** from the roots of *Mutisia homoeantha*.[4] Interestingly, a diastereomer of mutisianthol **1**, jungianol **2** was isolated from *Jungia malvaefolia* by the same group.[5] Jungianol and mutisianthol are plausibly derived in nature from an α-curcumene type precursor by intramolecular *ortho* and *para* alkylation respectively. The structure and stereochemical assignment of these natural products were made on the basis of spectroscopy data. Initially the *cis* relationship was assigned for the two side chains on the five membered rings in mutisianthol **1** and jungianol **2** by the isolation group. Later Ho *et al.* revised the relative stereochemistry of two side chains to *trans* by synthesizing both *cis* and *trans* isomers **6** and **7** starting from the indanone derivative.[6] Later Silva *et al.* also achieved the enantioselective synthesis of mutisianthol **1** using asymmetric hydrogenation and thalium mediated ring contraction of the tetraline derivative.[7]

Recently, we have reported the total synthesis of jungianol **2** using Lewis acid catalyzed Prins type cyclization.[8] So far only two syntheses of each natural product have been reported in the literature. Herein we report a concise total synthesis of mutisianthol **1** using modified Nazarov type cyclization.[9]

It was envisaged that mutisianthol **1** could be prepared from ester **8** by functional group manipulations. Ester **8** in turn could be generated from compound **9** by the Friedel–Crafts type reaction in Michael fashion. Compound **9** could be prepared from **10** using the five step protocol (Scheme 1).

To quickly check our strategy, we carried out the model studies starting from 3-methoxy acetophenone **11**. To begin with, the Wittig–Horner reaction of 3-methoxy acetophenone **11** afforded α,β-unsaturated ester **12** in 80% yield. The sequential reduction of the double bond and the ester moiety generated alcohol **14** *via* **13**. Oxidation of alcohol **14** using IBX in EtOAc under reflux conditions generated aldehyde **15** in 94% yield. The Wittig reaction of aldehyde **15** using Ph_3PCHCO_2Me afforded the α,β-unsaturated ester **16** in 93% yield (Scheme 2).

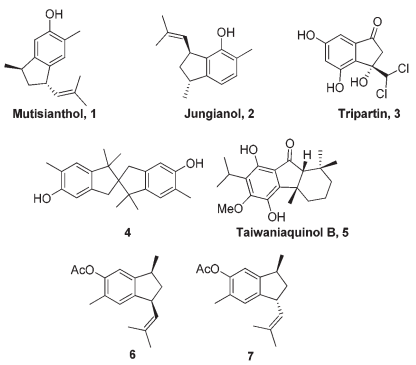
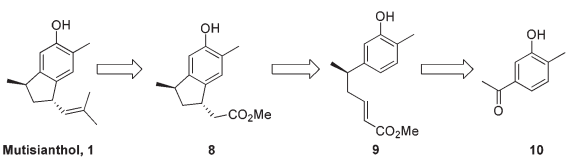


Fig. 1 Biologically active indane natural products and their analogues.



Scheme 1 Retrosynthetic analysis of mutisianthol **1**.

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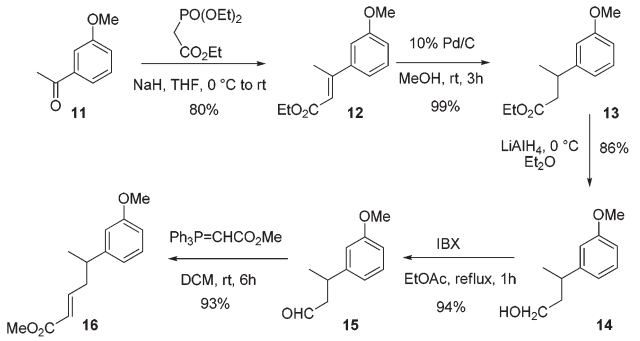
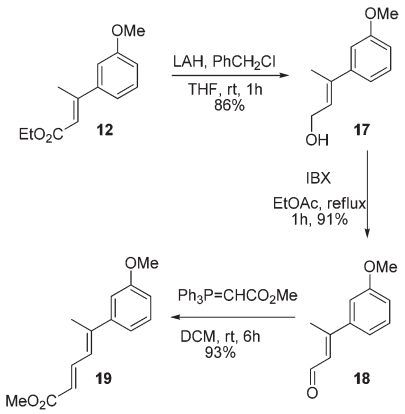


Scheme 2 Preparation of α,β-unsaturated ester **16**.

