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Studies on the diastereoselectivity in the IMDA reactions of terminally activated (*E*,*E*,*E*)-nona-1,6,8-trienes

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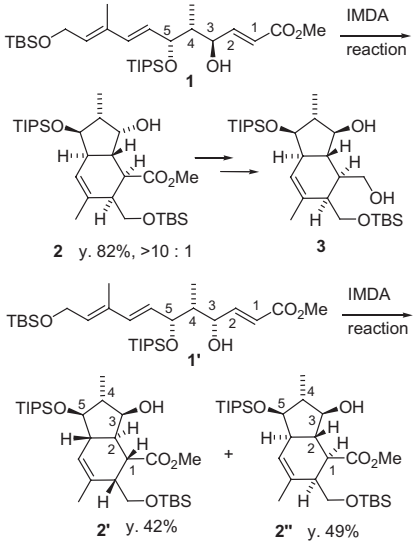
Abstract—The structure–diastereoselectivity relationships in the IMDA reactions of the terminally activated (*E*,*E*,*E*)-nona-1,6,8-trienes have been studied. It is found that the configuration of the C3 position bearing the protected hydroxyl group is crucial to the diastereoselectivity, and the magnitude of the ratio depends on the relative configuration of the C3–C5 positions. The results obtained in this study including the new successful IMDA reactions would be useful for the stereoselective synthesis of natural products containing a bicyclo[4.3.0]non-2-ene carbon skeleton.

The intramolecular Diels–Alder (IMDA) reaction in which the diene and dienophile are tethered by a connecting chain has become a most versatile method for the synthesis of polycyclic natural products.[1] Of particular interest is the selective introduction of stereogenic centers because the IMDA reaction simultaneously generates upto four new stereogenic centers, making this reaction valuable in natural products synthesis.

We reported synthesis of the AB ring moiety **3** (Scheme 1) of (+)-FR182877 (Fig. 1) via **2**, which was successfully prepared by the stereoselective IMDA reaction of **1** (>10:1, Scheme 1).[2] In that work, the IMDA reaction of **1′**, which was a diastereomer of **1** at the C3 position, was found to show the low diastereoselectivity (**2′** and **2″** in a ratio of 1:1.2). Hence, this dramatic change in the diastereoselectivity interested us greatly.

Although many IMDA reactions of the terminally activated (*E*,*E*,*E*)-nona-1,6,8-trienes have been reported,[2–8] there have been no studies on the structure–diastereoselectivity relationships in the IMDA reactions of the above substrates possessing stereogenic centers at the C3, C4, and C5 positions so far as we know. Such studies are useful for the stereoselective total synthesis of the reported bioactive natural products incorporating a



Scheme 1. IMDA reactions of **1** and **1′**.[2]

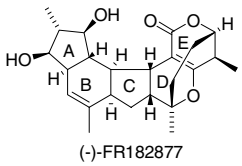


Figure 1. Structure of (−)-FR182877.

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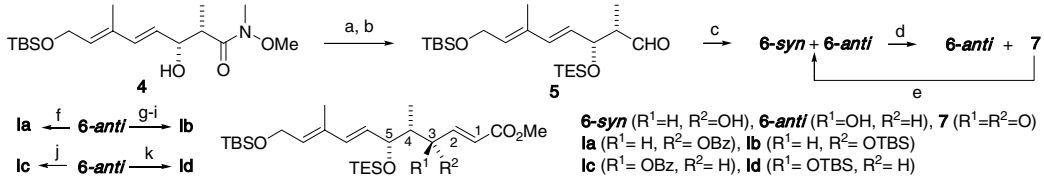
bicyclo[4.3.0]non-2-ene carbon skeleton[8,9] as well as the forthcoming congeners. Consequently, we were prompted to study the IMDA reactions of the derivatives of **1**, and we wish to report the structure–diastereoselectivity relationships of the terminally activated (*E*,*E*,*E*)-nona-1,6,8-trienes, which include new successful examples and suggest that the configuration of the C3 position bearing the protected hydroxyl group is crucial to the diastereoselectivity in the IMDA reaction of the above substrates.

