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Synthetic studies on (−)-FR182877: construction of the ABCD ring system via the intramolecular cycloadditions (2)

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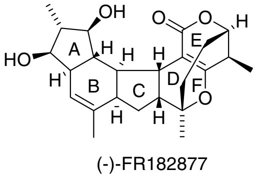
Abstract—Construction of the ABCD ring system of (−)-FR182877 via the intramolecular Diels–Alder (IMDA) reaction and the highly diastereoselective intramolecular hetero-Diels–Alder (IMHDA) reaction is described. The IMHDA reactions of the substrates incorporating the oxabutadiene with the *E*- or *Z*-alkene were examined, revealing that the sole product was obtained from both substrates and the *E*-alkene geometry was found to be crucial to obtaining the desired product.

In the preceding paper,[1] we described the construction of the AB ring system of (−)-FR182877 (Fig. 1) via the highly diastereoselective intramolecular Diels–Alder (IMDA) reaction of the α,β-unsaturated aldehyde (Scheme 1), which was prepared from **1** by the stereoselective reduction and following cleavage of the dimethyl acetal under the acidic conditions. Subsequent construction of the CD ring system was carried out via the intramolecular hetero-Diels–Alder (IMHDA) reaction of **4**, which was generated in situ by the dehydrogenation of **3** with benzeneseleninic acid anhydride, providing **5a** as the major product and the desired **5b** as the minor product. From additional studies, we assumed that the diastereoselectivity of the IMHDA reaction of **4** depends on the alkene geometry in the oxabutadine moiety.



(-)-FR182877

Figure 1. Structure of (−)-FR182877.

The IMHDA reaction is a powerful method to construct a heterocyclic compound possessing stereogenic centers. Thus, the IMHDA reaction could provide dihydropyrans incorporating up to three stereogenic centers such as **5a** and **5b** in one reaction. Therefore, we decided to investigate the relationships between the alkene geometry of the oxabutadiene in the substrate with the diastereoselectivity of the IMHDA reactions. We report herein the highly diastereoselective IMHDA reactions providing a single product that lead to the total synthesis of (−)-FR182877.

To investigate the relationships between the alkene geometry of the oxabutadiene in the substrate and the diastereoselectivity of the IMHDA reaction, we prepared the substrates possessing the established alkene geometry. We first prepared **7** (Scheme 2), incorporating the oxabutadiene with an *E*-alkene, and examined its IMHDA reaction. Product **6**, which possesses the requisite configuration for the total synthesis of (−)-FR182877, was expected to form diastereoselectively from **7** because the most energetically favored transition state derived from **7** was considered to afford **6**. In addition, the alkenyl hydrogen of the dihydropyran moiety of **6** is reactive, so that a substituent could be introduced at this position to construct the remaining ring systems required for the total synthesis of (−)-FR182877. Compound **7** was expected to be prepared from **8**, which could be obtained by the IMDA reaction of **9**, which in turn was thought to be prepared by the Horner–Wadsworth–Emmons reaction of **10** with **11**.

