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Synthetic studies on (–)-FR182877: construction of the ABCD ring system via the intramolecular cycloadditions (1)

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Abstract—Construction of the ABCD ring system of (–)-FR182877 via the highly diastereoselective intramolecular Diels–Alder (IMDA) reaction is described. The IMDA reaction of the α,β-unsaturated aldehyde generated in situ from the corresponding acetal successfully provided the desired product **14** possessing the AB ring system as the single diastereomer. The CD ring system was constructed by the subsequent IMHDA reaction and the additional experiment suggested that the diastereoselectivity of the IMHDA reaction could be related to the *E*/*Z* geometry of alkene **17**, which was generated in situ from **16**.

Sato and co-workers in Fujisawa Pharmaceutical Company isolated (–)-FR182877 (Fig. 1) from *Streptomyces* sp. no. 9885 in 1998.[1a] (–)-FR182877 exhibited the taxol-like potent activity of promoting microtubule assembly to induce cell cycle arrest.[1b] The structure of (–)-FR182877 was unprecedented, possessing a hexacyclic skeleton incorporating a bridgehead alkenyl ether and twelve stereogenic centers. Its absolute configuration was first reported as the enantiomer of the structure shown in Figure 1[1c] but was corrected later.[1d,2,3]

The novel and complex structure as well as the promising bioactivity of (–)-FR182877 have attracted synthetic chemists to its total synthesis. In addition, recently

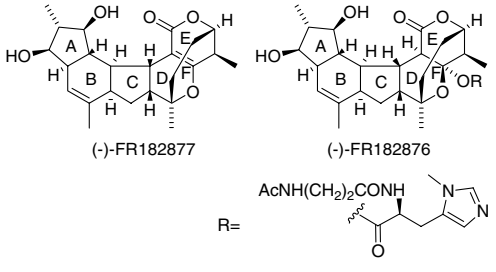

Figure 1. Structure of (–)-FR182877 and (–)-FR182876.

reported (–)-FR182876 (Fig. 1),[1e] which was more stable and water-soluble than (–)-FR182877 but showed almost same bioactivity as that of (–)-FR182877, incited further interest in these polycyclic natural products. Although two groups succeeded in the total synthesis of (–)-FR182877,[2,3] the complex polycyclic structure and the taxol-like bioactivity of (–)-FR182877 have heightened our interest[4] and that of other synthetic chemists in its total synthesis via different synthetic approaches.[5–8] We herein report construction of the ABCD ring system of (–)-FR182877 via the two intramolecular cycloadditions.

Since our report of the synthesis of the AB ring system of (–)-FR182877 via the diastereoselective intramolecular Diels–Alder (IMDA) reaction,[4] the construction of the CDEF ring system has remained undone. The EF ring system was highly strained; hence, it was rational to construct this moiety in the late stage of the total synthesis. Consequently, we next sought to construct the CD ring system of (–)-FR182877 from the compound incorporating the AB ring system.

We set compound **1** (Scheme 1) as a target molecule in this study because **1** possesses the ABCD ring system of (–)-FR182877. The configuration of one hydroxyl group in the A-ring system is reversed, but this has been found to be inverted.[4a] This reversed configuration in **1** was originally set in **5** (Scheme 1) to attain the high

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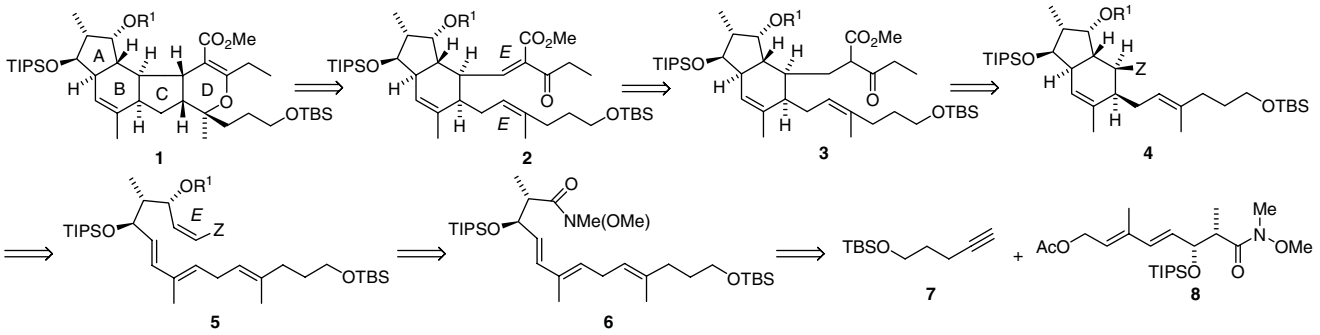