We prepared all the diastereomers and congeners of **1** derived from the C3, C4, and C5 stereogenic centers,[10] and examined their IMDA reactions. The C4,5-*syn* series, **Ia**–**d**, was prepared from **4**[2] according to the reported method for preparing **1** and **1′** (Scheme 2).[2] The structures of **Ia**–**d** were determined by comparing their ^{1}H NMR spectrums with those of **1** and **1′**.[11]

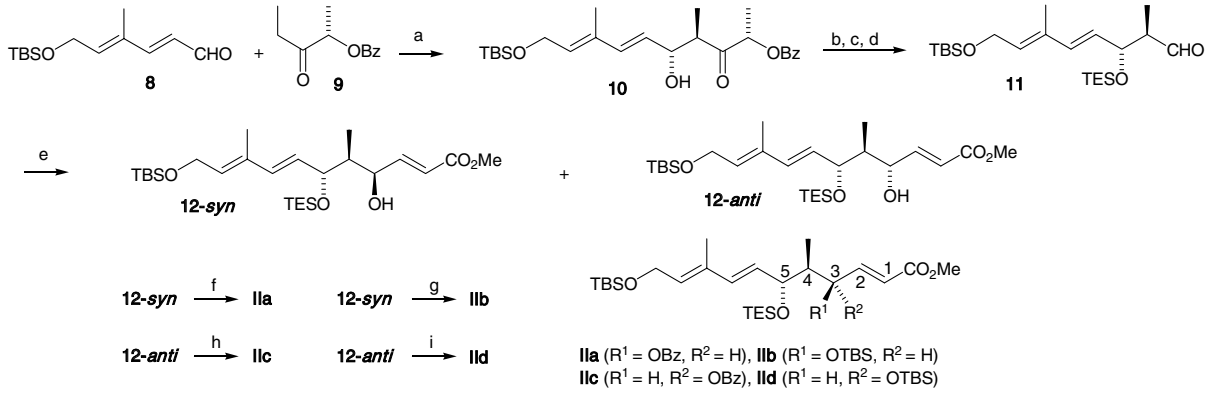
The C4,5-*anti* series, **IIa**–**d**, was prepared as shown in Scheme 3, starting from the *anti*-selective aldol reaction of aldehyde **8**[12] and ketone **9**.[13] The resultant alcohol **10** was protected as the triethylsilyl ether, followed by reduction with $LiBH_4$ and oxidative cleavage with $NaIO_4$ to afford aldehyde **11**. Kishi–Nozaki coupling of **11** with methyl (*E*)-3-iodoacrylate gave separable diastereomers **12-*syn*** and **12-*anti***, which were converted to benzoates **IIa** and **IIc**, respectively, and were also converted to silyl ethers **IId** and **IIb**, respectively.

We additionally prepared the simplified racemic substrates **IIIa**–**d**, which lack the C4 methyl group, and **IVa**–**c** which possess only the C3 stereogenic centers (Schemes 4 and 5). Thus, addition of methyl lithium to aldehyde **8**, and the following MnO_2 oxidation generated methyl ketone **13**. An aldol reaction of **13** with methyl (*E*)-4-oxo-2-butenoate[14] afforded **14**, which was converted to benzoate **15**, followed by Luche reduction[15] to give a separable mixture of **16-*syn*** and **16-*anti***. Compounds **IIIa**–**d** were prepared from **16-*syn*** by the conventional methods as shown in Scheme 4, and their relative configuration was successfully determined by ^{13}C NMR of the corresponding acetonides.[16] Preparation of **IVa**–**b** is shown in Scheme 5. Acetate **19**, prepared from **8** via Luche reduction and following acetylation, was coupled with the Weinreb amide of phenylsulfonylacetic acid using Pd(0), followed by removal of the phenyl sulfonyl group and subsequent DIBAL-H reduction affording **20**. Kishi–Nozaki coupling of **20** with methyl (*E*)-3-iodoacrylate generated **21**, and the benzoate **IVa** and TBS ether **IVb** were prepared in the usual manner.

