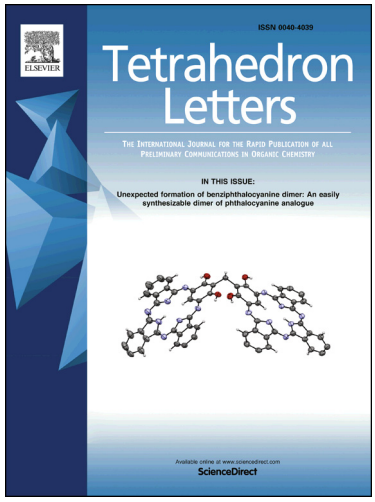

Formal total synthesis of stigmatellin A

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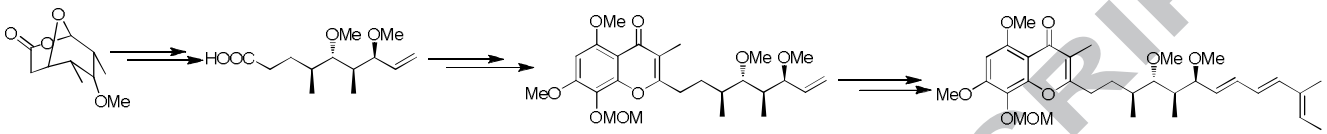

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Formal total synthesis of stigmatellin A

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ABSTRACT

An efficient and stereoselective approach for the formal total synthesis of Stigmatellin A has been described. The key steps involved in this synthesis are desymmetrization of the bicyclic olefin to introduce two methyl and two hydroxyl chiral centers, Friedel Crafts acylation, regioselective demethylation, Baker-Venkataraman rearrangement and Grubbs cross metathesis.

Stigmatellin A and B are two novel antibiotics, which were isolated from the gliding bacterium *Stigmatella aurantiaca* .[1] They are powerful inhibitors of electron transport in chloroplasts and mitochondria.[2] The absolute configuration of Stigmatellin A was confirmed as (*S,S,S,S*) by chemical correlation.[3] The salient features of this stigmatellin A include the presence of chromone system, four stereogenic centers and conjugated triene. Due to its fascinating structural features and inherent antibiotic behavior, there reports are on its total synthesis.[4,5,6]

Following our interest on the total synthesis of biologically active polyketide natural products by adopting desymmetrization strategy.[7,8] We herein describe the formal total synthesis of stigmatellin A .

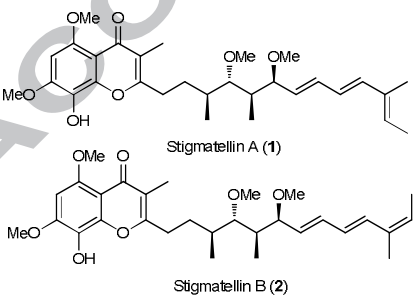
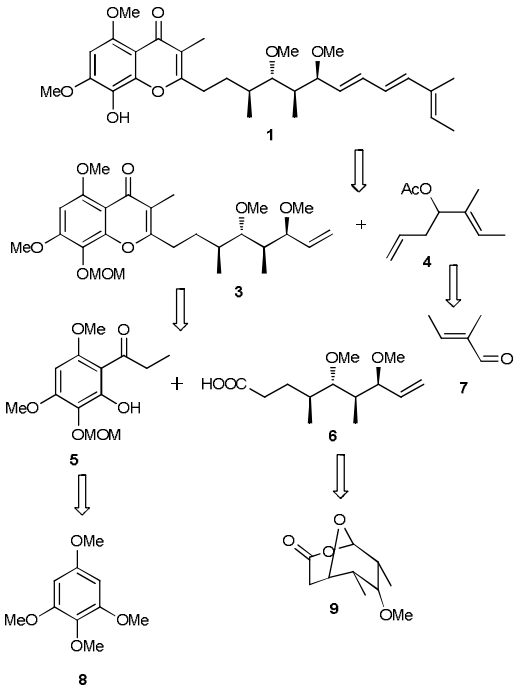
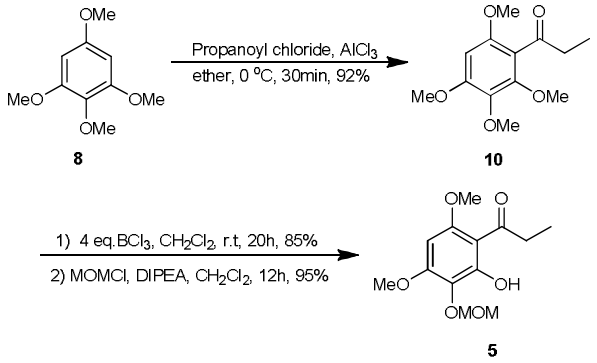


Fig. 1. Structures of stigmatellin A(**1**) and B(**2**).

