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Synthesis of natural product inulavosin via $Ga(OTf)_3$-Catalyzed Hetero Diels–Alder Dimerization of salicyl alcohol derivative

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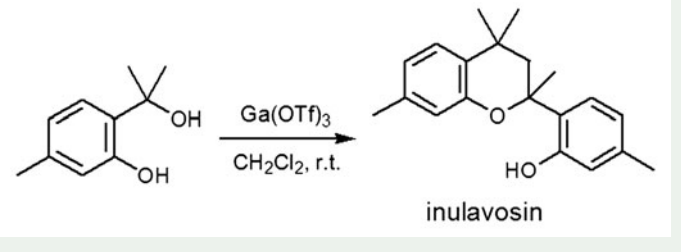
ABSTRACT

Inulavosin, a natural melanogenesis inhibitor, has been synthesized smoothly from readily available and inexpensive starting materials by using a $Ga(OTf)_3$-catalyzed room temperature hetero Diels–Alder dimerization of salicyl alcohol derivative and a regioselective phenol monobromination as the key steps.



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1. Introduction

Inulavosin (**1**, Figure 1), a dimer of thymol (**2**), was isolated from the roots of *Inula nervosa* (Compositae) in 1995 (Yoshida et al. 1995). This racemic natural product displays a range of biological activities such as antibacterial (Yoshida et al. 1995), piscicidal (Yoshida et al. 1995), antifungal (Kim et al. 2017), and melanogenesis inhibitory properties (Fujita et al. 2009; Zhou et al. 2016). Inulavosin (**1**) is difficult to obtain in large quantities on account of its limited quantities from natural sources (Yoshida et al. 1995). To overcome this problem, development of an efficient strategy for the synthesis of this bioactive natural product becomes a high priority. To date, synthesis of inulavosin and its derivatives has attracted attention from the synthetic

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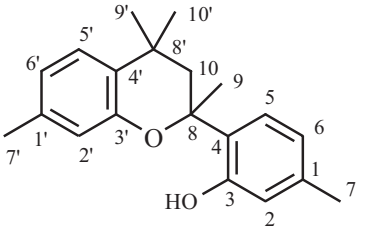
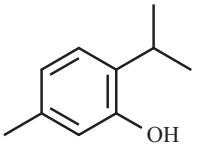
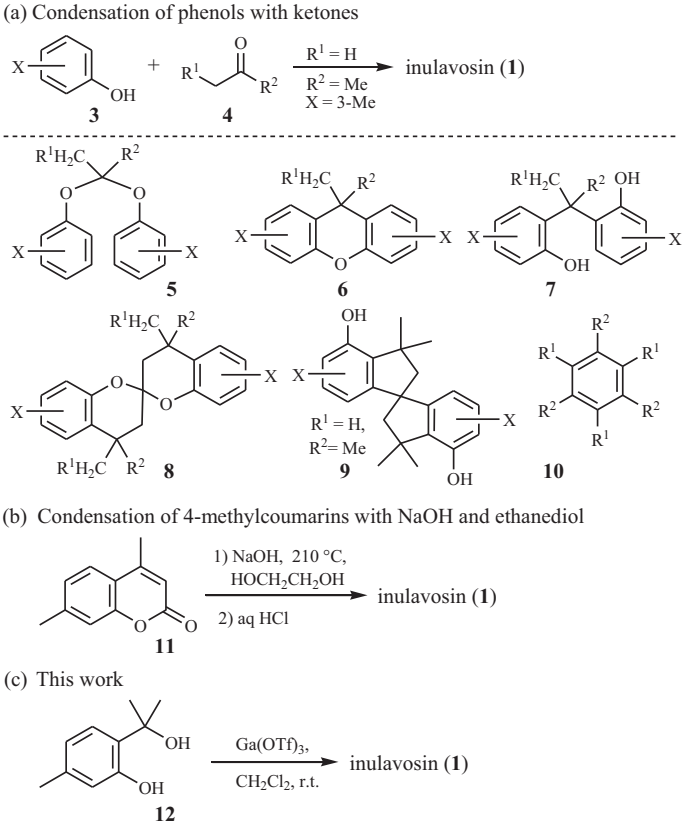


inulavosin (**1**)



thymol (**2**)

Figure 1. Inulavosin (**1**) and thymol (**2**).



