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Synthetic studies on FR182877: an asymmetric synthesis of the AB ring moiety of FR182877 via a diastereoselective intramolecular Diels–Alder reaction

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Abstract—An asymmetric synthesis of the AB ring moiety of FR182877, possessing seven asymmetric centers, via a diastereoselective IMDA reaction is described.

FR182877 (Fig. 1), a compound formerly known as WS9885B, was isolated from the fermentation broth of *Streptomyces* sp. No9885 by the research group of Fujisawa Pharmaceutical Company in 1998, and its absolute structure and biological activity have been reported.[1,2] These reports have disclosed the unprecedented hexacyclic structure of FR182877 including a bridgehead alkenyl ether,[3] and 12 asymmetric centers, as well as its Taxol®-like potent cytotoxic biological activity. The complex structure and promising biological activity of FR182877 have provided us with a strong motive to achieve its total synthesis.[4] In this paper we report an asymmetric synthesis of the AB ring moiety of FR182877 via a diastereoselective intramolecular Diels–Alder (IMDA) reaction.

We planned to synthesize the AB ring moiety of FR182877 first, then the C ring moiety, and the DEF ring moiety at the end of the synthesis because the DEF ring moiety is so strained and reactive that an alkenyl ether in the DEF ring moiety is easily oxidized in air to afford an epoxide.[1] Thus, we set compound **1** as a key intermediate in our synthesis, and from which we envisioned to construct the C ring moiety. Our retrosynthetic analysis of the AB ring moiety is shown in Scheme 1.

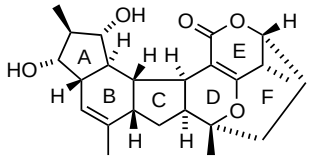

Figure 1. FR182877.

Since compound **1** is a *trans*-bicyclo[4.3.0]non-2-ene derivative, it is rational to construct the AB ring moiety via the IMDA reaction of **2**. Because **2** is a terminally activated nonatriene possessing *E*,*E*-diene and *E*-dienophile in its molecule, if the IMDA reaction proceeds via *endo* transition state, **2** would afford the *trans*-fused cycloadduct with the desired relative configuration on the B ring. Actually, many reports show that *trans*-fused cycloadducts are favored in the cyclization of such terminally activated nonatrienes.[5,6]

However, the diastereoselectivity of the IMDA reaction of chiral nonatrienes is rather complicated, and sometimes unexpected results have been obtained.[5] The substrates possessing allylic heteroatom substituents, particularly allylic alkoxy groups, give interesting results because these substituents are less sterically demanding than alkyl groups and electronic effects may intervene such that an axial orientation in the transition state is sometimes favored.[5] The IMDA reaction of triene **2**, possessing three successive asymmetric centers with two allylic hydroxy groups between *E*,*E*-diene and *E*-dienophile, has not been studied so far as we know.[7] Hence, we started the synthesis of **2** and the investigation of its IMDA reaction.

Keywords: FR182877; intramolecular Diels–Alder reaction; asymmetric synthesis.

