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Synthesis of C14–C21 acid fragments of cytochalasin Z_8 *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 Z_8 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 Z_7–Z_9 (**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 Z_8 (**2**, Chart 1) is structurally related to cytochalasins Z_7 and Z_9 and features highly substituted hydroisoindol-1-one fused with a 12-membered macrolactone ring at the C-8 and C-9 positions. Cytochalasin Z_8 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 linear[3] or convergent[4] 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 Z_8 prompted us to pursue its total synthesis and render it to be readily available for biological investigations.

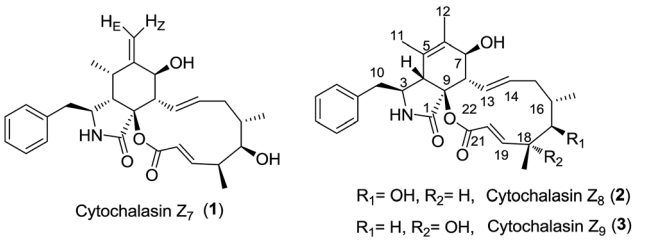

Chart 1 Structures of cytochalasin Z_7–Z_9.

The retrosynthetic strategy is depicted in Scheme 1. Intramolecular ring-closing metathesis (RCM) strategy[8] 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 condensation[10] of aldehyde **6** with Abiko's chiral norephedrine-derived propionate (1*R*,2*S*)-**7** (ref. 11) and *B*-alkyl Suzuki–Miyaura cross-coupling[12] 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 reduction[15] (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

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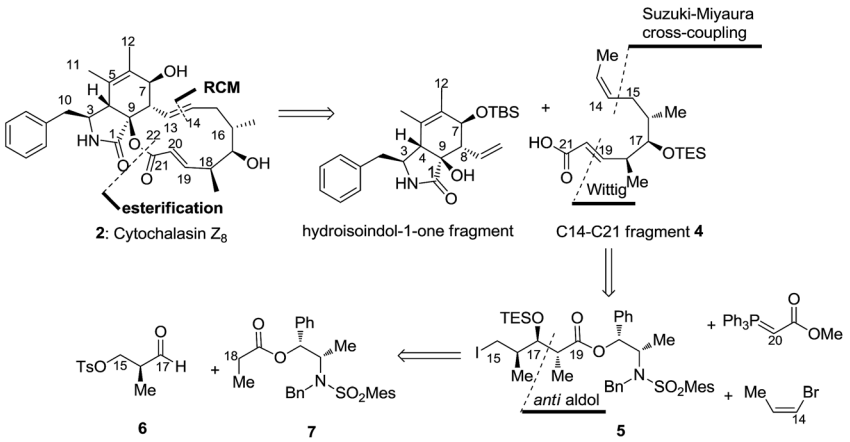
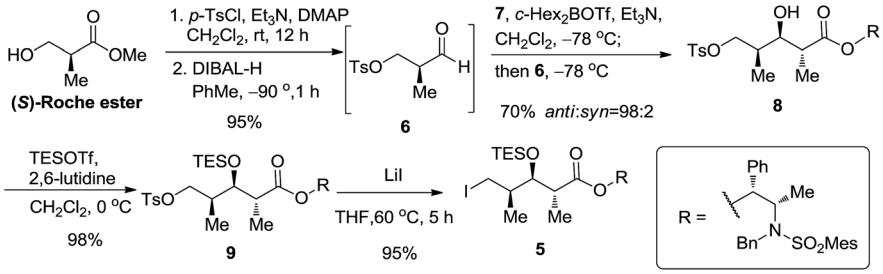


Scheme 1 Retrosynthetic bond disconnections of cytochalasin Z_8 (2) yielding C14–C21 acid fragment **4** and hydroisoindol-1-one fragment.



Scheme 2 Synthesis of alkyl iodide **6**.

