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Synthesis of C14–C21 acid fragments of cytochalasin Z₈ via *anti*-selective aldol condensation and *B*-alkyl Suzuki–Miyaura cross-coupling†

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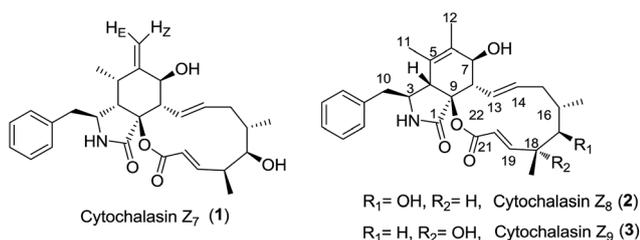
An efficient synthesis of the C14–C21 acid fragment of cytochalasin Z₈ was accomplished in 10 steps with 14% overall yield. Boron-mediated *anti*-selective aldol condensation and Pd(OAc)₂–Aphos–Y-catalysed *B*-alkyl Suzuki–Miyaura cross-coupling were employed to construct the requisite C17 and C18 stereogenic centres and alkene subunit.

Cytochalasins are secondary fungal metabolites with a wide range of biological activities that target cytoskeletal processes.¹ Cytochalasins Z₇–Z₉ (1–3, Chart 1) were isolated from the marine-derived fungus *Spicaria elegans*, and their structures and absolute configurations were established by Zhu *et al.*² Cytochalasin Z₈ (2, Chart 1) is structurally related to cytochalasins Z₇ and Z₉, and features highly substituted hydroisoindol-1-one fused with a 12-membered macrolactone ring at the C-8 and C-9 positions. Cytochalasin Z₈ has been reported to exert cytotoxicity against P388 and A-549 cell lines with IC₅₀ values of 56 and 21 μM, respectively, and therefore has significant potential in cell biology and medicine. A number of laboratories have worked towards total synthesis of the cytochalasin family and developed linear³ or convergent⁴ strategies for their total synthesis. Total synthesis of cytochalasin congeners was accomplished by the laboratories of Stork,^{3a,4a} Thomas,^{3b,3c,3e,3f}

Trost,^{4d} Vedejs (zygosporin E),^{4b,4c,4e} Myers,⁵ Liu and Tang (periconiasins A–E)⁶ and Nay (periconiasin G).⁷ To the best of our knowledge, total synthesis of cytochalasin with a 12-membered macrocyclic ring has not been reported. The intriguing molecular architecture and potent biological activity of cytochalasin Z₈ prompted us to pursue its total synthesis and render it to be readily available for biological investigations.

The retrosynthetic strategy is depicted in Scheme 1. Intramolecular ring-closing metathesis (RCM) strategy⁸ which is a promising tool for constructing macrolactone is often used for synthesising macrolides.⁹ We envisioned an RCM reaction at C13 and C14 positions and an esterification for assembling a 12-membered macrolactone. Thus, acid fragment 4 was required for the total synthesis of 2. Our strategy was flexible and it allowed rapid access to structural analogues. In this study, we report the synthesis of C14–C21 acid fragment 4 via a highly *anti*-selective aldol condensation¹⁰ of aldehyde 6 with Abiko's chiral norephedrine-derived propionate (1*R*,2*S*)-7 (ref. 11) and *B*-alkyl Suzuki–Miyaura cross-coupling¹² of chiral alkyl iodide 5 with (*Z*)-1-bromoprop-1-ene.

Our first task was to construct C16–C18 *syn-anti* stereotriad.¹³ The aldehyde functionality in 6 was expected to undergo an *anti*-selective aldol reaction with the (*E*)-boron enolate generated from Abiko's chiral propionate 7 for installing C17–C18 *anti* stereochemistry according to our synthetic strategy in Scheme 1. We initially prepared crude aldehyde 6 from commercially available (*S*)-methyl 3-hydroxy-2-methyl propionate (Roche ester)¹⁴ by tosylation and partial ester reduction¹⁵ (Scheme 2). The unstable crude aldehyde 6, without column chromatographic purification, was immediately used with the (*E*)-boron enolate derived from 7 for *anti*-selective aldol reaction to secure the *syn/anti* stereotriad in 8. The key intermediate 8 was prepared in high diastereoselectivity of 98 : 2 (determined by proton nuclear magnetic resonance spectroscopy) and in the desired absolute configuration as predicted by the chiral

