Natural Product Synthesis

DOI: 10.1002/anie.200900097

Total Synthesis of (−)-FR182877 through Tandem IMDA–IMHDA Reactions and Stereoselective Transition-Metal-Mediated Transformations**

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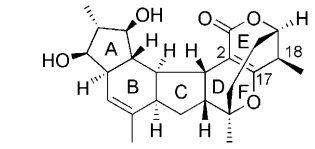
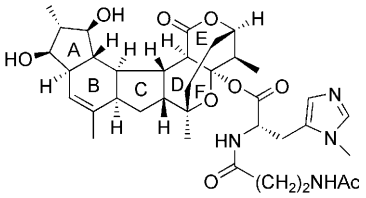
A research group at the Fujisawa (now, Astellas) Pharmaceutical Company isolated (−)-FR182877[1a–d] and its congener, (−)-FR182876[1e], from *Streptomyces* sp. no. 9885. (−)-FR182877 binds and stabilizes microtubules, exhibiting potent cytotoxic activity toward a number of human cancer cell lines with a potency comparable to that of Taxol.[1] The in vivo assay of (−)-FR182877 using mouse models revealed its promising antitumor activity,[1c] suggesting its potency as a lead compound for chemotherapeutic agents. (−)-FR182877 features a unique hexacyclic structure with twelve contiguous stereogenic centers and a reactive "push–pull" alkene[1c] distorted by the ethylene bridge. Its remarkable biological profile and unprecedented structural features has made (−)-FR182877 an attractive compound for total synthesis[2–5] as well as chemical biology studies.[6]



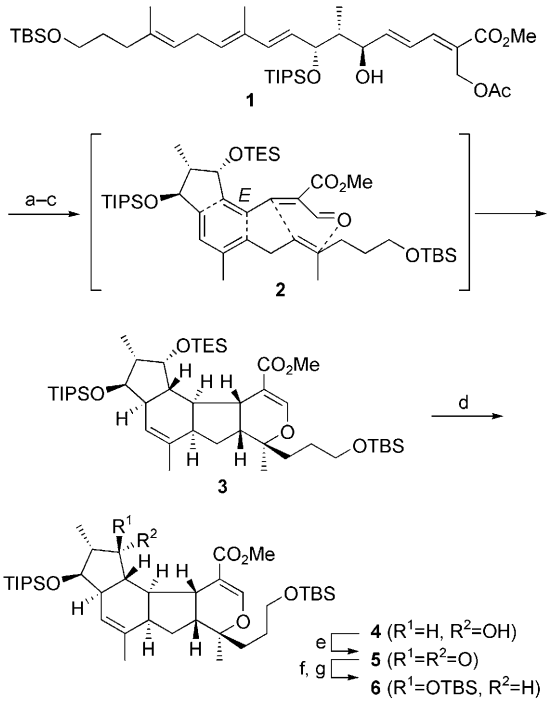
(−)-FR182877



(−)-FR182876

The groups led by Sorensen[2] and Evans[3] have independently reported elegant asymmetric total syntheses of (−)-FR182877 through closely related strategies, involving consecutive transannular cycloadditions. Our interests in the total synthesis of this complex architecture and the recently disclosed unique mode of action of this compound[6c] have prompted us to report herein an alternate synthetic approach to (−)-FR182877.

The stereoselective syntheses of the AB-ring and the CD-ring moieties were accomplished by the intramolecular Diels–Alder (IMDA) reaction and the intramolecular hetero-Diels–Alder (IMHDA) reaction,[4c,d] respectively. We surmised that these cycloadditions could be sequential; that is, the one-pot tandem IMDA–IMHDA reaction of the acyclic substrate **2** (Scheme 1) could provide the tetracyclic com-



Scheme 1. Synthesis of **6** by the tandem IMDA–IMHDA reaction: a) TESCl, imidazole, CH_2Cl_2, RT, 30 min; b) K_2CO_3, MeOH, RT, 30 min, 75% (2 steps); c) MnO_2, toluene, 80°C, 2 d, 28%; d) PPTS (cat.), MeOH, RT, 1.5 h, 82%; e) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 30 min, 89%; f) BH_3·THF, THF, −20°C, 30 min, 75%, (24:1 d.r.); g) TBSOTf, Et_3N, CH_2Cl_2, RT, 2 h, 94%. PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl.

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[**] This work was supported financially in part by a Waseda University Grant for Special Research Projects, a Grant-in-Aid for Scientific Research (B), and the Global COE program "Center for Practical Chemical Wisdom" by MEXT. We thank Tomoyuki Nakazato for early experiments. IMDA: intramolecular Diels–Alder, IMHDA: intramolecular hetero-Diels–Alder.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200900097.

pound **3**. Therefore, we prepared **2** from the previously reported compound **1**[4d,7] to examine the tandem reaction.