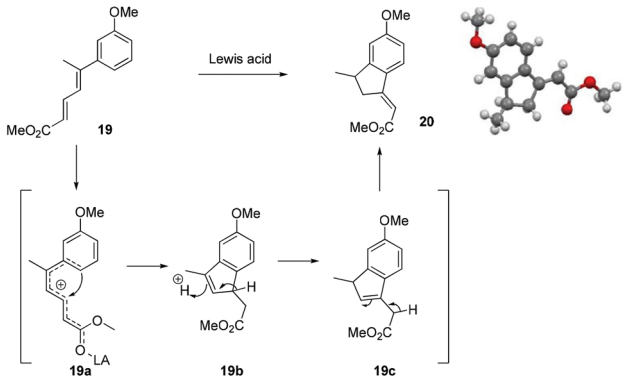


Scheme 3 Synthesis of diene ester **19**.

Having the key precursor **16** in hand, we next turned our attention towards the key Friedel–Crafts reaction in Michael fashion. To our disappointment treatment of compound **16** with different Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, $TiCl_4$, $Cu(OTf)_2$, $BiCl_3$ under various reaction conditions failed to generate the desired product and in most cases we recovered the starting material.

At this stage we also became interested to check the outcome of the reaction of diene ester **19** with Lewis acid. It was contemplated that diene ester **19** on treatment with Lewis acid might generate a Nazarov type cationic intermediate **19a** which on cyclization could afford the indane derivative **20**.[9] Compound **19** was prepared from the earlier intermediate **12** by using alane reduction, oxidation and the Wittig reaction sequence (Scheme 3).

To our delight treatment of diene ester **19** with $BF_3{\cdot}OEt_2$ afforded the indane derivative **20** in 24% yield by Nazarov type cyclization followed by double isomerisation of the olefin to a more stable position between the ester group and the phenyl ring. After screening different Lewis acids, it was found that $TiCl_4$ in DCM was the best reagent for this cyclization, generating the indane derivative **20** in 60% yield (Scheme 4, Table 1). The structure and stereochemistry of the double bond of compound **20** was unambiguously established by single crystal X-ray analysis.[10]



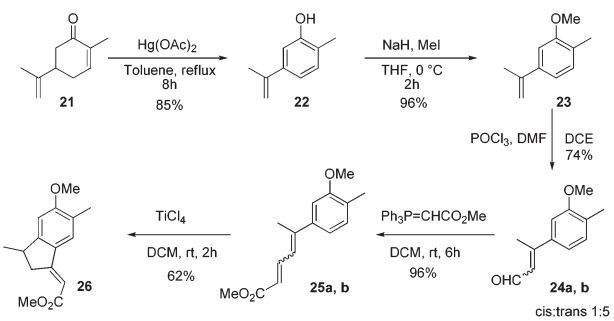
Scheme 4 Modified Nazarov type cyclization.

Table 1 Optimization of the reaction conditions[a]

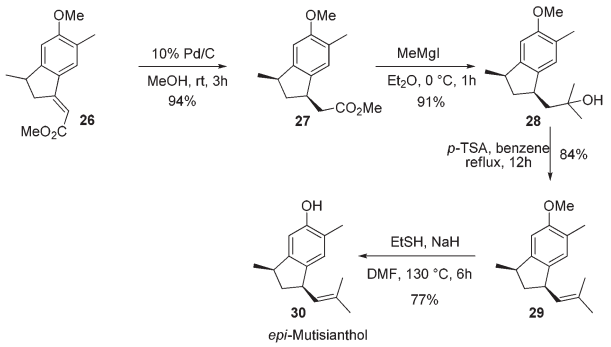
Entry	Catalyst	Time	Solvent	Yield (%)
1	*p*-TSA	24 h	DCM	NR
2	$Bi(OTf)_3$	24 h	DCM	NR
3	$BiCl_3$	24 h	DCM	NR
4	$InBr_3$	24 h	DCM	NR
5	TFA	24 h	DCM	NR
6	$AlCl_3$	24 h	DCM	Trace
7	$BF_3{\cdot}OEt_2$	10 h	DCM	24
8	$FeCl_3$	2 h	DCM	45
9	TfOH	2 h	DCM	54
10	$TiCl_4$	2 h	DCM	60

[a] Reaction conditions: **19** (0.2 mmol), catalyst (0.2 mmol), solvent (3 ml).