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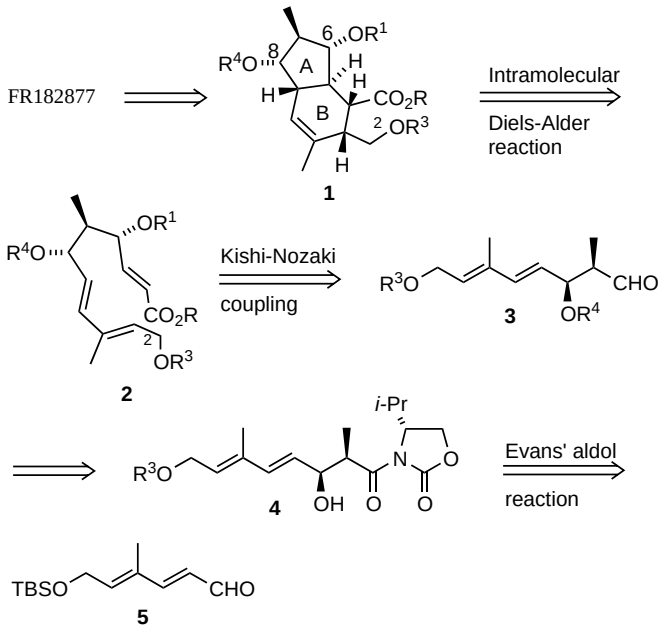
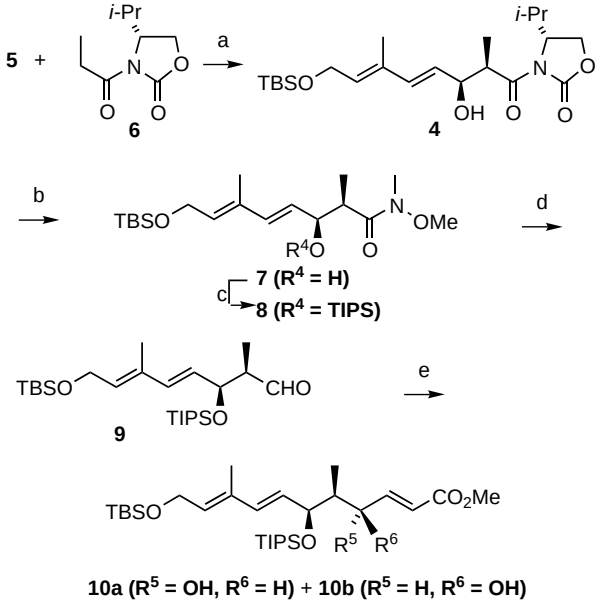
Our retrosynthetic analysis of **2** is shown in Scheme 1. Triene **2** would be synthesized by Kishi–Nozaki coupling of (*E*)-methyl 2-iodoacrylate[8] with aldehyde **3** though the diastereoselective construction of C-6 asymmetric center[9] in **3** should be a problem. Aldehyde **3** was expected to be obtained via compound **4** which would be prepared by Evans' *syn*-selective asymmetric aldol reaction[10] using the known aldehyde **5**.[11] Synthesis of the substrates for the IMDA reaction is shown in Scheme 2.



Scheme 1. Retrosynthetic analysis of the AB ring moiety of FR182877.



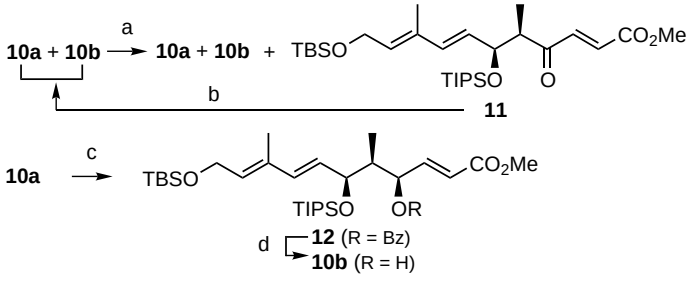
Scheme 2. *Reagents and conditions*: (a) *n*-Bu_2BOTf, TEA, CH_2Cl_2, −78°C to rt, 96%; (b) MeONHMe-HCl, Me_3Al, THF, 0°C to rt; (c) TIPSOTf, TEA, CH_2Cl_2, 0°C, 93% (two steps); (d) DIBAL-H, THF, −78°C, 94%; (e) methyl (*E*)-2-iodoacrylate, $NiCl_2$, $CrCl_2$, $NaHCO_3$, THF, rt, **10a**+**10b** = 93%, (**10a**:**10b** = 2:1).

Aldol reaction of **5** with **6** under the Evans condition afforded *syn*-product **4** with high selectivity; however, hydrolysis of **4** or direct conversion of the TIPS ether of **4** to the corresponding aldehyde was low-yielding under any conditions. Hence, **4** was converted to Weinreb amide **7**, which was then silylated, and the resulting TIPS ether **8** was successfully transformed to the aldehyde **9** in high yield.