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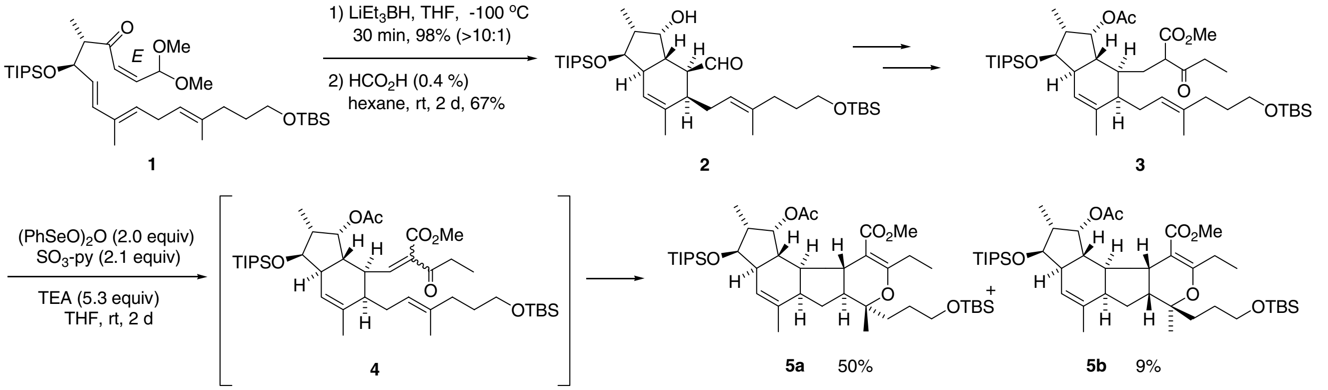
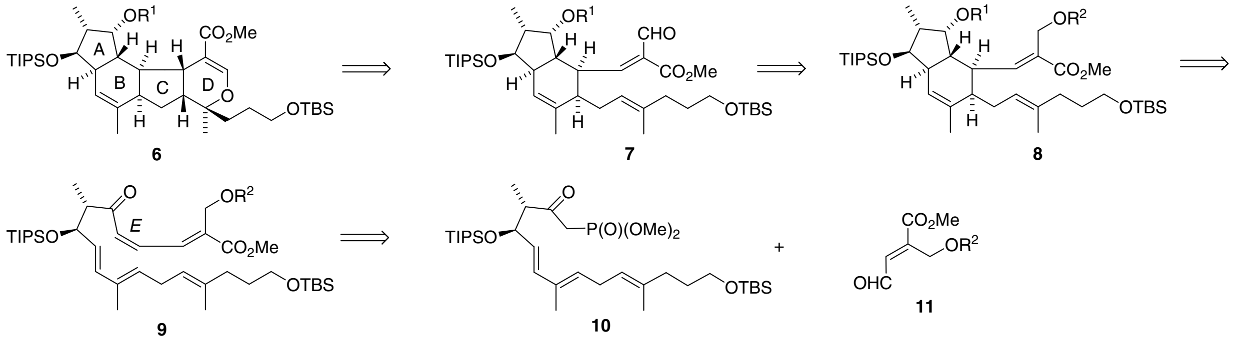


Scheme 1. Synthesis of **5a** and **5b** via the IMDA reaction and the IMHDA reaction.



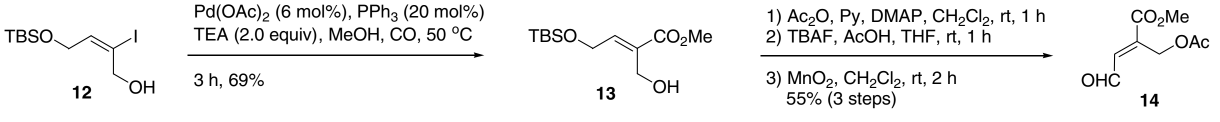
Scheme 2. Retrosynthetic analysis of **6**.

Considering the transformation after compound **8**, we employed an acetyl group for the protective group R_2 in **11**,[2] and compound **14** (Scheme 3) was prepared from the known compound **12** via four steps, Pd-mediated methyl ester formation, acetylation, desilylation, and MnO_2 oxidation.

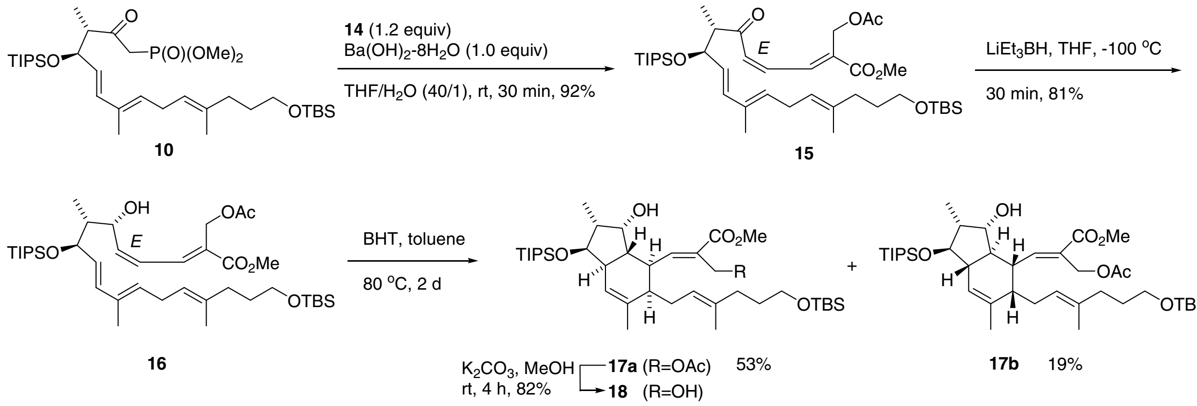
Reaction of **10** with **14** (Scheme 4) proceeded in high yield to provide **15** as the sole product, which was reduced to **16** by lithium triethylborohydride with excellent diastereoselectivity. Although the IMDA reaction of **16** afforded a mixture of two diastereomers, the major product was **17a** (50%) and the minor was **17b** (19%). The acetyl group in **17a** was selectively removed by K_2CO_3 in methanol to afford **18**.

