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A Negishi cross-coupling reaction enables the total synthesis of (+)-stachyflin

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ABSTRACT

We present a full account on the development of the total synthesis of the antiviral meroterpenoid (+)-stachyflin. The decalin subunit is rapidly accessed by an *exo*-selective Diels–Alder reaction, whereas the isonindolinone was synthesized *via* a highly efficient and practical *de novo* route starting from dimedone. A challenging sp^2–sp^3 Negishi cross-coupling reaction enabled construction of the crucial C15–C16 bond that connects the arene with the decalin subunit. For the final installation of the *cis*-decalin framework, a Lewis acid-catalyzed cyclization was applied.

1. Introduction

Polycyclic meroterpenoids possess high structural diversity, show diverse biological activities and belong to one of the most fascinating classes of natural products.[1] Stachyflin (**1**)[2], aureol (**2**)[3] and cyclosmenospongine (**3**)[4] are closely related members of this family that were isolated from fungi or marine sponges (Fig. 1A). Stachyflin (**1**) is the most biologically active representative of this class and shows nanomolar activity ($IC_{50} = 3$ nmol) against the influenza A virus.[2,5] In contrast to common therapeutics,[6] **1** binds to the glycoprotein hemagglutinin to prevent viral infection.[7] Due to its novel mode of action, **1** is a promising candidate for further pharmacological studies.[8] Apart from its biological activity, members of the aureol family (**1**–**3**) feature a tetracyclic benzo[*d*]xanthene core (ABCD), in which the decalin subunit (AB) is connected *via* a dihydropyran ring (C) to the arene (D). Additionally, stachyflin (**1**) bears a fifth stereogenic center at the C3 position and features an isoindolinone. This structural motif is also present in stachybotrylactam I (**4**)[9] and memnobotrin A (**5**)[10], otherwise it is rarely presented in natural products[11] (Fig. 1B). While the decalin subunit of stachyflin (**1**) is *cis*-oriented (highlighted in green), cyclosmenospongine (**3**) features a *trans*-fused decalin (highlighted in blue). Both *cis*- and *trans*-fused decalin subunits were also found in related tetracyclic meroterpenoids isolated from *Dysidea* sp. marine sponge. This includes cycloaurenone B (6)[12] and dysiherbol B (**7**)[13], which possess an indane-type core and exhibit high cytotoxic activity (Fig. 1C).

Since the first isolation of aureol (**2**) in 1980,[3] numerous elegant syntheses have been developed. For the construction of the C-ring, a cationic rearrangement has emerged as the most prominent strategy.[14] Typically, an epoxide or a double bond is activated by a Lewis- or Brønsted-acid, triggering a series of Wagner–Meerwein-shifts with the resulting final carbocation being trapped by a phenol. For the construction of the required cyclization precursor, a variety of approaches were investigated to link the aryl and decalin subunits (Scheme 1). In 1998, Mori and coworkers presented the first total synthesis of stachyflin (**1**).[15] The highlighted C–C bond was already present in acetal **9**, which underwent a Noyori aldol condensation with enol ether **8** to give benzylic alcohol **10**. Installing the isoindolinone und decalin subunit led to a racemic sample of the natural product **1**. This disconnection was further developed by Katoh to achieve the first enantioselective synthesis of **1** in a more convergent manner.[16] The groups of Katoh and

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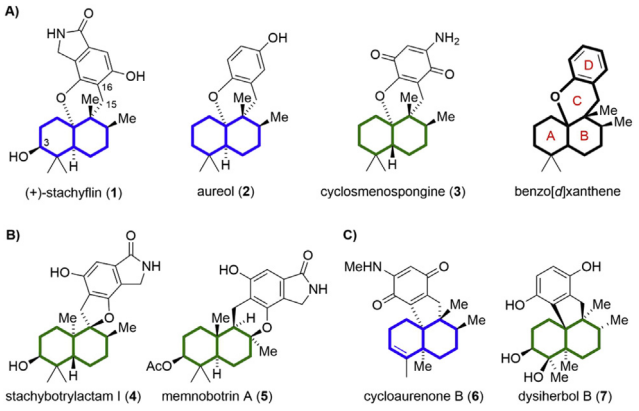
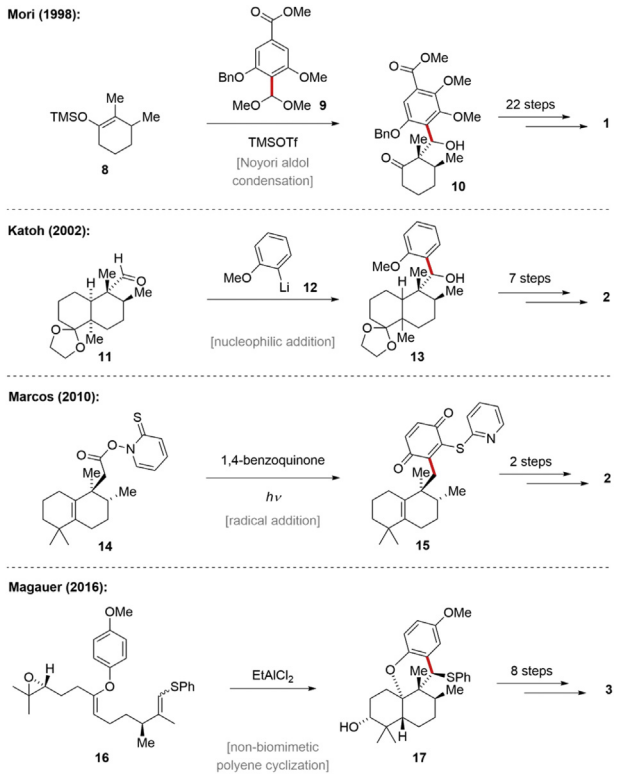


Fig. 1. A) Selected members of the aureol family. B) Isoindolinone-containing polycyclic meroterpenoids. C) *Cis*- and *trans*-fused decalin motifs in tetracyclic meroterpenoids isolated from *Dysidea* sp. marine sponge.