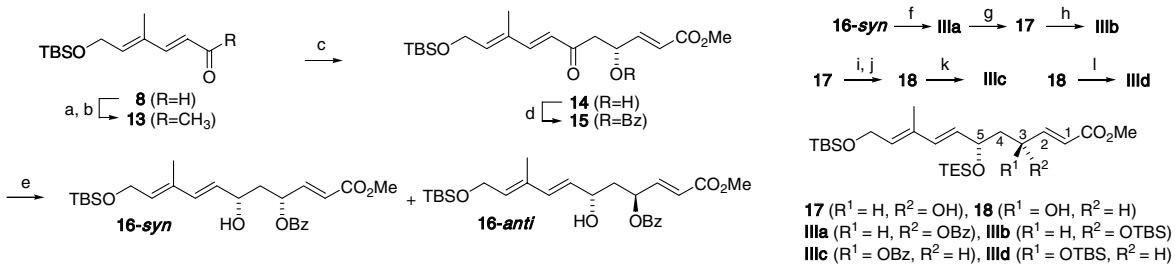
The IMDA reactions of the C4,5-*syn* series, **Ia**–**d**, are summarized in Table 1; the IMDA reaction of **Ia** generated **AIa** and **BIa** in a ratio of 1.1:1 (entry 1), and the IMDA reaction of **Ib** generated **AIb** and **BIb** in a ratio of 2.5:1 (entry 2). On the other hand, the IMDA reactions of **Ic** and **Id**, possessing C3,4-*anti* relative configu-



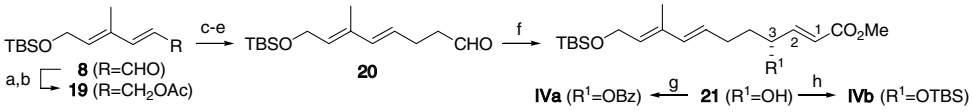
Scheme 2. Reagents and conditions: (a) TESCl, imidazole, DMAP, DMF, rt, 92%; (b) DIBAL-H, THF, −78 °C, 92%; (c) $NiCl_2$ (cat.), $CrCl_2$, methyl (*E*)-3-iodoacrylate, $NaHCO_3$, THF, rt, 96%, *syn*/*anti* = 2:5; (d) MnO_2, CH_2Cl_2, rt, **6-*anti*** (47%, *anti* only), **7** (47%); (e) $NaBH(OMe)_3$, MeOH, rt, 30 min, 64%, *syn*/*anti* = 1:1; (f) PPh_3, DEAD, BzOH, toluene, rt, 74% (at 70% conversion); (g) PPh_3, DEAD, CH_2ClCO_2H, toluene, rt, 80% (at 82% conversion); (h) K_2CO_3, MeOH, rt, 86%; (i) TBSCl, imidazole, DMAP, DMF, CH_2Cl_2, rt, 95% (at 75% conversion); (j) Bz_2O, DMAP, CH_2Cl_2, rt, 7 h, 83% (at 88% conversion); (k) TBSCl, imidazole, DMAP, DMF, CH_2Cl_2, rt, 94% (at 71% conversion).



Scheme 3. Reagents and conditions: (a) *c*-Hex_2BCl, Me_2NEt, Et_2O, −78 °C then −20 °C; (b) TESCl, imidazole, DMAP, CH_2Cl_2, DMF, 96% (two steps); (c) $LiBH_4$, THF, −78 °C, rt; (d) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, 89% (two steps); (e) methyl (*E*)-3-iodoacrylate, $NiCl_2$, $CrCl_2$, THF, **12-*syn*** (42%), **12-*anti*** (53%); (f) Bz_2O, DMAP, CH_2Cl_2, rt, 72%; (g) TBSOTf, DIPEA, CH_2Cl_2, rt, 79%; (h) Bz_2O, DMAP, CH_2Cl_2, rt, 71%; (i) TBSOTf, DIPEA, CH_2Cl_2, rt, 83%.