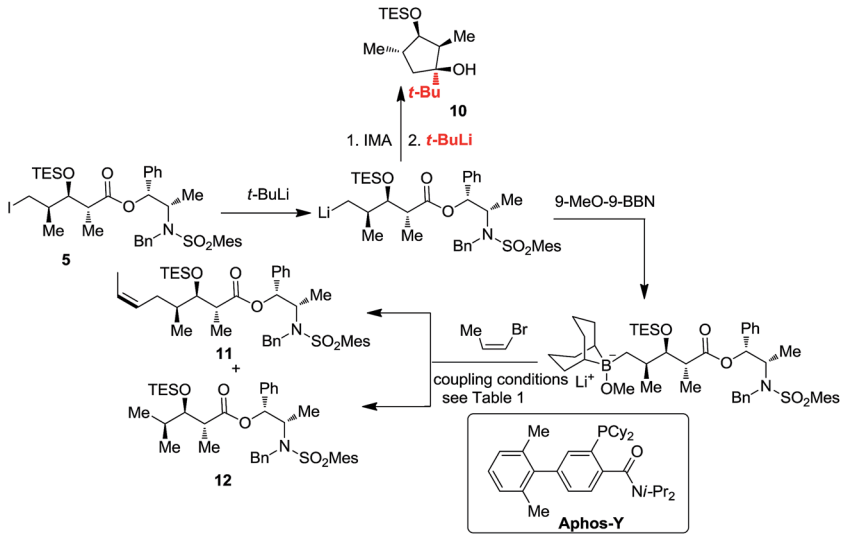
auxiliary in **7**. The influence of the stereogenic centre of aldehyde **6** on the stereochemical course of the aldol reaction was not observed. The hydroxyl group in **8** was then protected as TES ether **9** (TESOTf, 2, 6-lutidine, 98% yield). Iodide replacement of the tosylate group in **9** with 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 conditions[16] 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 Et_2O–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 $K_3PO_4 \cdot 3H_2O$ as the base in THF–H_2O 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

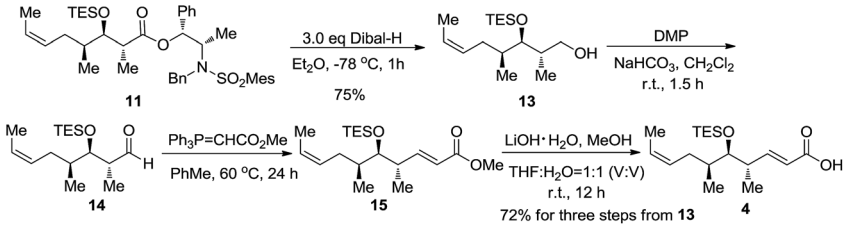
Table 1 Results of cross coupling of chiral alkyl iodide **5** with (*Z*)-1-bromoprop-1-ene

	Conditions	Conditions	
Entry	Step 1	Step 2	Yield[a] (%)
1	2.8 eq. *t*-BuLi, 3.0 eq. 9-MeO-9-BBN, Et_2O/THF, −78 °C then r.t. for 2 h	5.0 mol% $Pd(OAc)_2$, 7.5 mol% Aphos-Y, 3.0 eq. $K_3PO_4 \cdot 3H_2O$, 18.0 eq. H_2O, THF, r.t. (14 h)	15; (21; 15)
2	3.8 eq. *t*-BuLi, 5.0 eq. 9-MeO-9-BBN, Et_2O/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. $K_3PO_4 \cdot 3H_2O$, 18.0 eq. H_2O, THF, r.t. (14 h)	32; (19; 32)
3	4.0 eq. *t*-BuLi, 4.5 eq. 9-MeO-9-BBN, Et_2O/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. $K_3PO_4 \cdot 3H_2O$, 18.0 eq. H_2O, 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 oxidation[19] in the presence of $NaHCO_3$ converted **13** into the corresponding aldehyde **14**. Aldehyde **14** was subjected to Wittig olefination with the stabilised ylide, $Ph_3P{=}CHCO_2Me$, 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/H_2O 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 Z_8. 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 $C(sp^2)$–$C(sp^3)$ 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 Z_8 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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