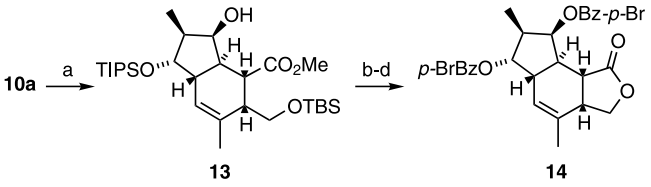
We hoped that a 1,2-asymmetric induction, which could be explained by the Felkin–Anh model, would occur in the Kishi–Nozaki coupling[12] of the aldehyde **9** with methyl (*E*)-2-iodoacrylate. The coupling reaction proceeded smoothly to afford products (**10a**+**10b**) in 93% yield, but the diastereoselectivity was only 2:1 (= **10a**:**10b**).[13,14] Furthermore, **10a** was inseparable from **10b** by silica gel column chromatography, and derivatizations of **10a** and **10b** gave no separable mixture.

Fortunately, we found that MnO_2 oxidation of **10b** was faster than that of **10a** (Scheme 3). Hence, the conditions for the MnO_2 oxidation were optimized, and finally when 3.5 equivalent of MnO_2 to the starting material (**10a**+**10b**) by weight was used for this reaction, the starting material (**10a**+**10b**) was recovered in 42% yield and the ratio of **10a**:**10b** was improved to 20:1.[15] At the same time, ketone **11** was obtained in 51% yield, and **11** was easily separated by silica gel chromatography. Compound **11** was easily reduced to the starting material (**10a**+**10b**) by $NaBH(OMe)_3$ in 82% yield (**10a**:**10b** = 2:1). Repeating this oxidation–separation–reduction cycle, almost pure **10a** was obtained. Compound **10a** was converted to **12** by the Mitsunobu reaction, and the following methanolysis afforded pure **10b**.

With substrates (**10a**, **10b**, and **12**) in hand, we next examined the IMDA reactions. First, **10a** was subjected to the IMDA reaction; thus, **10a** was dissolved in toluene and heated at 80°C in the presence of BHT under Ar atmosphere. Though completion of the reaction required 24 h, the reaction proceeded cleanly to



Scheme 3. *Reagents and conditions*: (a) MnO_2 (3.5 equiv. to **10** by weight), CH_2Cl_2, rt, 50 min, **10a**+**10b** = 42%, (**10a**:**10b** = 20:1), **11** (51%); (b) $NaB(OMe)_3H$, MeOH, rt, **10a**+**10b** = 82%, (**10a**:**10b** = 2:1); (c) PPh_3, DEAD, BzOH, toluene, 71%; (d) K_2CO_3, MeOH, 0°C to rt, 58%.



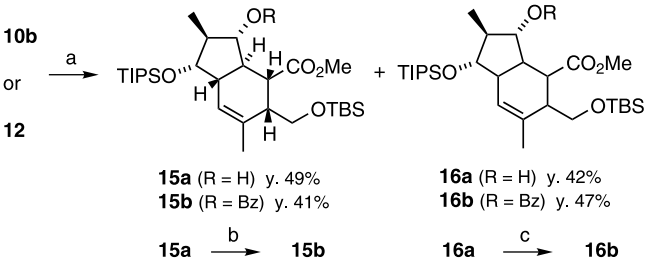
Scheme 4. *Reagents and conditions*: (a) BHT, toluene, 80°C, 24 h, 82% (>10:1); (b) *p*-BrBzCl, DMAP, CH_2Cl_2, rt, 94%; (c) TBAF, THF, rt, quant. (d) *p*-BrBzCl, DMAP, CH_2Cl_2, rt, 83%.

afford two products and the major product **13** was isolated in 82% yield with >10:1 selectivity (Scheme 4). The major product **13** was successfully transformed to a crystalline *p*-bromobenzoate **14**,[16] and its whole structure was confirmed by X-ray crystallographic analysis. The result of the X-ray crystallographic analysis clearly shows that all asymmetric centers in **13** have been constructed as we expected (Fig. 2).