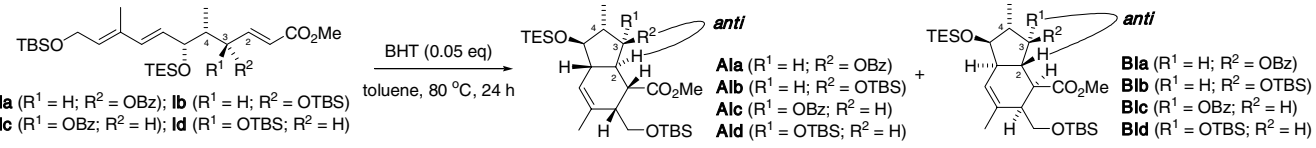


Scheme 4. Reagents and conditions: (a) MeLi, THF, −78 °C, 83%; (b) MnO_2, CH_2Cl_2, rt, 91%; (c) LDA, then methyl (*E*)-4-oxo-2-butenoate, THF, −78 °C, 69%; (d) BzCl, DMAP, pyridine, CH_2Cl_2, rt, 62%; (e) $CeCl_3{\cdot}6H_2O$, $NaBH_4$, MeOH, rt, **16-*syn*** (41%), **16-*anti*** (14%); (f) TESOTf, TEA, CH_2Cl_2, rt, 93%; (g) K_2CO_3, MeOH, rt, 75% (at 56% conversion); (h) imidazole, DMAP, TBSCl, DMF, rt, 89%; (i) PPh_3, $ClCH_2COOH$, DEAD, toluene, rt, 87%; (j) K_2CO_3, MeOH, rt, 77%; (k) BzCl, DMAP, pyridine, CH_2Cl_2, rt, 92% (at 44% conversion); (l) imidazole, DMAP, TBSCl, DMF, rt, 80%.



Scheme 5. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 90%; (b) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 95%; (c) $PhSO_2CH_2CONMe(OMe)$, NaH, $Pd_2(dba)_3$, PPh_3, reflux, 94%; (d) Mg, MeOH, rt, 94%; (e) DIBAL-H, THF, −78 °C, 99%; (f) methyl (*E*)-3-iodoacrylate, $NiCl_2$, $CrCl_2$, $NaHCO_3$, THF, rt, 91%; (g) Bz_2O, DMAP, CH_2Cl_2, rt, 97%; (h) TBSOTf, DIPEA, CH_2Cl_2, rt, 98%.

Table 1. IMDA reactions of **Ia–d**[a]



Entry	R^1	R^2	Substrate	Yield (%) of **A**[b]	Yield (%) of **B**[b]	**A**:**B**
1	H	OBz	**Ia**	46	40	1.1:1
2	H	OTBS	**Ib**	68	27	2.5:1
3	OBz	H	**Ic**	16	65	1:4.1
4	OTBS	H	**Id**	11	77	1:7.0

[a] The IMDA reactions of **Ia–d** were carried out under the same conditions as those for the IMDA reaction of **1**.[2]
[b] Isolated yield.

ration, showed the reversed diastereoselectivity; that is, the IMDA reaction of **Ic** generated **AIc** and **BIc** in a ratio of 1:4.1 (entry 3), and the IMDA reaction of **Id** generated **AId** and **BId** in a ratio of 1:7.0 (entry 4).

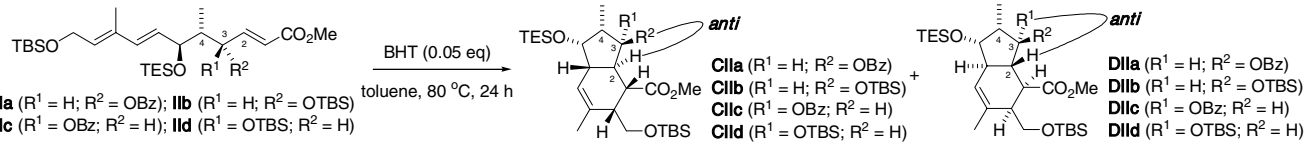
The IMDA reactions of the C4,5-*anti* series, **IIa–d**, were carried out under the same conditions as those for **1**[2] (Table 2). The IMDA reactions of **IIa–d** showed the same trend in their diastereoselectivity as that of **Ia–d**. Thus, **CIIa** and **DIIa** formed in a ratio of 1.8:1 (entry 1), and **CIIb** and **DIIb** formed in a ratio of 1.9:1 (entry 2). The IMDA reactions of **IIc** and **IId** afforded the corresponding **CII** and **DII** in a high diastereomeric ratio of 1:>10 (entries 3 and 4).