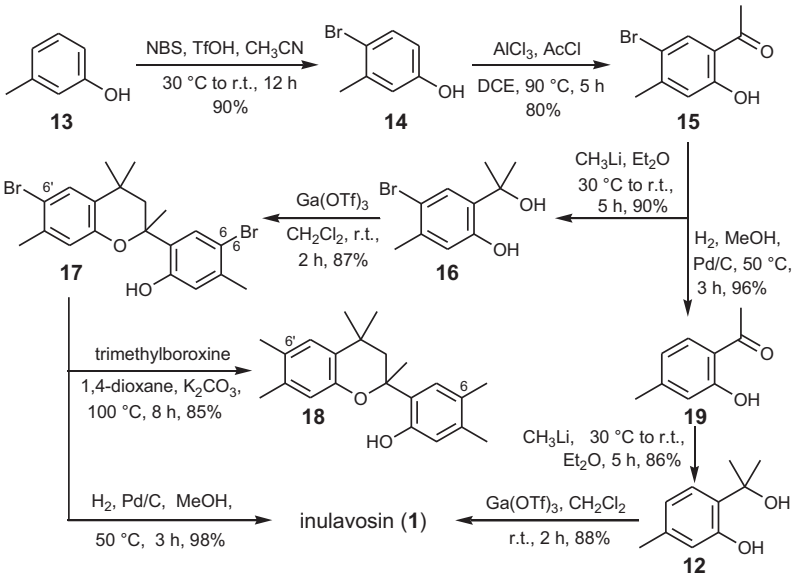
Scheme 1. Synthetic endeavours on inulavosin (**1**) and its derivatives.

community (Baker et al. 1951; Kamat et al. 1998; Livant et al. 1997; Menezes et al. 2011). The condensation of *m*-cresol and acetone in the presence of a protic acid, such as hydrochloric acid, seems to be one of the simplest methods for the synthesis inulavosin (Scheme 1a). This synthetic strategy, although has been described previously (Baker et al. 1951), might be problematic. Indeed, a highly complex mixture was obtained when *m*-cresol was condensed with acetone in the presence of various protic acids (HCl, H_2SO_4, *p*-TsOH, MsOH, etc). It is because that phenols (**3**) can react with alkyl ketones (**4**) in the presence of a protic acid to afford ketals (**5**, Causse 1892), xanthenes (**6**, Khosropour et al. 2005), 2,2-diphenylpropanes (**7**, Malhotra and Banerjee 1990),

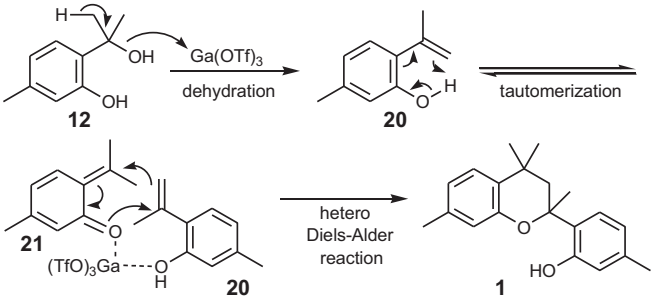
spirobichromans (**8**, Harada and Usui 1987), and 2,2′,3,3′-tetrahydro-1,1′-spirobis-indenes (**9**, Scheme 1a, Xue et al. 2012). Alkyl ketones (**4**) can undergo cyclotrimerization in the presence of a protic acid to give 1,3,5-triarylbenzenes (**10**, Jing et al. 2005), which makes this endeavor more demanding (Scheme 1a). To circumvent this problem, Kamat developed a selective synthesis of inulavosin (**1**) by treatment of 4,7-dimethylcoumarin (**11**) with sodium hydroxide (NaOH) and ethanediol under harsh conditions (210 °C) and subsequent reaction with aqueous HCl (Scheme 1b, Kamat et al. 1998). In this context, herein we report a selective synthesis of inulavosin (**1**) from salicyl alcohol **12** under milder conditions, which could be used for the preparation of sufficient quantities of this natural product for biological and medical studies (Scheme 1c).