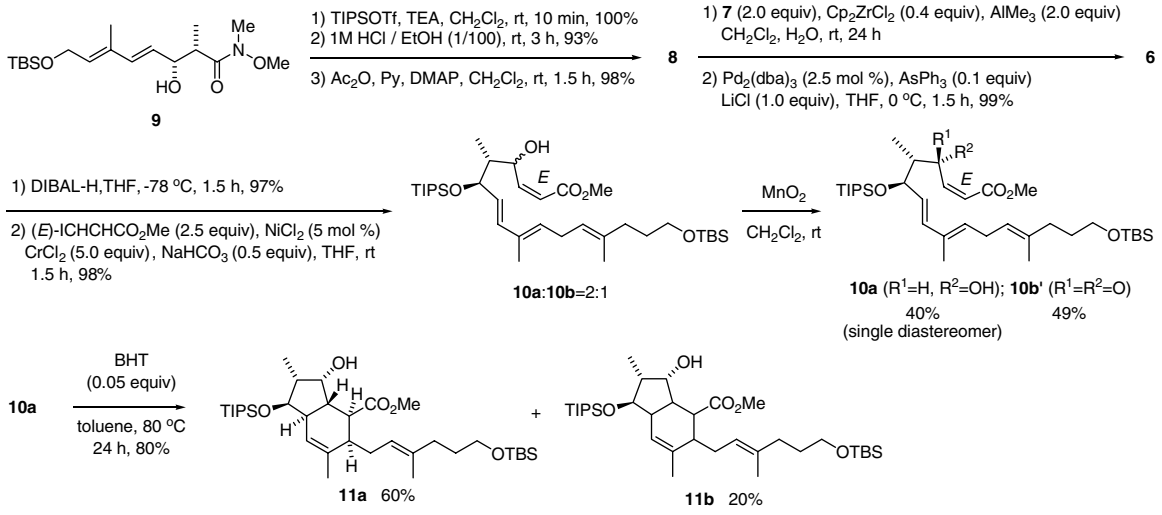
Scheme 1. Retrosynthetic analysis of **1**.

diastereoselectivity in the IMDA reaction.[4b] The CD ring system of **1** was envisioned to be constructed via the intramolecular hetero- Diels–Alder (IMHDA) reaction of **2**. The enone system in **2** was anticipated to be reactive because of its highly electron deficient nature due to the two attached electron withdrawing groups. Hence, **2** was planned to generate in situ from β-keto ester **3** by dehydrogenation, or alternatively, from aldehyde **4** (Z = CHO) via Knoevenagel condensation. β-Keto ester **3** would be obtained by the alkylation of methyl 3-oxo-pentanoate with **4** (Z = CH_2I), which was thought to be derived from aldehyde **4** (Z = CHO), which in turn could be prepared via the IMDA reaction of **5**. Compound **5** was expected to be obtained from amide **6**, which would be obtained by Negishi coupling reaction[9] of the readily available **7** with **8**.

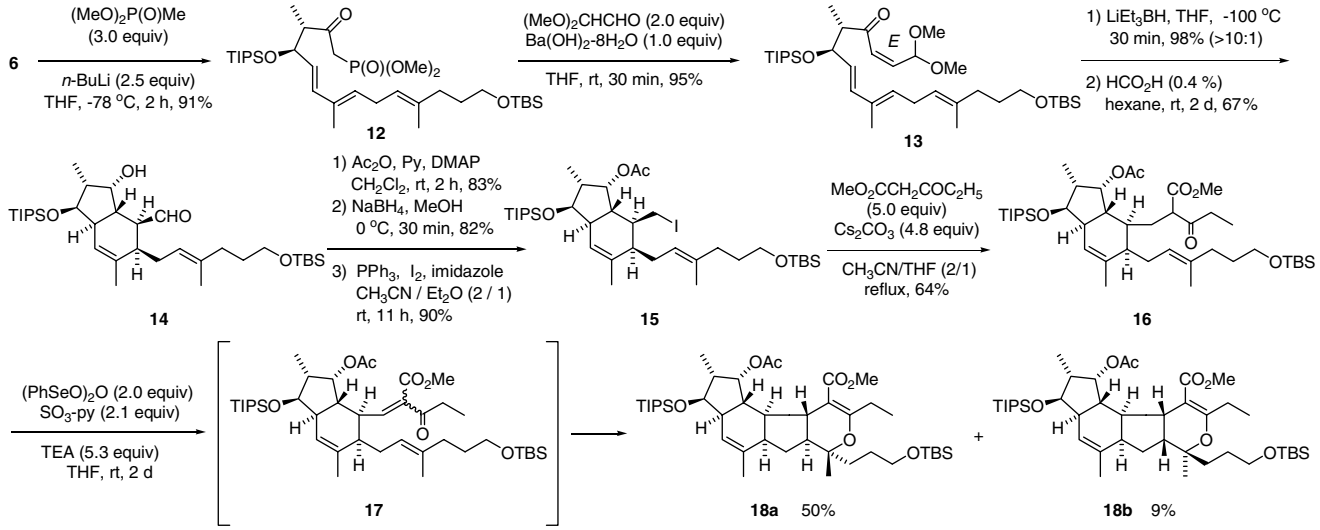
We prepared **8** from the reported **9**[4b] (Scheme 2). Thus, alcohol **9** was protected as a TIPS ether (100%), followed by the selective removal of the TBS ether with 1 M HCl in EtOH (93%) and subsequent acetylation to provide **8** (98%). Negishi coupling reaction of **7** with **8** under the conventional conditions[9] resulted in a certain leftover amount of **8**, but we found that the use of LiCl and Ph_3As greatly improved the yield of **6**. We also found that the carbometalation of **7** under Wipf's conditions[10] dramatically accelerated the reaction; finally, the yield was increased to 99%. Reduction of **6** with DIBAL-H provided the corresponding aldehyde in excellent yield (97%), which was subjected to Nozaki–Hiyama–Kishi reaction with (*E*)-methyl 2-iodoacrylate[4] to afford a mixture of **10a** and **10b** (98%, 2:1). This mixture was fortunately separated to **10a** (40%) and **10b′** (49%) by the kinetic oxidative separation using MnO_2, which was previously reported by us.[4]

