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Utility of a chiral 1,3-dioxane template in stereoselective intramolecular Diels–Alder reactions

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Abstract—The ethylidene acetal of D-erythrose was used as a template for stereoselective IMDA reactions: high *endo* selectivity and yields in favor of the cis product were observed with 1,3,9-trienes, resulting from a boat transition state. For natural product synthesis, the reaction was successfully applied to a diene with terminal *Z*-olefin.

In a program for the asymmetric total synthesis of the cytotoxic diterpene hainanolide,[1,2] we focused on the Diels–Alder reaction[3] to build the pivotal cyclohexane ring of the molecule from which stem all the stereocenters (Fig. 1). It was a challenging matter to get the methyl substituent relatively positioned on the correct side of the ring. The use of *Z*-diene **14** as a Diels–Alder substrate therefore emerged as a straightforward solution depending on the diastereofacial selectivity. Because of the poor reactivity of such *Z*-dienes, harsh thermal conditions[4] or Lewis acid catalysis[5] were expected to be used during the cycloaddition. At the same time, a high degree of stereocontrol was needed to promote the formation of the cis junction (*endo* selectivity). This has been reported to be favored by internal carbonyl within 1,3,9-triene systems,[6] whereas the trans junction is usually promoted by 1,3,8-trienes.[7] We therefore looked in the chiral pool for a template pertaining to high stability and efficient stereocontrol capabilities, in order to build the chiral 1,3,9-decatriene precursor **14**.

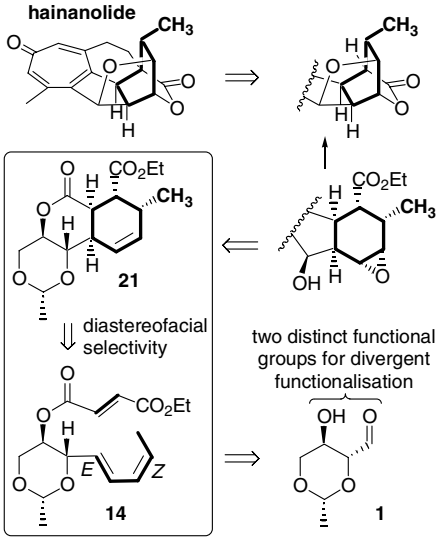

Figure 1.

Common sugars display a high density of useful stereocenters for functional group interconversions and for asymmetry transfer to novel sp^3 centers. D-Glucose in particular is the precursor of (1′*R*)-(−)-2,4-*O*-ethylidene-D-erythrose (**1**).[8] This C_4-building block (Fig. 1) contains interesting functional features—an asymmetric 1,3-dioxane ring flanked with a free hydroxyl group and an aldehyde—which make it highly valuable in organic synthesis. It was therefore particularly well adapted to build the needed tethered triene **14** for the planned stereocontrolled intramolecular Diels–Alder reaction (IMDA).

Keywords: Diels–Alder reaction; Stereoselectivity; *Z*-Diene; *endo*-Boat transition state; Total synthesis.
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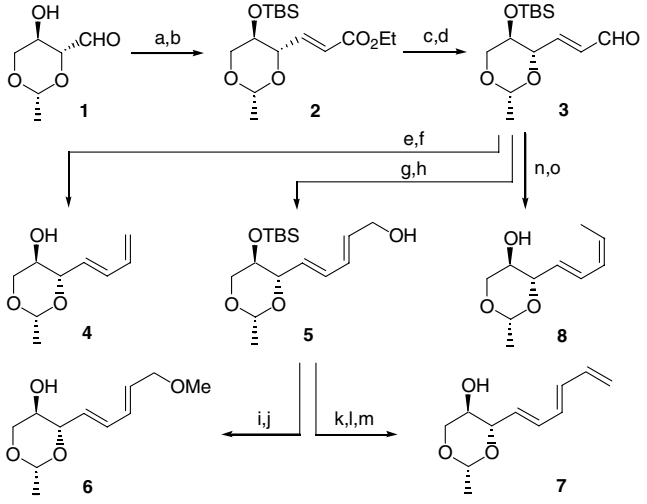
The present report shows that the chiral dioxane tether can be a powerful inducer of asymmetry in the thermal [4+2] cycloaddition. As expected, the stereoselectivity of the reaction favored a cis junction (*endo* addition), while a boat transition state was proposed without ambiguity. The methodology was successfully applied to *Z*-terminal olefin **14** and to other substrates. Once the reaction performed, the dioxane ring in compound **21** was easily unraveled to further progress in the synthesis of hainanolide.

All 1,3,9-triene precursors were thus built from (1′*R*)-(−)-2,4-*O*-ethylidene-D-erythrose (**1**) (Scheme 1). It was synthesized from D-glucose in two steps according to the literature.[8] The diene part was made from the aldehyde function present on the dioxane ring. A Wittig–Horner–Emmons reaction first installed an *E*-double bond within an α,β-unsaturated ester[8] and the remaining hydroxyl group was silylated (TBSCl) to get compound **2**.