Protection of the hydroxy group of compound **1** as a triethylsilyl ether, followed by removal of the acetyl group and subsequent treatment of the resultant alcohol with MnO_2 in methylene chloride at room temperature afforded a complex mixture. However, slow oxidation with MnO_2 in toluene at 80 °C provided the desired tetracyclic compound **3** in 28 % yield.[8] Extensive analysis of the products did not reveal any other tetracyclic isomers, but undesired bicyclic side products with fused five- and six-membered rings and an aldehyde function were found in the reaction mixture.

These results indicated that the first IMDA reaction produced a mixture of diastereomers, but the undesired product did not undergo the subsequent IMHDA reaction. The relatively low yield (28 %) is most likely linked to the second IMHDA reaction because the previously reported IMHDA reaction of the substrate incorporating the AB ring[4d] was low-yielding (32 %) owing to the formation of unidentified polar side products. If the yield of the IMHDA reaction in the current tandem reaction is similar to that (32 %) of the previous IMHDA reaction in the stepwise synthesis, the yield of the first IMDA reaction in the tandem reaction would be 87.5 % (= 28 %/0.32), suggesting the diastereoselectivity of the first IMDA reaction would be 7:1 (= 87.5:12.5). This trend in stereoselectivity well agrees with that observed in the previously reported IMDA reactions of substrates including a dienophile with an allylic protected or unprotected hydroxy group.[4b–d] We have not clarified the reason for this trend in stereoselectivity, but the stereoelectronic effect induced by the allylic substituent play a role.[4b,9]

The overall yield of **4** from compound **1** was only slightly improved over that of our previous stepwise synthesis.[4d] However, in contrast with the IMDA reaction in the stepwise synthesis, the desired compound **3** was more easily separated from other products in the tandem IMDA–IMHDA reaction. To the best of our knowledge, this tandem reaction of the acyclic compound is unique.[10]

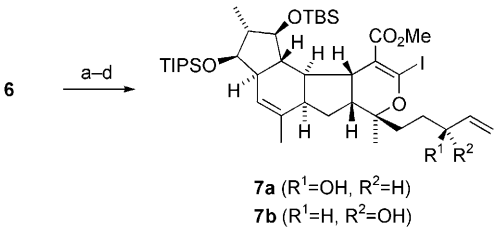
Before addressing the construction of the strained EF-ring moiety, we set out to invert the C6 stereogenic center of alcohol **4**, which was necessary for the stereoselective IMDA reaction.[4] Attempted Mitsunobu inversion of alcohol **4** gave no products; hence, alcohol **4** was subjected to Dess–Martin oxidation to afford ketone **5**, which was treated with BH_3 at −20 °C[11] to provide the desired β alcohol as the major product (75 %, 24:1 d.r.). This alcohol was then converted to the TBS ether **6** for further transformations.

After several unfruitful attempts to construct the strained seven-membered F ring,[12] we finally found that the palladium-mediated 7-*exo*-trig cyclization[13] was effective. Preparation of the substrate for the Mizoroki–Heck reaction is shown in Scheme 2. Treatment of compound **6** with LDA and subsequent reaction with iodine afforded the desired iodoalkene. The TBS group was removed, the intermediate was subjected to Dess–Martin oxidation, and finally reaction with vinylzinc bromide prepared in situ provided a separable mixture of compounds **7a** and **7b**.

Treatment of **7b** with $[Pd(PPh_3)_4]$ gave no desired product (Table 1, entry 1), but the use of $[Pd_2(dba)_3]$ and dppf in refluxing acetonitrile successfully induced the 7-*exo*-trig cyclization, providing compound **8b** in 59 % yield (Table 1, entry 2). The yield decreased in DMF (Table 1, entry 3), but after several attempts, we found that the reaction of **7b** in toluene at 100 °C gave an improved yield of 88 % (Table 1, entry 4), and the reaction of **7a** under the same reaction conditions afforded compound **8a** in 73 % yield (Table 1, entry 5).

Next we examined the isomerization of allylic alcohol **8** to α-methyl ketone **9** (Table 2). Various transition-metal reagents have been reported to effect this transformation.[14] We first examined the ruthenium-mediated reaction,[15a,b] but the reaction of compound **8** (a mixture of compounds **8a** and **8b**[16]) merely afforded the corresponding dienone (Table 2, entries 1 and 2). We found that the rhodium-mediated reaction[15c] afforded a mixture of compound **9**, its epimer, and compound **10** which has a double bond at the C17–C18 position (Table 2, entry 3). Finally, the iridium-mediated reaction[15d] successfully provided a mixture of compound **9** and its epimer, which was epimerized as expected to provide compound **9** after treatment with DBU (Table 2, entry 4).[17]

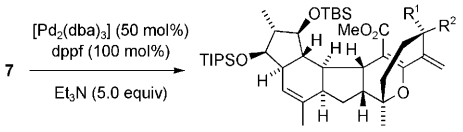
Reduction of ketone **9** with $NaBH_4$ took place at the less hindered side to afford the corresponding alcohol **11** as the sole product (Scheme 3). The silyl protecting groups of **11** were removed by treatment with HF·Py. Subsequent transformations, which were previously reported by Evans et al.[3]



7a (R^1=OH, R^2=H)
7b (R^1=H, R^2=OH)

Scheme 2. Conversion of **6** to **7**: a) LDA, THF, −78 °C, 2.5 h, then I_2, −78 °C, 30 min, 86 %; b) PPTS, MeOH, RT, 24 h, 96 %; c) Dess–Martin periodinane, CH_2Cl_2, RT, 30 min, 93 %; d) $ZnCl_2$, vinylmagnesium bromide, THF, RT, 15 min, 73 %. LDA = lithium diisopropylamide.