The IMDA reaction of **10a** provided a mixture of **11a** (60%) and **11b** (20%) (Scheme 2). The structure of **11a** was elucidated by the NOE experiments on its derivative,[11] revealing that **11a** had the desired stereochemistry. Although **11a** was the potential intermediate for further synthetic studies, the overall yield in Scheme 2 was unsatisfactory; hence, another synthetic approach was pursued. Since we found that **10a** was stereoselectively obtained by the reduction of **10b′**, the substrate for the IMDA reaction, which was actually its precursor **13**, was prepared from **12** (Scheme 3).

That is, the reaction of amide **6** with an excess amount of lithiated dimethyl methylphosphonate provided β-keto phosphonate **12** in 91% yield. Horner–Wadsworth–Emmons reaction of **12** with dimethoxyacetaldehyde using barium hydroxide as the base[12] provided **13** with excellent yield (95%) and *E*-selectivity. Reduction of **13** by lithium triethylborohydride at −100 °C success-



Scheme 2. Preparation of **10a** and its IMDA reaction.



Scheme 3. Synthesis of **18b**.

fully provided the desired alcohol (98%) with high diastereoselectivity (>10:1), which was well explained by the Felkin model.

Hydrolysis of the acetal in the product with 0.4% HCO_2H in hexane generated the corresponding aldehyde, which underwent the IMDA reaction spontaneously to provide the desired product **14** as the single diastereomer (67%). The stereochemistry of **14** was confirmed as that shown in Scheme 3 by the chemical correlation with the compound derived from **11a**.[11]

To construct the enone system incorporated in compound **2**, Knoevanagel condensation of **14** with methyl 3-oxopentanoate was first attempted, but no desired product was obtained under any conditions. Hence, **14** was converted to iodide **15** via acetylation (83%), $NaBH_4$ reduction (82%), and iodination (90%) to examine the reaction with methyl 3-oxopentanoate. The alkylation reaction of methyl 3-oxopentanoate with the iodide **15** in DMF/THF (2/1) using K_2CO_3 formed **16** (24%) along with the O-alkylated product (35%), but finally, use of Cs_2CO_3 in CH_3CN/THF provided **16** (64%) and reduced the O-alkylated product (22%).

β-Keto ester **16** in hand, introduction of the double bond into **16** for the IMHDA reaction was examined. Among the conditions surveyed, we found that use of benzeneselenenic acid anhydride[3] gave the best result, causing dehydrogenation, followed by the IMHDA reaction to provide **18a** (50%) and **18b** (9%).

The major product **18a** was converted to the crystalline derivative, and its structure was successfully determined by the X-ray crystallographic analysis,[11,13] indicating that the structure of **18a** was the undesired isomer, as shown in Scheme 3. The minor product **18b** gave no crystalline derivative and the NOE experiments on **18b** did not determine the structure; however, the NOESY spectrum of the derivative prepared from **18b** successfully determined the structure of **18b** as the desired isomer.[11]

The plausible transition state models are proposed in Figure 2, which could explain the diastereoselectivity of the IMHDA reaction of **17**. Considering the $A^{1,3}$-strain existing in **17**, we believe that the three transition state models, **TS-1**, **TS-2**, and **TS-3**, are important. **TS-1** could be more stable than **TS-2** because the steric strain shown in Figure 2. Transition states derived from **17E** would be limited to **TS-3** because two $A^{1,3}$-strains arose from the trisubstituted alkenes. The transition state models proposed in Figure 2 suggested that the product **18a** would be derived from **17Z** via **TS-1**, and **18b** from both **17Z** and **17E** via **TS-2** and **TS-3**, respectively. Consequently, the desired product **18b** could be produced from **17E**.