Retrosynthetically, stigmatellin A (Scheme 1) can be cleaved into three fragments, i.e aromatic fragment **5**, acid fragment **6** (chiral) and dienyl acetate **4**. Aromatic part **5** was proposed to be synthesized from tetramethoxy benzene *via* Friedel Crafts acylation and regioselective demethylation. The carboxylic acid moiety **6** could be obtained from a known bicyclic lactone **9**. Chromone system **3** was proposed to be synthesized *via* the esterfication of aromatic hydroxyl group **5** with acid fragment **6** followed by Baker-Venkataraman rearrangement. The fragment **4** could be obtained from a commercially available tiglic aldehyde **7** *via* the Barbier allylation. Stigmatellin A(1) could be synthesized by the coupling of fragments **3** and **4** through a cross-metathesis followed by elimination reaction.



Scheme 1. Retrosynthesis of stigmatellin A

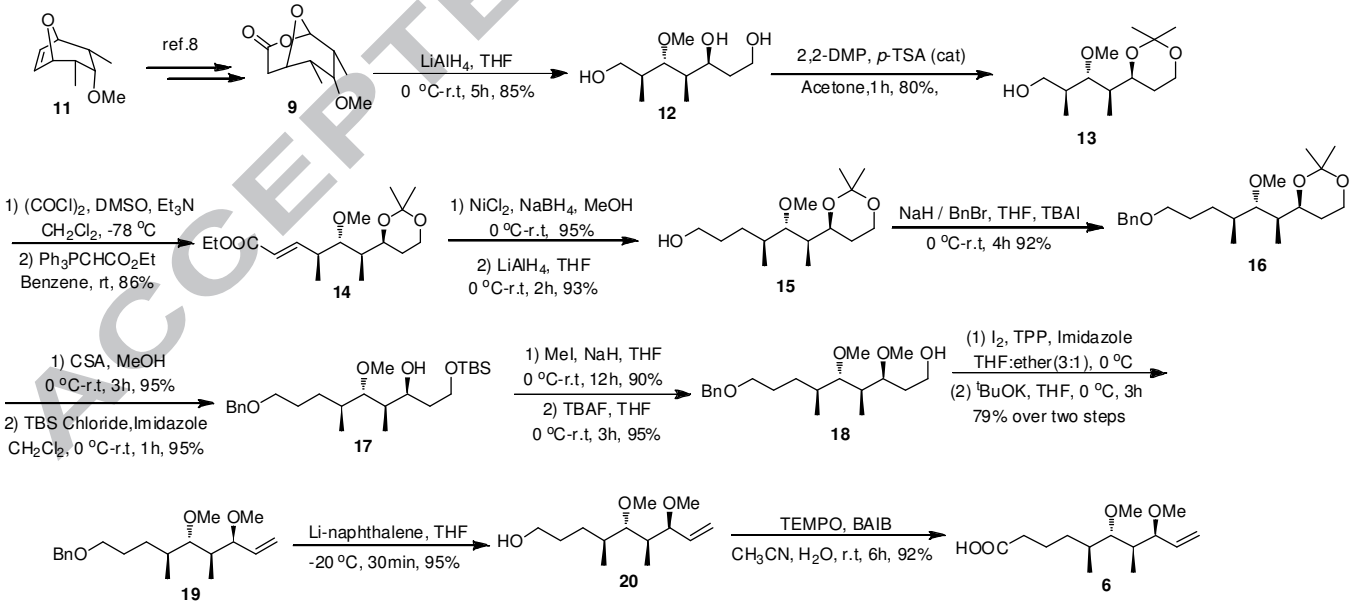


Scheme 2. Synthesis of aromatic fragment **5**

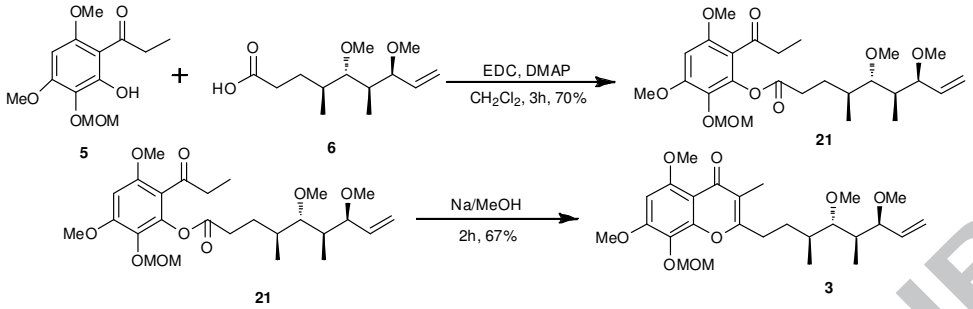
Accordingly, the synthesis of aromatic fragment **5** began from a readily available tetramethoxy benzene **8**. The Friedel-Crafts acylation of tetramethoxy benzene **8** with propanoyl chloride in the presence $AlCl_3$ afforded the ketone **10**.[9] Regioselective deprotection of methyl groups from compound **10** using BCl_3 afforded the dihydroxy compound.[10] The chemoselective protection of one of the hydroxyl groups using MOM chloride, DIPEA in CH_2Cl_2 afforded the aromatic fragment **5** in 80% yield over two steps (Scheme 2). The analytical data of **5** was found to be identical with the data reported in literature.[4]

The synthesis of acid fragment **6** began with the reductive cleavage of bicyclic lactone **9**. The key intermediate **9** was synthesized by desymmetrization of bicyclic olefin **11**.[8] Thus the treatment of **9** with $LiAlH_4$ in dry THF afforded the triol **12** in 85% yield,[7e] which was then protected as its acetonide using 2,2-DMP, *p*-TSA in CH_2Cl_2 to afford the compound **13** in 80% yield.