Table 1: Intramolecular Heck reaction of iodoalkene **7**.

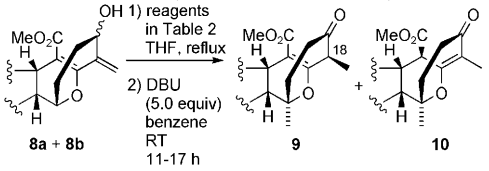


8a (R^1=OH, R^2=H)
8b (R^1=H, R^2=OH)

Entry	**7**	Solvent	*T* [°C]	*t* [h]	Yield [%][a,b]
1[c]	**7b**	MeCN	reflux	24	–[d]
2	**7b**	MeCN	reflux	4	**8b** (59)
3	**7b**	DMF	100	1	**8b** (23)
4	**7b**	toluene	100	1	**8b** (88)
5	**7a**	toluene	100	1	**8a** (73)

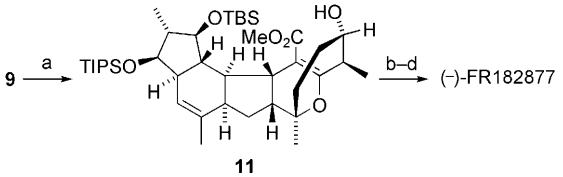
[a] Yield of isolated product. [b] For the determination of respective structures, see the Supporting Information. [c] $[Pd(PPh_3)_4]$ was used. [d] No products except the deiodinated compound were obtained. dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Table 2: Isomerization of allylic alcohol **8** to α-methyl ketone **9**.



Entry	Reagents (equiv)	*t* [h]	Yield [%][a]	
			9	**10**
1[b]	[{$RuCl_2$(*p*-cymene)}$_2$] (1.0), K_2CO_3 (3.0)	4	–[d]	–
2[b,c]	[$RuCl_2(PPh_3)_3$] (1.0), K_2CO_3 (3.0)	12	–[e]	–
3	[$RhCl(PPh_3)_3$] (1.0), *n*BuLi (1.0)	0.5	53	28
4	[{IrCl(cod)}$_2$] (10.0), K_2CO_3 (20.0)	24	62	0

[a] Yield of isolated product. [b] Results before the treatment with DBU. [c] The reaction in toluene. [d] Dienone was isolated in 92% yield. [e] Dienone was isolated in 67% yield. cod = cycloocta-1,5-diene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 3. Completion of the synthesis of (−)-FR182877: a) $NaBH_4$, MeOH, 0°C, 30 min, 84%; b) HF·Py, THF, 60°C, 24 h, 91%; c) TMSOK, THF, RT, 11 h; d) Mukaiyama's reagent, $NaHCO_3$, CH_2Cl_2, RT, 22 h, 59% (2 steps). Mukaiyama's reagent = 1-methyl-2-chloropyridinium iodide, Py = pyridine, TMS = trimethylsilyl.

(cleavage of the methyl ester with TMSOK followed by lactonization with Mukaiyama's reagent[18]) completed the total synthesis of (−)-FR182877. The synthesized compound was identical with the natural product in all respects (^{1}H and ^{13}C NMR, IR, and mass spectra, optical rotation).

In summary, an asymmetric total synthesis of (−)-FR182877 has been achieved. This total synthesis features: 1) a one-pot stereoselective tandem IMDA–IMHDA reaction to afford the tetracyclic compound **3**, which includes the ABCD ring system of (−)-FR182877 with seven newly generated, correct stereogenic centers, 2) the palladium-mediated 7-*exo*-trig reaction for the construction of the strained seven-membered F ring, and 3) the iridium-mediated isomerization of an allylic alcohol to the α-methyl ketone followed by epimerization and stereoselective reduction. Since recent studies[6c] disclosed the irreversible binding of (−)-FR182877 to a previously unidentified site on the outer wall of microtubules, we have commenced structure–activity studies based on this total synthesis, and the results will be reported in due course.

Received: January 7, 2009
Published online: February 18, 2009

Keywords: antitumor agents · cycloaddition · natural products · polycycles · strained molecules

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[7] For the preparation of compound **1**, see the Supporting Information.

[8] Compound **4**, derived from compound **3**, was spectroscopically identical with the known compound[4d] in all respects.

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[16] A mixture of compounds **8a** and **8b** was used for the reactions because separately the two compounds yielded almost the same results.

[17] PM3 calculations suggested that compound **9** is be more stable (> 2.5 kcal mol^{-1}) than its C18 epimer.

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