On the other hand, the IMDA reaction of **10b** afforded **15a** (y.49%), **16a** (y.42%), and **12** afforded **15b** (y.41%), **16b** (y.47%), respectively (Scheme 5).[17] Compound **13** was converted to **15b** by the Mitsunobu reaction, and **15a** was benzoylated to afford **15b** (Schemes 5 and 7), so that structures of **15a** and **15b** were determined as shown in Scheme 5. The selectivities of the IMDA reactions of **10a**, **10b**, and **12** must be discussed carefully after further investigation because the selectivities observed cannot be explained only by the steric interactions in the *endo* transition states.[5]

Considering the results of the IMDA reactions described above, **13** is a most promising intermediate to develop the construction of the C ring and the DEF ring moieties because the yield of **13** was good, whereas both **10b** and **12** afforded the desired products in less than 50% yield. Furthermore, asymmetric centers on the B-ring of **16a** and **16b** cannot be inverted. Hence, we next examined the inversion of the C-6 asymmetric center of **13**.

The inversion of the C-6 asymmetric center of **13** by the Mitsunobu protocol resulted in low yield, and the yield did not exceed 15% in spite of extensive optimizations. Therefore, we next tried the inversion by an oxidation–reduction sequential operation for **13**. Thus, **13** was oxidized to ketone **17** by Dess–Martin oxidation without epimerization, and then a diastereoselective reduction of **17** was examined (Scheme 6). Anticipating the predominant formation of the energetically favored alcohol **18**, the reduction via a radical anion intermediate was carried out. However, **18** was not formed selectively by such reduction.[18] Hence, other reducing reagents were examined, and we found that reduction



Scheme 5. *Reagents and conditions*: (a) BHT, toluene, 80°C, 24 h; (b) Bz_2O, DMAP, 1,2-dichloroethane, reflux, 64%; (c) Bz_2O, DMAP, CH_2Cl_2, rt, 73%.

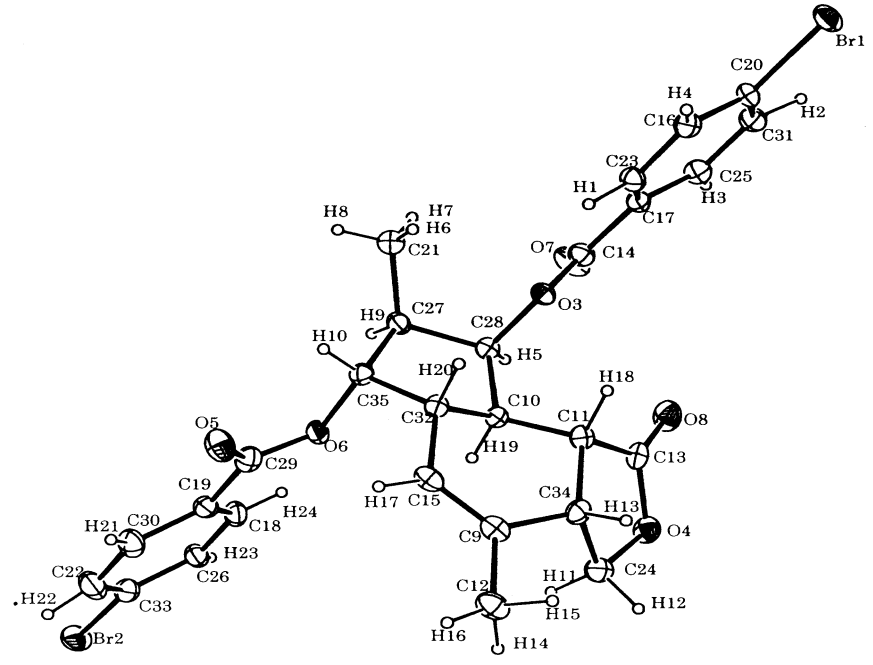
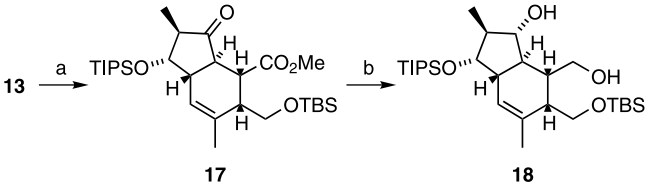
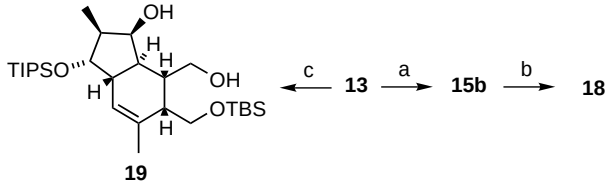


Figure 2. X-Ray crystal structure of **14**.