[11] Swern oxidation[12] of the primary alcohol **13** followed by a two carbon Wittig reaction resulted in the formation of α,β-unsaturated ester **14** in 86% yield. Reduction of the double bond from compound **14** using $NaBH_4$ and $NiCl_2$ in MeOH[13] afforded the saturated ester, which was further reduced with $LiAlH_4$ in THF to give the alcohol **15** in 87% yield. The free hydroxyl group of **15** was protected as its benzyl ether using benzyl bromide and NaH in presence of a phase transfer catalyst (TBAI) in THF to afford the compound **16** in 92% yield. Deprotection of the acetonide group **16** using C.S.A in MeOH afforded the diol. The selective protection of primary hydroxyl group with TBDMSCl using imidazole in CH_2Cl_2 the TBS ether **17** in 90% yields. Methylation of the free hydroxyl group with MeI using NaH in THF afforded the methyl ether. A subsequent desilylation using TBAF in THF gave the alcohol **18** in 90% yields. The primary alcohol **18** was then converted into iodo derivative by a standard protocol[14] involving I_2, TPP and imidazole, which up on treatment with *t*-BuOK in dry THF at 0 °C gave the terminal olefin **19** in 79% yield. Debenzylation of compound **19** under radical conditions using Li-naphthalenide in anhydrous THF at 30 °C gave the alcohol **20** in 95% yield.[15] A subsequent oxidation of the hydroxyl group of **20** using TEMPO/BAIB in a mixture of CH_3CN and water gave the acid **6** in 92% yield (Scheme 3).[16]

The coupling of acid **6** with aromatic hydroxyl group **5** using DCC, DMAP in CH_2Cl_2 afforded the ester **21** along with the water insoluble dicyclohexyl urea.[17] In order to facilitate the ease of isolation of the product, the combination of EDC and DMAP was used to afford the pure ester **21** in 70% yield. The ester **21** was then converted into chromone **3** in 67% yield by means Baker-Venkataraman rearrangement[4] using Na in dry methanol under reflux for 2h (Scheme 4).

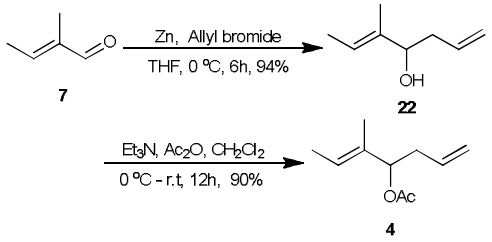


Scheme 3. Synthesis of acid fragment **6**



Scheme 4. Synthesis of chromone fragment **3**

Synthesis of dienyl acetate fragment **4** began from a readily available tiglic aldehyde **7**. Allylation of the tiglic aldehyde **7** with allyl bromide in the presence of zinc and aq. NH_4Cl in THF afforded the racemic alcohol **22** in 94% yields. Protection free hydroxyl group as its acetyl ester using Ac_2O, Et_3N in the presence DMAP gave the compound **4** in 90% yield (Scheme 5).