The *E*/*Z* ratio of the enone intermediate **17** in situ generated from **16** was unable to be determined because **17** was too reactive to isolate. Consequently, to collect the information about the *E*/*Z* ratio of **17**, compound **19**, lacking the alkene to be reacted, was prepared and subjected to the same dehydrogenation conditions (Scheme 4). As a result, the *E*/*Z* ratio of enone **20** was found to be 1/2.4.[15] This ratio does not exactly correspond to the ratio of **18a** and **18b** but suggests the diastereoselectivity of the IMHDA reaction of **17** could be related to its *E*/*Z* ratio. In addition, if the equilibrium between **17E** and **17Z** exists under the conditions in Scheme 3 and the IMHDA from **17Z** is faster, preferential formation of **18a** could be explained rationally.

In summary, construction of the ABCD ring system of FR182877 via two intramolecular cycloadditions was developed. The IMDA reaction of the α,β-unsaturated aldehyde generated in situ from **13** provided the desired product **14** as the single isomer and the subsequent IMHDA reaction was found to provide the CD ring system. The diastereoselectivity of the IMHDA reaction should be improved for further synthetic studies, but the analysis of the transition states of **16** suggested that the use of *E*-alkene for the IMHDA could improve the diastereoselectivity. Consequently, next we examined the IMHDA reaction of the substrate possessing the

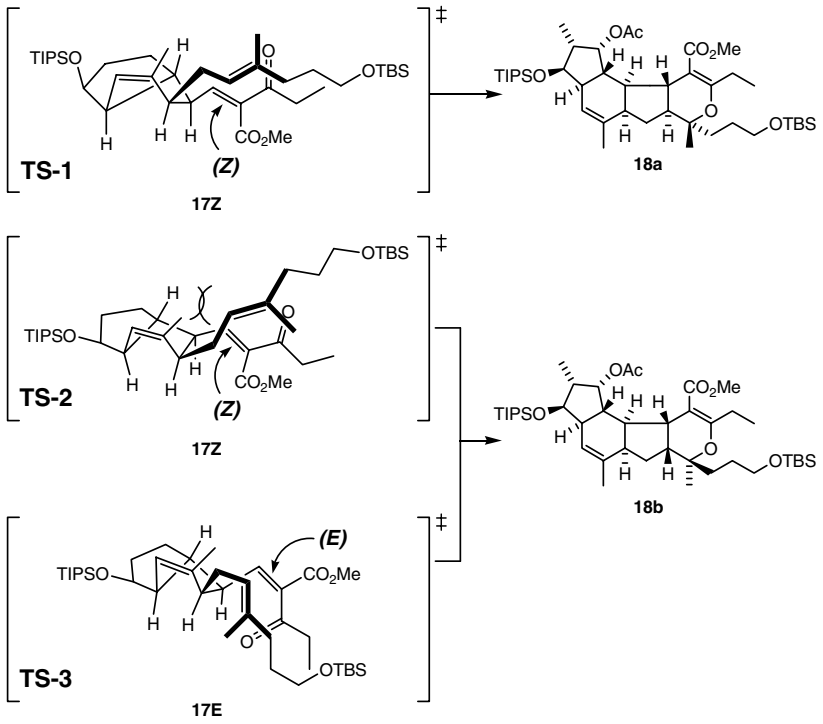
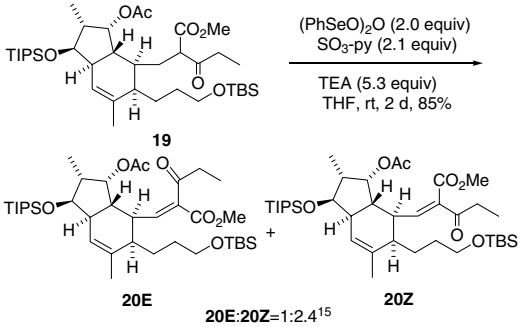


Figure 2. Plausible transition states of the IMHDA of **17**.[14]



Scheme 4. Dehydrogenation reaction of **19**.

E-alkene and the results will be reported in the following paper.

Acknowledgments

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Supplementary data

The structure determination of **11a**, **14**, **18a**, and **18b** based on the ^{1}H NMR experiments. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.051.

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13. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 650070. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
14. The substituents in the transition state models are omittted for clarity.
15. The yield was a combined yield and the ratio was determined by 400 MHz ^{1}H NMR.