Scheme 6. *Reagents and conditions*: (a) Dess–Martin reagent, $NaHCO_3$, CH_2Cl_2, rt, 90%; (b) DIBAL-H, CH_2Cl_2, −78°C, 70%, (**18**:**19** = 4.4:1).



Scheme 7. *Reagents and conditions*: (a) PBu_3, DEAD, BzOH, toluene, rt, 13%; (b) DIBAL-H, CH_2Cl_2, −78°C, 35%; (c) DIBAL-H, CH_2Cl_2, −78°C, 59%.

of **17** by DIABAL-H afforded **18**[19] in 70% isolated yield with 4.4:1 (=**18**:**13**) selectivity.[20] Since the spectral data of **18** was consistent with that of the diol obtained from **15b**, and **13** was reduced to the corresponding diol **19** (Scheme 7),[21] the structure of **18** was determined as shown in Scheme 6. Diol **18** was separable from its epimer **19** by silica gel column chromatography, so that three chiral intermediates, **15a**, **15b**, and **18**, possessing all the desired asymmetric centers for the synthesis of FR182877 have been prepared.

In summary, we have succeeded in an asymmetric synthesis of the AB ring moiety of FR182877, possessing seven asymmetric centers, via a diastereoselective IMDA reaction. Further synthetic studies on FR182877 including construction of the C ring and the DEF ring moieties will be reported in due course.

Acknowledgements

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11. The known compound **5** was easily prepared from the commercially available aldehyde. See: Zhang, H.; Lerro, K. A.; Takekuma, S.-I.; Baek, D.-J.; Moquin-Pattey, C.; Boehm, M. F.; Nakanishi, K. *J. Am. Chem. Soc*. **1994**, *116*, 6823–6831.
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13. Optimization of this reaction (investigation of solvent, temperature, and additive) has been examined, but no promising result has been observed. Use of chiral ligands (spartein and Evans' bisoxazoline ligand) had no effect on this reaction.
14. Alcohols **10a** and **10b** were transformed to the corresponding acetonides, and the relative configurations were determined by the coupling constant of the ^1H NMR.
15. In this MnO_2 oxidation not only the amount of MnO_2, but also the reaction time was important. The reaction time over 50 min reduced the recovery yield of **10a**. **Procedure for MnO_2 oxidation of 10a+10b.** To a stirred solution of **10a**+**10b** (4.08 g, 7.53 mmol) in CH_2Cl_2 (100 ml) was added MnO_2 (14.28 g) in one portion at room temperature. After stirring the reaction mixture for 50 min under Ar atmosphere at room temperature, MnO_2 in the reaction mixture was filtered through Celite, and the filtrate was evaporated to dryness. The obtained residue was subjected to silica gel column chromatography (hexane:ethyl acetate = 20:1) to afford **10a**+**10b** (1.72 g, 42%, **10a**:**10b** = 20:1) and **11** (2.08 g, 51%).
16. **14**: White crystal (hexane-CH_2Cl_2), mp 233°C (decomp.); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (2H, d, J = 8.3 Hz), 7.82 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.3 Hz), 7.59