Scheme 5. Synthesis of dienyl acetate fragment **4**

In order to couple compound **4** and **3,** we adopted the olefin cross-metathesis strategy using Grubbs catalyst[18]. Initially, we attempted the reaction in the presence of free hydroxyl group in fragment **4** and fragment **3** using Grubbs 2nd generation catalyst in the formation **24** in 40% yield. Next we performed the reaction with protected hydroxyl group as acetate in fragment **4** and fragment **3** using Grubbs 2nd generation catalyst leading to exclusive formation of *trans* product **25** in high 92% yield. Hydrolysis of the acetate in compound **25** using K_2CO_3 in MeOH resulted secondary alcohol **24** in 80% yield. Mesylation of the secondary hydroxyl group in compound **24** using MsCl, TEA in CH_2Cl_2 followed by elimination using NaI, DBU in DME gave the triene **26** in 57% yield (Scheme 6).

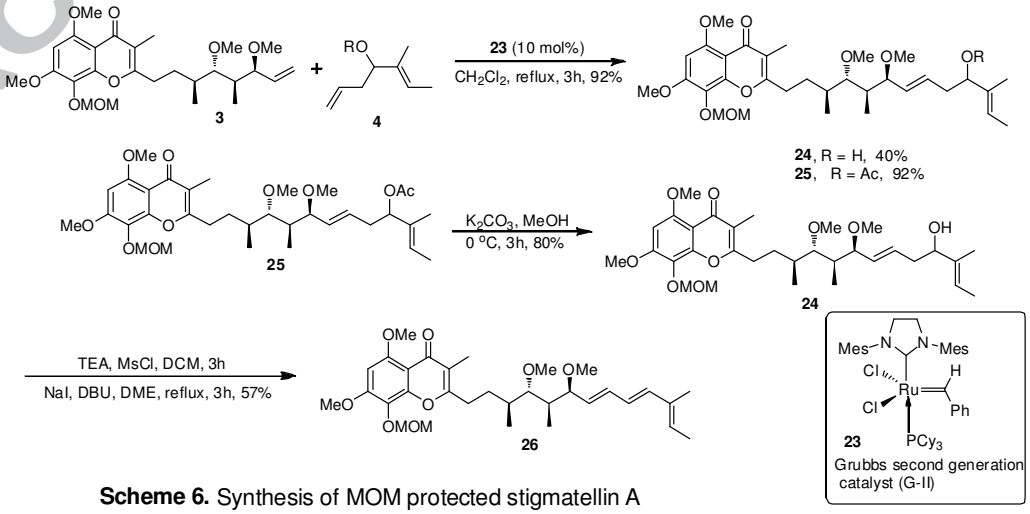
To the total synthesis of stigmatellin A, we attempted the deprotection of MOM ether of compound **26** using various reagents under different conditions as shown in Table **1**. Unfortunately, none of them gave the desired product

Table 1: Deprotection of MOM ether in compound **26** under different conditions

Sl.No	Reaction condition	Results
1	5N HCl in CH_2Cl_2, 30min	Complex of mixture of compounds
2	2 N HCl in THF, 3h	Complex of mixture of compounds
3	$TiCl_4$ in CH_2Cl_2 , 0 °C , 15min	Complex of mixture of compounds
4	TMSCl, NaI in CH_2Cl_2:CH_3CN (1:1)	Complex of mixture of compounds
5	Montmorillonite K 10 Clay in CH_2Cl_2, r.t, 1h	No reaction
6	Montmorillonite K 10 Clay in CH_2Cl_2, 50 °C, 1h	Complex of mixture of compounds
7	$CeCl_3$, $7H_2O$, reflux, 1h	No reaction
8	$CeCl_3.7H_2O$, reflux, 3h	Complex of mixture of compounds

Conclusion

In conclusion, the stereoselective formal total synthesis of stigmatellin A has been accomplished through a desymmetrization strategy. The required chiral centers were established through Brown's asymmetric hydroboration. Baker-Venkataraman rearrangement has been successfully adopted to construct the chromone ring system. Grubbs cross metathesis has been utilized to generate internal olefin in the target molecule. Our approach is simple and very useful to prepare key fragments of stigmatellin A.



Scheme 6. Synthesis of MOM protected stigmatellin A

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Supplementary Material

Supplementary data associated with this article can be found, in the online version at

Highlights

- It describes the formal total synthesis of stigmatellin A
- Friedel-Crafts acylation was achieved using Lewis acid.
- Chromone system was constructed by Baker-Venkataraman rearrangement.
- Desymmetrization has been adapted to establish chiral centers.
- Side chain was extended by Grubbs-cross metathesis.