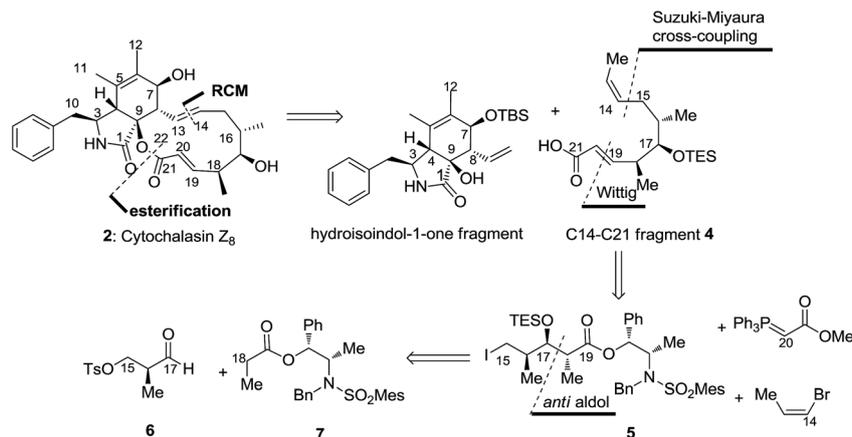
Chart 1 Structures of cytochalasin Z₇–Z₉.

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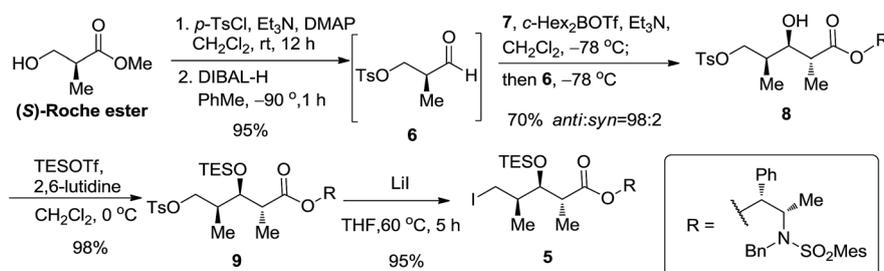
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† Electronic supplementary information (ESI) available: Experimental details and scanned copies of ¹H and ¹³C NMR spectra for new compounds. See DOI: 10.1039/c7ra13391j





Scheme 1 Retrosynthetic bond disconnections of cytochalasin Z_8 (2) yielding C14–C21 acid fragment 4 and hydroisoindol-1-one fragment.



Scheme 2 Synthesis of alkyl iodide 6.

auxiliary in 7. The influence of the stereogenic centre of aldehyde 6 on the stereochemical course of the aldol reaction was not observed. The hydroxyl group in 8 was then protected as TES ether 9 (TESOTf, 2, 6-lutidine, 98% yield). Iodide replacement of the tosylate group in 9 with LiI–THF furnished alkyl iodide 5 in 95% yield (Scheme 2).

The cross-coupling reaction of chiral alkyl iodide 5 with (*Z*)-1-bromoprop-1-ene was performed under the established conditions¹⁶ for the ‘9-MeO-9-BBN variant’ of the *B*-alkyl Suzuki–Miyaura cross-coupling reaction.^{12f,17} Alkyl iodide 5 was treated with *t*-BuLi in the presence of 9-MeO-9-BBN in Et₂O–THF to form the corresponding borinate species which was subjected to Pd(OAc)₂–Aphos-Y-catalysed^{16,18} cross-coupling reaction with (*Z*)-

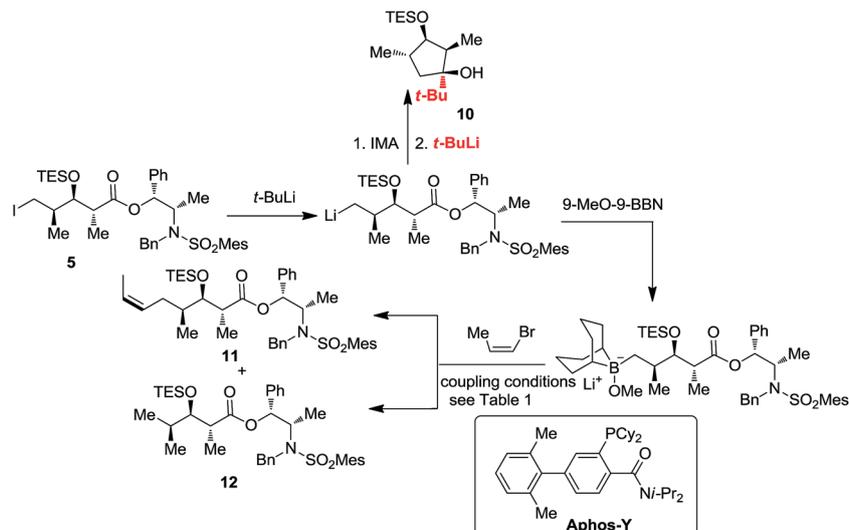
1-bromoprop-1-ene in the presence of K₃PO₄·3H₂O as the base in THF–H₂O at room temperature to furnish 11 in 15% yield along with cyclopentanol 10 and deiodinated byproduct 12 (entry 1, Table 1). We speculated that cyclopentanol byproduct 10 would be formed in the following pathway. Treatment of 5 with *t*-BuLi formed alkyllithium which underwent an intramolecular cycloaddition to form cyclopentanone; cyclopentanol 10 was formed by the addition of *t*-BuLi (Scheme 3). These results suggested that the formation of 10 could be suppressed by controlling reaction temperature. The first step reaction was maintained under low temperatures for a long time before warming up. After adding *t*-BuLi and THF, the reaction temperature was sequentially kept at –78 °C for 30 min, at –40 °C for 30 min, at –20 °C for 30 min and