(2H, d, $J=8.3$ Hz), 5.87 (1H, dd, $J=5.9$, 4.4 Hz), 5.73 (1H, s), 5.22 (1H, dd, $J=5.6$, 1.2 Hz), 4.64 (1H, dd, $J=8.8$, 8.8 Hz), 3.99 (1H, dd, $J=10.3$, 8.8 Hz), 3.16 (1H, ddd, $J=10.3$, 8.8, 8.5 Hz), 2.99–2.90 (2H, m), 2.64 (1H, ddq, $J=7.6$, 5.9, 1.2 Hz), 2.35 (1H, ddd, $J=12.7$, 12.7, 4.4 Hz), 1.68 (3H, s), 1.15 (3H, d, $J=7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta=176.3$, 165.4, 164.5, 134.4, 131.8(2C), 131.8(2C), 131.0(2C), 131.0(2C), 128.8, 128.7, 128.3, 128.2, 122.2, 81.03, 73.96, 71.71, 47.60, 43.66, 42.50, 40.53, 38.47, 21.16, 13.21; IR (KBr) ν_{max} 2972, 2932, 2884, 1766, 1732, 1708, 1592, 1398, 1274, 1172, 1104, 1070, 1012, 756 cm^{-1}; FAB MS $[M+H]^+$ calcd for $C_{27}H_{25}Br_2O_6$: 603.0018, found: 603.0016; $[\alpha]_D^{19}$ +68.7 (c 0.28, $CHCl_3$); Crystallographic data: empirical formula = $C_{27}H_{24}Br_2O_6$; formula weight = 604.29; crystal system = monoclinic; space group = $P2_1/a$ (#4); $a=6.0055(3)$ Å; $b=13.1683(4)$ Å; $c=15.4577(8)$ Å; $\beta=92.662(1)°$; $V=1221.11(8)$ Å^3; $Z=2$; $D_{calc}=1.643$ g/cm^3; crystal dimensions = 0.15×0.15×0.10 mm; data collection temp = 123.0±1 K; radiation = MoKα ($\lambda=0.71069$ Å); μ(MoKα) = 33.71 cm^{-1}; number of reflections measured = 11353; number of unique reflections = 2909 ($R_{int}=0.061$); Residuals: $R_1(I>2\sigma(I))=0.031$; Residuals: $_wR_2=0.107$.

17. Yields are isolated yields. Structures of **16a** and **16b** have not been determined, but the relative configurations of **16a** and **16b** are assumed to be the same because ^{1}H NMR of **16a** and **16b** showed almost the same coupling constants between the protons on the B rings.
18. For example, reduction of **17** by SmI_2 afforded **13** as the sole product.
19. **18**: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=5.52$ (1H, s), 4.07 (1H, b), 3.90 (2H, m), 3.81 (1H, d, $J=3.9$ Hz), 3.78 (1H, dd, $J=11.5$, 9.3 Hz), 3.68–3.63 (2H, m), 3.48 (1H, dd, $J=9.3$, 4.9 Hz), 2.35 (1H, ddd, $J=11.7$, 11.5, 9.5 Hz), 2.26 (1H, m), 1.98–1.91 (2H, m), 1.87–1.80 (1H, m), 1.71 (3H, s), 1.13 (3H, d, $J=7.6$ Hz), 1.06–0.95 (21H, m), 0.92 (9H, s), 0.12 (3H, s), 0.11 (3H, s); FAB MS $[M+H]^+$ calcd for $C_{28}H_{57}O_2Si_2$: 513.3795, found: 513.3803.
20. This selectivity has not been explained clearly and more investigation is needed, but it seems that the selectivity cannot be explained only by the steric hindrance around the carbonyl group.
21. **19**: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta=5.60$ (1H, s), 4.24 (1H, dd, $J=4.9$, 4.2 Hz), 3.93–3.82 (3H, m), 3.67 (1H, dd, $J=10.7$, 8.5 Hz), 3.58 (1H, dd, $J=10.7$, 10.7 Hz), 2.44–2.36 (2H, m), 2.20–2.08 (2H, m), 1.99 (1H, ddd, $J=12.2$, 11.7, 3.2 Hz), 1.73 (3H, s), 1.07 (3H, d, $J=7.8$ Hz), 1.05–0.95 (21H, m), 0.91 (9H, s), 0.09 (3H, s), 0.08 (3H, s); FAB MS $[M+H]^+$ calcd for $C_{28}H_{57}O_2Si_2$: 513.3795, found: 513.3785.