Treatment of **18** with MnO_2 in CH_2Cl_2 at room temperature slowly provided the desired product **19** (17%) with concomitant formation of **20** (16%) after 24 h (Table 1, entry 1). The NOESY spectrum of **19** clearly indicated the NOE correlations as shown in Figure 2, suggesting that the relative configuration of **19** was constructed as expected.[4] The aldehyde derived from **18** was not detected; therefore, the aldehyde generated in situ could undergo the IMHDA reaction immediately to afford **19**, which would be hydrolyzed to **20** by moisture included in the reaction medium. Conversion of **20** to **19** was examined under various conditions; however, most of the conditions merely caused decomposition of **20**, and the best result (22% yield, Scheme 5) was obtained by simply heating **20** in toluene (Scheme 5). Reaction of **18** with MnO_2 in refluxing CH_2Cl_2 afforded only **19** in 26% yield (entry 2), and the reaction in toluene at 50 °C (entry 3) slightly improved the yield (30%). The reaction at 80 °C (entry 4) shortened the reaction time to 4 h, providing **19** in 32% yield; however, the yield was not improved further in spite of extensive optimization.[3]

We next prepared **27a** (Scheme 7), the *Z*-isomer of **18**, to investigate its IMHDA reaction. Synthesis of **27a** started with the DIBAL-H reduction of known **21** (Scheme 6),[5] followed by TBS protection, Pd-mediated methyl ester formation, deprotection of TBS with TBAF, acetylation of the resultant alcohol, and hydrolysis of the acetal to provide **24**.

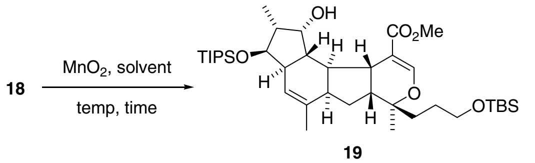


Scheme 3. Preparation of **14** from **12**.



Scheme 4. Preparation of **18** from **10** via the IMDA reaction of **16**.

Table 1. The IMHDA reaction of **18**



Entry	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	CH_2Cl_2	rt	24	17 (**19**) + 16 (**20**)
2	CH_2Cl_2	Reflux	24	26
3	Toluene	50	24	30
4	Toluene	80	4	32

[a] Isolated yields.

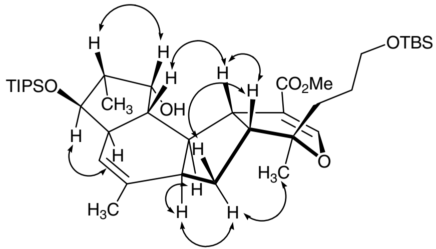
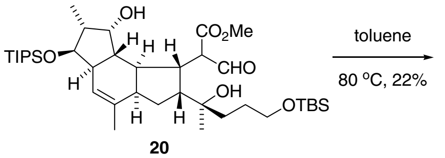
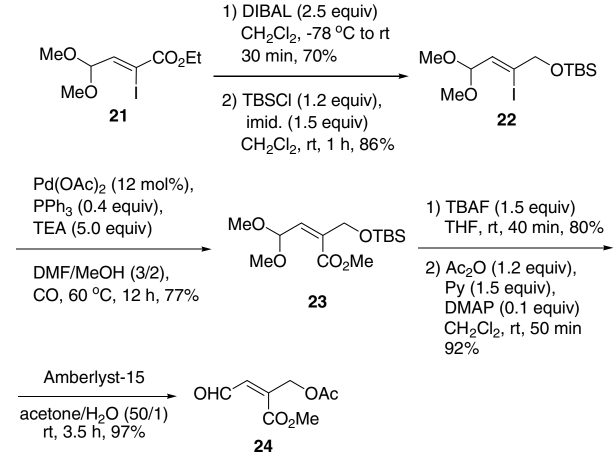