Table 1 Results of cross coupling of chiral alkyl iodide 5 with (*Z*)-1-bromoprop-1-ene

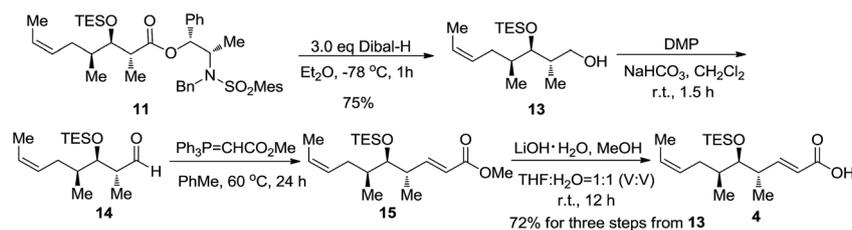
Entry	Conditions		Yield ^a (%)
	Step 1	Step 2	
1	2.8 eq. <i>t</i> -BuLi, 3.0 eq. 9-MeO-9-BBN, Et ₂ O/THF, –78 °C then r.t. for 2 h	5.0 mol% Pd(OAc) ₂ , 7.5 mol% Aphos-Y, 3.0 eq. K ₃ PO ₄ ·3H ₂ O, 18.0 eq. H ₂ O, THF, r.t. (14 h)	15; (21; 15)
2	3.8 eq. <i>t</i> -BuLi, 5.0 eq. 9-MeO-9-BBN, Et ₂ O/THF, –78 °C (30 min), –40 °C (30 min), –20 °C (90 min), r.t. (2 h)	5.0 mol% Pd(OAc) ₂ , 7.5 mol% Aphos-Y, 3.0 eq. K ₃ PO ₄ ·3H ₂ O, 18.0 eq. H ₂ O, THF, r.t. (14 h)	32; (19; 32)
3	4.0 eq. <i>t</i> -BuLi, 4.5 eq. 9-MeO-9-BBN, Et ₂ O/THF, –78 °C (30 min), –40 °C (30 min), –20 °C (90 min), r.t. (2 h)	10 mol% Pd(OAc) ₂ , 15 mol% Aphos-Y, 3.0 eq. K ₃ PO ₄ ·3H ₂ O, 18.0 eq. H ₂ O, THF, r.t. (12 h)	40; (17; 10)

^a Isolated yield of product 11. Data in the parentheses are the isolated yields of cyclopentanol 10 and deiodinated byproduct 12, respectively.





Scheme 3 Cross-coupling of chiral alkyl iodide 5 with (*Z*)-1-bromoprop-1-ene.



Scheme 4 Synthesis of C14–C21 acid fragment 4.

at room temperature for 2 h. The newly formed borinate species was subjected to coupling reaction with (*Z*)-1-bromoprop-1-ene. The yield was improved to 40% (entry 3, Table 1), and deiodinated byproduct **12** was inhibited to a large extent but could not be eliminated (in 10% yield). This condition might be associated with the steric hindrance imposed by the bulky TES and Abiko's chiral ester moieties of **5**.

The completion of the total synthesis of acid fragment **4** is illustrated in Scheme 4. Reduction of **11** with DIBAL-H provided the resultant primary alcohol **13** in 75% isolated yield. Dess–Martin periodinane oxidation¹⁹ in the presence of NaHCO₃ converted **13** into the corresponding aldehyde **14**. Aldehyde **14** was subjected to Wittig olefination with the stabilised ylide, Ph₃P=CHCO₂Me, in toluene at 60 °C to produce α,β -unsaturated ester **15** with exclusive *E* configuration for the newly formed disubstituted double bond. The hydrolysis of methyl ester **15** with LiOH in THF/H₂O at room temperature furnished the target C14–C21 acid fragment **4** in 72% overall yield for the three steps.

Conclusions

We developed a concise synthesis of the C14–C21 acid fragment **4** of cytochalasin Z₈. The *anti*-selective aldol reaction of **6** with the (*E*)-boron enolate derived from Abiko's chiral propionate **7**

achieved the desired C16–C18 *syn/anti* stereotriad in high diastereoselectivity presumably attained *via* a reagent control process. (*Z*)-Alkene functionality was introduced by the Pd(OAc)₂–Aphos-Y-catalysed C(sp²)–C(sp³) bond formation reaction of chiral alkyl iodide **5** with (*Z*)-1-bromoprop-1-ene. The target acid fragment **4** could be prepared from chiral (*S*)-Roche ester by a 10-step sequence in an overall yield of 14%. The strategy is concise and flexible to produce additional analogues of cytochalasin Z₈ in enantiomerically pure form. Efforts to achieve this goal are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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