The preferential formation of the products with the *anti*-relative configuration between the C–H bond at the C2 position and the C–O bond at the C3 position did not change in the IMDA reactions of **IIIa–d**, which lack the C4 methyl group (Table 3), and nor also in the reactions of **IVa–b** which possess only the C3 stereogenic center (Table 4).

In addition to the trend in the diastereoselectivity described above, the relationships between the relative configuration and the diastereomeric ratio in Table 3 are quite similar to those in Table 1, thereby suggesting that the steric effect of the C4 methyl group on the diastereoselectivity is negligible in the case of the C4,5-*syn* series. In contrast, compared with the results in Tables 1, 3 and 4, the high diastereoselectivity (1:>10, entries 3 and 4) in the IMDA reactions of the C4,5-*anti* **IIc** and **IId** (Table 2) is noteworthy, clearly indicating that the relative configuration of the C3–C5 positions is crucial to the high selectivity.

The transition state models which can explain the preferential formation of the major products in the IMDA

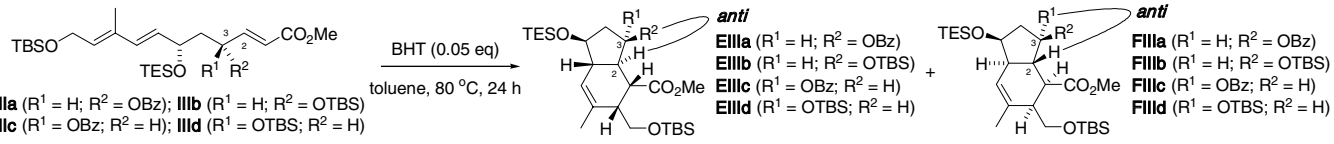
Table 2. IMDA reactions of **IIa–d**[a]



Entry	R^1	R^2	Substrate	Yield (%) of **C**[b]	Yield (%) of **D**[b]	**C**:**D**
1	H	OBz	**IIa**	50	28	1.8:1
2	H	OTBS	**IIb**	60	31	1.9:1
3	OBz	H	**IIc**	—[c]	72	1:>10[d]
4	OTBS	H	**IId**	—[c]	74	1:>10[d]

[a,b]See the footnotes to Table 1.
[c] Yield was not calculated because the product contained impurity.
[d] Ratio determined by ^{1}H NMR.

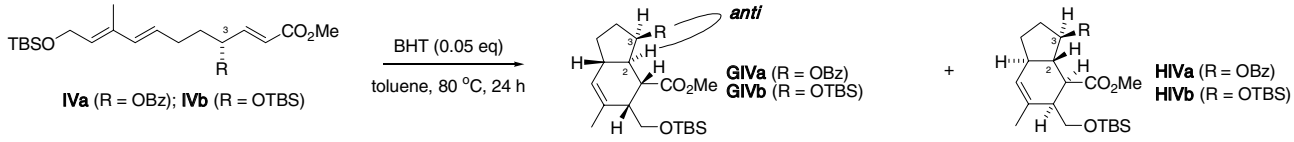
Table 3. IMDA reactions of **IIIa–d**[a]



Entry	R^1	R^2	Substrate	Yield (%) of **E**[b]	Yield (%) of **F**[b]	**E**:**F**
1	H	OBz	**IIIa**	44	31	1.4:1
2	H	OTBS	**IIIb**	66	15	4.4:1
3	OBz	H	**IIIc**	15	67	1:4.5
4	OTBS	H	**IIId**	11	72	1:6.5

[a,b]See the footnotes to Table 1.