After establishing the reaction conditions, we next targeted the total synthesis of mutisianthol **1**. The suitably substituted diene ester **25** was prepared from the known compound **22**.[11] The Vilsmeier–Haack reaction of compound **23** using $POCl_3$/DMF generated α,β-unsaturated aldehydes **24a,b** as a 1 : 5 mixture of *cis* and *trans* isomers,[12] which was carefully separated by silica gel column chromatography. An independent Wittig reaction of aldehydes **24a,b** using Ph_3PCHCO_2Me afforded the α,β-unsaturated esters **25a,b**. Both *cis* and *trans* isomers on independent treatment with $TiCl_4$ in DCM afforded the indane derivative **26** in 62% yield. Also the mixture of isomers on treatment with $TiCl_4$ in DCM at RT generated compound **26** in 62% yield (Scheme 5). The above



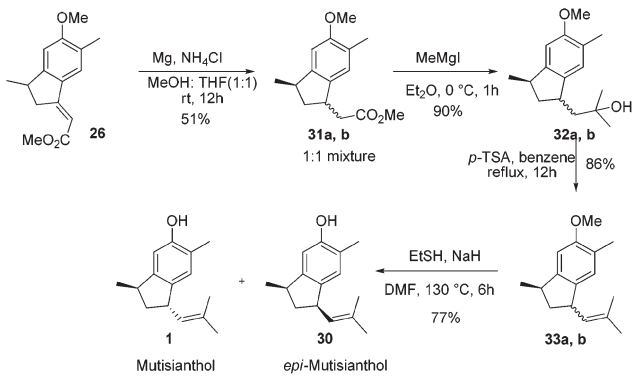
Scheme 5 Preparation of α,β-unsaturated ester **26**.



Scheme 6 Synthesis of *epi*-mutisianthol.

observation shows that generation of a mixture of double bond isomers in the Vilsmeier–Haack reaction is inconsequential for the Nazarov type cyclization.

After having the key indane derivative **26** in hand, our next target was stereoselective reduction of the double bond to generate the *trans* isomer with respect to methyl group and functional group manipulations of the ester group for the generation of an isobutene side chain. Hydrogenation of the double bond using 10% Pd/C exclusively generated the *cis* isomer **27** in 94% yield. Stereochemistry of the compound **27** was further confirmed by converting it into *epi*-mutisianthol **30.** Thus, treatment of ester **27** with excess of MeMgI generated the tertiary alcohol **28** which under *p*-TSA conditions afforded the dehydrated product **29.** Deprotection of methyl ether under basic conditions afforded *epi*-mutisianthol **30** in 77% yield (Scheme 6).[7] For the stereo selective reduction of the double bond to generate the *trans* isomer with respect to the methyl group, we have tried different reduction conditions, in which, refluxing with $Cr(CO)_6$ under dioxane and Mg–$ZnCl_2$ conditions failed to generate the desired product and in both cases the starting material was recovered. Compound **26** with Zn–KOH in refluxing EtOH and also with $NaCNBH_3$ in TFA furnished a complex reaction mixture. Surprisingly, the Birch reduction protocol furnished exclusively the *cis* isomer. The reaction of unsaturated ester **26** with magnesium and NH_4Cl in 1 : 1 mixture of methanol and THF yielded 1 : 1 inseparable mixture of *cis* and *trans* esters **31a,b** in 51% yield. The addition of excess methyl Grignard reagent to esters **31a,b** generated the mixture of tertiary alcohols **32a,b** in 90% yield, which on dehydration using *p*-TSA in refluxing benzene afforded compounds **33a,b** in 86% yield. Deprotection of methyl ether under basic conditions using ethane thiol and sodium hydride in DMF generated the 1 : 1 mixture of mutisianthol **1** and *epi*-mutisianthol **30** in 77% combined yield (Scheme 7).[7]



Scheme 7 Synthesis of mutisianthol and *epi*-mutisianthol.

Separation of mutisianthol **1** and *epi*-mutisianthol **30** was done by careful silica gel column chromatography. The spectral data of compound **1** (^1H, ^{13}C, IR, HRMS) were identical to the natural mutisianthol.

Conclusions

In conclusion, we have developed a Lewis acid mediated Nazarov type cyclization for the construction of a substituted indane, which was further applied in the concise total synthesis of natural product mutisianthol **1** in 9 steps with 5.5% overall yield from carvone and *epi*-mutisianthol **30** in 9 steps with 19.9% overall yield.

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