Figure 2. NOE correlations observed in the NOESY spectrum of **19**.



Scheme 5. Conversion of **20** to **19**.

Horner–Wadsworth–Emmons reaction of **10** with **24** was low-yielding (Scheme 7, 34% yield)[6] but provided **25** as the sole product. The subsequent reduction of **25** with lithium triethylborohydride at low temperature afforded the desired **26** as the major product (dr = 10/1). As the diastereomeric mixture was inseparable, it was subjected to the IMDA reaction as a mixture, providing **27a** (50%), **27b** (20%), and **27c** + **27d** (6%, dr = 1/1).

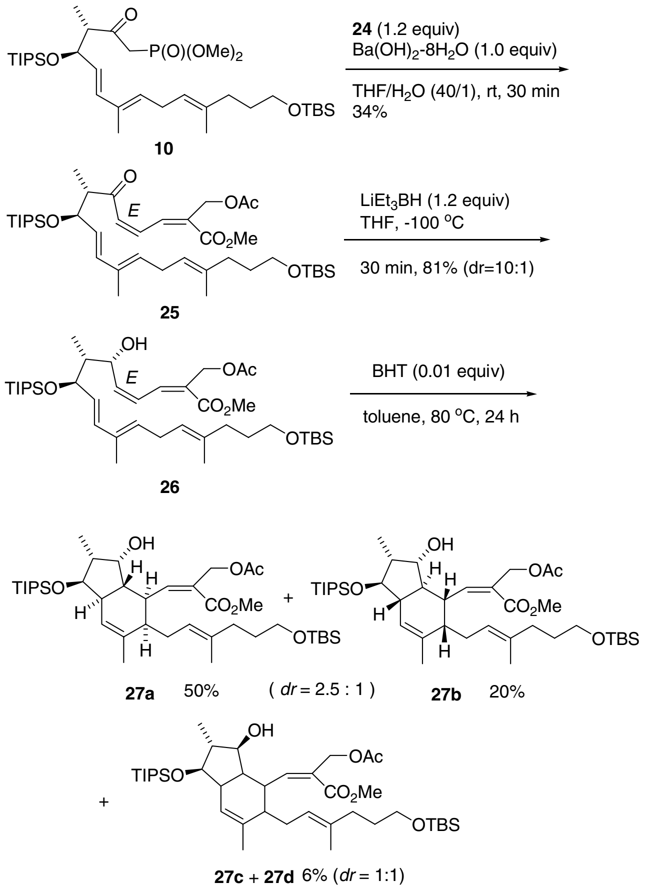


Scheme 6. Preparation of **24** from **21**.

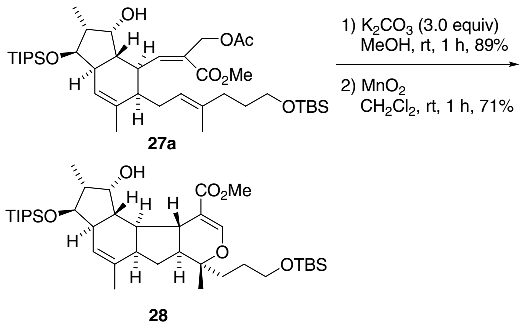
The acetyl group of **27a** was removed by K_2CO_3 in methanol, followed by treatment with MnO_2 at room temperature, affording **28** as the sole product (Scheme 8).[7] Compared with the IMHDA reaction of **18**, the reaction proceeded faster and the yield was better (71%). The NOE correlations shown in Figure 3 were found in the NOESY spectrum of **28**; hence, the relative configuration of **28** was elucidated as shown.