Table 4. IMDA reactions of **IVa–d**[a]



Entry	R	Substrate	Yield (%) of **G**[b]	Yield (%) of **H**[b]	**G**:**H**
1	OBz	**IVa**	61	23	2.7:1
2	OTBS	**IVb**	57	15	3.8:1

[a,b]See the footnotes to Table 1.

reactions of **Ia–d** and **IIa–d** are proposed in Figure 2. Since all the products in Tables 1 and 2 are the *endo*-adducts, the transition states are limited to TS-1 and TS-2 for the reactions of **Ia**, **Ib**, **IIa**, and **IIb**, and TS-3 and TS-4 for the reactions of **Ic**, **Id**, **IIc**, and **IId**. Since a carbon–oxygen bond possesses a rather low-lying σ^*_{CO}, when the allylic σ^*_{CO} orbital of the dienophile is aligned *anti* to the forming bonding in the IMDA reaction, its overlap with the HOMO of the transition state, consisting of a mixture of the HOMO of diene and the LUMO of dienophile, is maximized.[17] Consequently, considering the above stereoelectronic effect, TS-2 and TS-3 shown in Figure 2 are surmised to be energetically more favored than TS-1 and TS-4, respectively, because the σ^*_{CO} orbital at C3 position is surmised to align nearly *anti* to the forming bonding in the IMDA reaction. However, the major products formed in Tables 1 and 2 must generate through TS-1 or TS-4; hence, other factors stabilizing TS-1 and TS-4 or destabilizing TS-2 and TS-3 should exist in the IMDA reactions in Tables 1 and 2.

The stereoelectronic effect as described above cannot explain the outcome of the IMDA reactions of **IIIa–d** and **IVa–b** again, however, the reactions of **IVa–b** were suggestive because the products **GIVa–b**, which possess the *anti* relative configuration between C–H bond at the C2 position and C–O bond at the C3 position, were preferentially generated. These results clearly indicate that the configuration of the C3 stereogenic center bearing the protected hydroxyl group is crucial to the observed diastereoselectivity because **IVa–b** possess only one protected hydroxyl group at the stereogenic C3

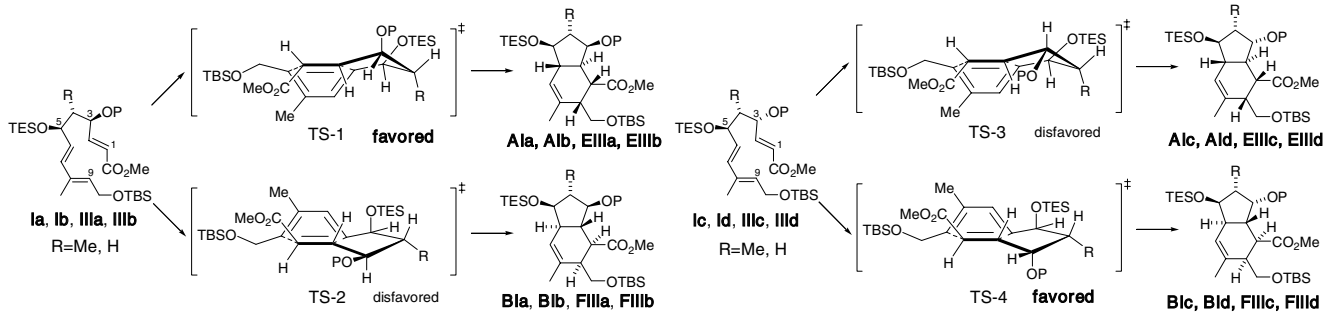


Figure 2.

position. Nevertheless, a careful analysis and discussion is required to account for the observed diastereoselectivity because various factors were surmised to influence the diastereoselectivity and the rationale as well as quantitative analysis for the diastereoselectivity awaits further studies on the IMDA reactions and theoretical calculations.

In conclusion, we found that the configuration of the stereogenic C3 position bearing the protected hydroxyl group is crucial to the diastereoselectivity in the IMDA reaction of the terminally activated (*E*,*E*,*E*)-nona-1,6,8-trienes, and also found the new successful IMDA reaction of the diastereomer of **1** which produced the products in a ratio of 1:>10. These results would be useful for constructing bioactive natural products containing a bicyclo[4.3.0]non-2-ene carbon skeleton. Further studies on the structure–diastereoselectivity relationships as well as the studies with the aid of theoretical calculations are in progress, and the results will be reported in due course.

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Supplementary data

The structure determination of all the products based on the ^{1}H NMR experiments and CIF files for the X-ray crystallographic analysis. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.118.

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