2. Results and discussion

As shown in Scheme 2, the synthesis of inulavosin (**1**) commenced with commercially available and inexpensive *m*-cresol (**13**). The high selectivity in the electrophilic aromatic monobromination of **13** was achieved by carefully controlling the reaction temperature. Reaction of **13** with NBS in acetonitrile (CH_3CN) in the presence of trifluoromethanesulfonic acid (TfOH) was performed at −30 °C and slowly warm up to room temperature, and then stirred at this temperature for 12 h to afford 4-bromophenol **14** in 90% yield. As a phenoxide anion usually tends to facilitate its *ortho* electrophilic aromatic bromination according to its average local ionization energy surfaces calculated by Brown and Cockroft (2013), TfOH was used to suppress the formation of the phenoxide anion, and thus obviate the *ortho* electrophilic aromatic bromination of **13**. Although a phenol usually tends to facilitate its *para* electrophilic aromatic substitution (Li et al. 2014), a higher reaction temperature would make more collisions effective, including the collisions at the position *ortho* to the phenolic hydroxyl group, and thereby result in a lower *para*-selectivity. Thus, the electrophilic aromatic bromination of **13** was performed at temperatures as low as possible, which made the collisions at the *ortho* position ineffective and thus increased the *para*-selectivity. Treatment of **14** with acetyl chloride (AcCl) in the presence of $AlCl_3$ in DCE at 90 °C for 5 h afforded acetophenone **15** in 80% yield, which was subjected to a nucleophilic addition reaction with methyllithium to provide salicyl alcohol **16** in 90% yield. The hetero Diels–Alder dimerization of **16** in DCE in the presence of diphenylphosphoric acid [$(PhO)_2P(O)OH$, 0.1 equiv.] at 100 °C gave **17** in 74% yield within 5 h. However, the reaction did not take place at a temperature less than 80 °C. After the optimization of reaction conditions by varying the catalysts [$(PhO)_2P(O)OH$, TFA, H_2SO_4, $BF_3 \cdot Et_2O$, LiCl, $MgCl_2$, $AlCl_3$, $FeCl_3$, $Cu(OTf)_2$, $Ga(OTf)_3$, $In(OTf)_3$, etc], the solvents (PhMe, CH_3CN, THF, Et_2O, CH_2Cl_2, hexane, DCE, etc] and the temperature (room temperature to 100 °C), the hetero Diels–Alder dimerization of **16** under mild reaction conditions has been achieved. Indeed, treatment of **16** in the presence of $Ga(OTf)_3$ at room temperature for 2 h gave 6,6′-dibromoinulavosin (**17**) in 87% yield. Coupling of **17** with trimethylboroxine afforded 6,6′-dimethylinulavosin (**18**, see Supporting Material for the synthesis of other inulavosin derivatives) in 85% yield, whereas reduction of **17** under the hydrogenolysis conditions afforded inulavosin (**1**) in 98% yield (Scheme 2). On the other hand, hydrogenolysis of **15** followed by reaction with methyllithium



Scheme 2. Synthesis of inulavosin (**1**) and its derivatives **17** and **18**. Reagents and conditions: NBS = N-bromosuccinimide. TfO = triflate. r.t. = room temperature. Ac = acetyl. DCE = 1,2-dichloroethane. Me = methyl.



Scheme 3. A possible reaction mechanism for the hetero Diels–Alder dimerization of salicyl alcohol **12**.

afforded salicyl alcohol derivative **12** in 83% overall yield, which underwent $Ga(OTf)_3$-catalyzed hetero Diels–Alder dimerization to give **1** in 88% yield (Scheme 2). The spectroscopic and spectrometric data (^{1}H NMR, ^{13}C NMR and HRMS) of the synthetic material are identical to those reported in the literature (Yoshida et al. 1995). The $Ga(OTf)_3$-catalyzed room temperature hetero Diels–Alder dimerization reaction facilitated this inulavosin synthesis under obviously milder conditions in comparison to Kamat inulavosin synthesis (room temperature versus 210 °C, Kamat et al. 1998). This inulavosin synthesis displays a higher chemoselectivity in comparison to Baker inulavosin synthesis (a sole product versus a complex mixture, Baker et al. 1951).

Although we are not able at this time to accurately explain the reaction pathways of the hetero Diels–Alder dimerization of salicyl alcohol **12**, a possible mechanism for this reaction is illustrated in Scheme 3. Dehydration of **12** in the presence of $Ga(OTf)_3$ generates allyl phenol **20**, which undergoes an enol-keto tautomerization to form

ortho-quinone methide **21** (Chiang and Kresge 2004; Das et al. 2014).[16] Finally, the hetero Diels–Alder reaction of **21** with **20** in the presence of $Ga(OTf)_3$ affords inulavosin (**1**) (Liang et al. 2010; Gharpure et al. 2013; Zhao et al. 2015; Allen et al. 2017).

3. Conclusions

In conclusion, we described a newly developed gallium(III) triflate-catalyzed room temperature hetero Diels–Alder dimerization of salicyl alcohols, which is employed to the practical syntheses of inulavosin and its derivatives. Further applications of this strategy for the synthesis of other natural products with related skeletons are in progress.

Disclosure statement

No potential conflict of interest was reported by the authors.

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