George also demonstrated a 1,2-addition as a C15–C16 bond disconnection strategy.[17] Herein, the metalated anisole **12** attacked aldehyde **11** to access benzylic alcohol **13**, which was further converted into aureol (**2**) in seven steps. This type of strategy was also used in a modular synthesis of several members of the aureol family in recent work by our group.[18] In 2010, the Marcos group reported the radical coupling of thiohydroxamic ester **14** and 1,4-benzoquinone.[19] Light-induced Barton decarboxylation led to a primary radical, which rapidly underwent a 1,4-addition to give quinone **15**. Aureol (**2**) was synthesized in two further steps. By utilizing more functionalized 1,4-benzoquinones, they were also able to synthesize cyclosmenospongine (**3**). Recently, a non-biomimetic polyene cyclization of precursor **16** was extensively investigated for the total synthesis of **3** in our laboratories.[20] In



Scheme 1. Reported strategies for the highlighted C–C bond formation.

contrast to all other strategies, which involve a late-stage dihydropyran formation by cationic cyclization, our strategy was based on a highly convergent synthesis that involves an early C–O bond formation in cyclization precursor **16**. In the course of the cyclization, the C15–C16 bond is generated *via* a formal hetero Diels–Alder reaction. Unfortunately, only the *trans*-fused decalin **17** was accessible by this method.[21] In order to address this limitation, we set out to develop a second generation strategy. Below we provide details about this strategy and describe the evolution of our total synthesis of (+)-stachyflin (**1**).

2. Results and discussion

From our retrosynthetic perspective and as illustrated in Scheme 2, we designed a convergent route to stachyflin (**1**). A well-precedented Lewis acid-catalyzed cyclization of **18** would provide the *cis*-decalin. For the construction of **18**, we envisioned a sterically demanding sp^2–sp^3 cross-coupling reaction to link both building blocks **19** and **20** at C16 and C15. The aromatic subunit of isoindolinone **19** could be accessed *via* an Alder–Rickert reaction of alkyne **21** and dimedone (**22**). Guided by a previously developed *exo*-selective Diels–Alder cycloaddition,[22] we envisioned this transformation to be adapted for the construction of the dehydrodecalin **20** starting from diene **23** and dienophile **24**.

2.1. Isoindolinone synthesis

Inspired by the work of Silva,[23] we envisioned the development of a new synthetic entry to isoindolines. For this purpose, dimedone (**22**) was converted to the highly reactive bis-siloxy diene, which underwent an Alder–Rickert cycloaddition with dimethyl acetylendicarboxylate (DMAD) to form the bicyclic intermediate **25** (Scheme 3A).[24] After aromatization through thermal extrusion of isobutene, the obtained resorcinol derivative **26** was regioselectively methylated to give **27**.[25] Exposure of **27** to trimethylaluminum (Me_3Al) and benzylamine ($BnNH_2$) afforded the corresponding *N*,*N*-dibenzylphthalimide, which was exposed to high vacuum at elevated temperature (1 mbar, 140 °C) to give phthalimide **28** in excellent yield (94%).[26] In the final step, the regioselective reduction of **28** to provide isoindolinone **29** was investigated. First attempts using lithium borohydride ($LiBH_4$) as reductant led to partial reduction to the undesired regioisomeric alcohol **30**. The use of $LiBH_4$ in the presence of trimethylsilyl chloride (TMSCl)[27] mostly resulted in overreduction to the isoindoline **31**. Eventually, by using catalytic amounts of sodium borohydride ($NaBH_4$) in the presence of borane regioselective reduction to alcohol **32** and isoindolinone **29** was observed. Extensive optimization of the stochiometry[28] and the use of a sealed tube to avoid loss of gaseous borane led to the formation of **29** in good yield (67%).[29] Based on previous mechanistic studies by Moriwake,[30] we propose the mechanism for the regioselective reduction of phthalimide **28** illustrated in Scheme 3B. Upon addition of borane and hydrogen generation, **33** is formed. Reduction of **33** should be assisted by intramolecular complexation to give borinate **34**. Regeneration of $NaBH_4$ through hydride transfer of borane affords **35**. Following second hydride transfer reaction led to **36** that is hydrolysed upon acidic work-up to give **29**. Our developed synthesis of **29** is high yielding and represents a convenient route to access isoindolinones featuring a complex substitution pattern. The six-steps synthesis includes only two silica gel chromatography purifications and is practical on large scale.

2.2. Dehydrodecalin building block synthesis

For the synthesis of the decalin ring system, we investigated an