Transition state models that afforded **19** and **28** could be proposed as **TS-1** and **TS-2**, respectively (Scheme 9).[8] The $A^{1,3}$-strain arising from the trisubstituted alkene in the oxabutadiene moiety is minimized in **TS-1** and **TS-2**; therefore, both models would be the most energetically favored transition states. As a result, the sole product would be formed in both cases. The results of the IMHDA reactions of **18′** and **27a′** well correspond to the results described in the preceding paper,[1] indicating that the alkene geometry in the oxabutadiene moiety is crucial for the high diastereoselectivity in these IMHDA reactions.

It should be mentioned that the IMHDA reactions of **18′** and **27a′** (Scheme 9) were carried out under the neutral conditions in the current studies, different from the conditions for **4** in Scheme 1. Therefore, considering



Scheme 7. Preparation of **26** from **10** and its IMDA reaction.



Scheme 8. The IMHDA reaction starting from **27a**.

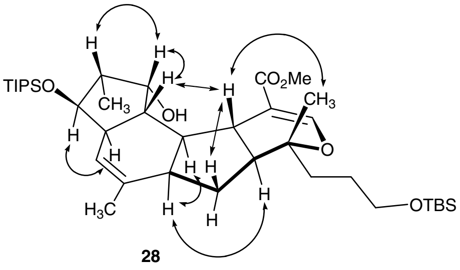


Figure 3. NOE correlations in the NOESY spectrum of **28**.

that the reaction of **27a′** was faster than that of **18′**, it cannot be ruled out that the preferential formation of **5a** (Scheme 1) could arise from the *E*–*Z* equilibrium of the IMHDA substrate **4** under the basic conditions.

In summary, the highly diastereoselective IMHDA reactions that provide a single product and would lead to the total synthesis of FR182877 have been developed. The high diastereoselectivity of the IMHDA reactions would arise from the $A^{1,3}$-strain in the transition states; that is, use of the oxabutadiene with the geometrically pure trisubstituted alkene was crucial for the high diastereoselectivity. Compound **19**, which was derived from the *E*-alkene **18** via the IMHDA reaction, is a key intermediate possessing a tetracyclic ring system required for the total synthesis of (−)-FR182877; hence, further transformation of **19** toward (−)-FR182877 is now under investigation.

Acknowledgments

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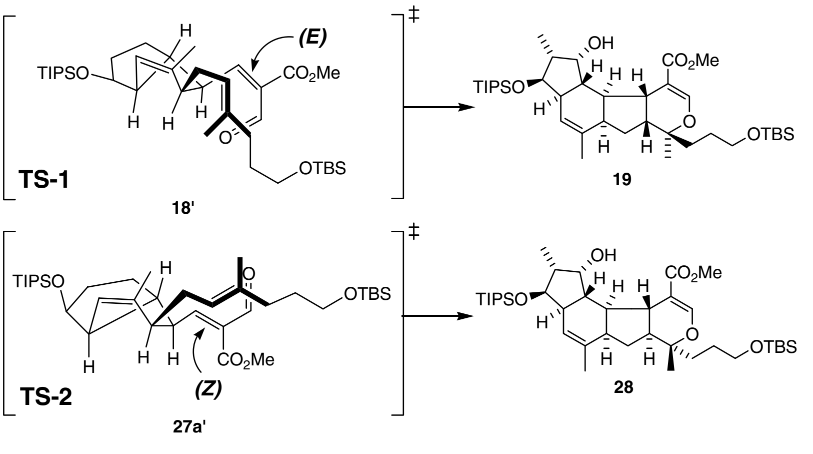

Scheme 9. Plausible transition states **TS-1** and **TS-2**.

References and notes

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2. Suffert, J.; Toussaint, D. *Tetrahedron Lett.* **1997**, *38*, 5507–5510.
3. The low yield could arise from formation of the structurally unidentified polar side-products.
4. Compound **19**: R_f 0.62 (hexane/ethyl acetate = 4:1); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.50$ (1H, s), 5.53 (1H, s), 4.29 (1H, dd, $J = 7.3$, 3.9 Hz), 3.97 (1H, d, $J = 4.9$ Hz), 3.68 (3H, s), 3.57 (2H, t, $J = 6.1$ Hz), 3.38 (1H, s), 2.91 (1H, d, $J = 7.3$ Hz), 2.62 (1H, m), 2.46–2.25 (3H, m), 2.20 (1H, dq, $J = 7.3$, 7.3 Hz), 1.94 (1H, ddd, $J = 13.2$, 13.2, 9.0 Hz), 1.78–1.70 (3H, m), 1.68–1.60 (4H, m), 1.59–1.29 (2H, m), 1.27 (3H, s), 1.09 (3H, t, $J = 7.3$ Hz), 1.06 (21H, m), 0.88 (9H, s), 0.03 (6H, s); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 168.5$, 154.5, 137.0, 122.6, 108.0, 81.1, 80.6, 71.6, 63.0, 51.3, 50.5, 46.6, 43.9, 43.1, 42.9, 41.4, 37.7, 33.4, 30.8, 27.3, 25.9 (3C), 23.3, 22.3, 18.3 (3C), 18.2 (4C), 13.2, 12.7 (3C), −5.2 (2C); IR (neat) $\nu_{\max}$: 3516, 2948, 1688, 1628, 1464, 1386, 1294, 1256, 1216, 1104, 836, 778 cm^{-1}; FAB HRMS [M+Na]$^+$ calcd for C$_{38}$H$_{68}$O$_6$Si$_2$Na, 699.4452; found, 699.4440; $[\alpha]_D^{23}$ −75.04 (*c* 0.8, CHCl$_3$).
5. (a) Braun, N. A.; Klein, I.; Spitzner, D.; Vogler, B.; Braun, S.; Borrmann, H.; Simon, A. *Liebigs Ann.* **1995**, 2165–2169; (b) Braun, N. A.; Bürkle, U.; Feth, M. P.; Klein, I.; Spitzner, D. *Eur. J. Org. Chem.* **1998**, 1569–1576.
6. The yield was not optimized.
7. Compound **28**: R_f 0.62 (hexane/ethyl acetate = 4:1); ^{1}H NMR (600 MHz, CDCl$_3$): $\delta = 7.53$ (1H, d, $J = 2.3$ Hz), 5.63 (1H, s), 5.19 (1H, s), 4.06 (1H, m), 4.01 (1H, dd, $J = 6.1$, 2.6 Hz), 3.68 (3H, s), 3.63 (2H, m), 2.71–2.66 (2H, m), 2.48 (1H, m), 2.32 (1H, ddd, $J = 12.0$, 5.6, 2.3 Hz), 2.02 (1H, m), 1.89 (1H, ddd, $J = 10.5$, 4.9, 4.9 Hz), 1.84 (1H, ddd, $J = 12.0$, 12.0, 4.9 Hz), 1.74 (1H, m), 1.66–1.56 (7H, m), 1.21 (3H, s), 1.16 (3H, d, $J = 7.4$ Hz), 1.06–1.00 (22H, m), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 168.4$, 156.8, 134.2, 124.4, 108.9, 83.7, 80.1, 71.4, 63.2, 52.4, 51.4, 50.5, 50.4, 47.6, 43.8, 39.8, 37.5, 36.5, 31.2, 26.4, 26.0 (3C), 22.4, 21.1, 18.4, 18.3 (6C), 13.5, 12.7 (3C), −5.3 (2C); IR (neat) $\nu_{\max}$: 3484, 2960, 1696, 1592, 1464, 1300, 1258, 1190, 1134, 1106, 834, 762 cm^{-1}; FAB HRMS [M+Na]$^+$ calcd for C$_{38}$H$_{68}$O$_6$Si$_2$Na, 699.4452; found, 699.4418; $[\alpha]_D^{23}$ −86.04 (*c* 1.1, CHCl$_3$).
8. The substituents in the transition state models are omitted for clarity.