Reduction of ester **2** by DIBALH and allylic alcohol oxidation by manganese dioxide gave aldehyde **3** (61% global yield from **1**). Dienes **4**–**8** were then obtained from a second Wittig olefination. A *E* configuration of the terminal double bond arose again from a Wittig–Horner–Emmons reaction followed by reduction of the ester into alcohol **5**. Then divergent functionalization led to the all *trans* diene **6** (methylation of the NaH-generated alcoholate) or to triene **7** (MnO_2 oxidation to an aldehyde then Wittig methylenation), after deprotection. Alternatively, a *Z* configuration was obtained when submitting aldehyde **3** to the non stabilized ylide $Ph_3P{=}CHCH_3$ under 'salt free' conditions, thus giving diene **8** after deprotection (*Z*:*E* 93:7). Esterification of alcohols **4**, **6**–**8** in the presence of an α,β-unsaturated acyl donor (fumaroyl, maleyl, acryloyl) finally furnished the Diels–Alder substrates **9**–**15** (Table 1). The synthetic utility of the method was exemplified by a reaction sequence performed on a 30 g scale to get fumarate **14**, a synthetic intermediate of hainanolide.



Scheme 1. Reagents and conditions: (a) triethylphosphonoacetate, NaH, THF, 0 °C; (b) TBSCl, imidazole, DMAP, CH_2Cl_2, reflux (66%, two steps); (c) DIBALH, CH_2Cl_2, −78 °C→rt; (d) MnO_2, CH_2Cl_2, rt (92%, two steps); (e) $MePh_3PBr$, NaHMDS, THF, −78 °C; (f) TBAF, THF (70%, two steps); (g) triethylphosphonoacetate, NaH, THF, 0 °C; (h) DIBALH, CH_2Cl_2, −78 °C (89%, two steps); (i) NaH, THF then CH_3I, 0 °C; (j) TBAF, THF (85%, two steps); (k) MnO_2, CH_2Cl_2, rt; (l) $MePh_3PBr$, NaHMDS, THF, −78 °C; (m) TBAF, THF (90%, three steps).

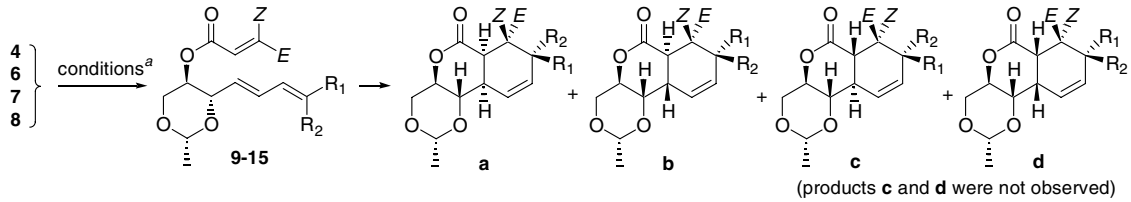
The thermolysis outcome of 1,3,9-decatriene **9**–**15** is reported in Table 1. We began by exploring the conditions on triene **9** (entries 1–5). Thus heating compound **9** for 18 h in refluxing toluene and in the presence of BHT (0.2 equiv) gave both isomers **16a** and **16b** in 85% and 13% yield, respectively (87:13 ratio). A sealed-tube toluene solution of **9** heated at 200 °C for only 1.5 h gave **16a** and **16b** in 96% combined yield (86:14). In refluxing DMF the cycloadducts were obtained in 80% yield after 1 h (83:17 ratio), while in DMSO at 200 °C degradation was observed and only 40% of **16a** could be isolated. Cycloaddition also proceeded when the reaction was catalyzed by a Lewis acid (Et_2AlCl) in CH_2Cl_2 at −30 °C. Under these conditions however, degradation of the starting material was responsible for a low yield of **16a** (33%), although complete selectivity was observed. Following these preliminary experiments, the use of toluene at elevated temperature (200–220 °C) and in the presence of a polymerization inhibitor (BHT) was chosen as the default conditions for this transformation.

Table 1, entries 6–11 provide several other examples of the reaction, showing the best stereoselectivity (92:8) for acrylate ester **11** (entry 7). In the case of triene **13** (entry 9), we suspected polymerization to be responsible for an instability of the compound and for the low yields observed after the thermolysis. Hopefully the presence of a (*E*,*Z*)-diene facing the fumarate dienophile in **14** (entry 10) did not preclude the cycloaddition happening, though it was performed in much longer reaction time (110 h). In this case indeed, cycloadducts **21a** and **21b**[9] were isolated in 80% global yield with a 3:1 selectivity. On the contrary, maleate **15** (entry 11) was unreactive and finally decomposed under the conditions used.

Interestingly, in all cases only two isomers (**a** and **b** series) were observed, showing that the diene part adopted two possible conformations in the transition state (Fig. 2), while the dienophile moiety always gave complete facial selectivity. The *endo* rule was respected, with the internal carbonyl guiding the cyclization and favoring the conformation **9a**. The *endo*:*exo* selectivity ranged from 75:25 to 92:8. Moreover, relatively to the dioxane ring, the preferred diene conformation in **9a** could be reinforced by repulsive interactions between the lone pair electrons of the dioxane oxygen and the $\pi_{C=C}$ orbital of the diene.[10] The CH-eclipsed diene would thus be an energy minimum that could only be adopted by transition state **9a**, compared to the staggered form **9b**–**d**.

Consequently, the *trans*,*cis*-fused 6/6/6 tricyclic system (**16a**) was the main product and likely resulted from the *endo*-boat transition state **9a** (Fig. 2). The *exo*-boat conformation **9b** afforded the minor trans,trans-isomer **16b**. The products from the chair transition states **9c**

Table 1. Application of the thermal Diels–Alder reaction to 1,3,9–trienes **9–15**



Entry	Triene[a]	Cycloadducts (**a** and **b**)	R_1	R_2	*E*	*Z*	Conditions[b]	*T* (°C)	*t* (h)	% **a**	% **b**	Ratio **a**:**b**
1	**9**	**16**	H	H	CO_2Et	H	PhMe, BHT (0.2 equiv)	110	18	85	13	87:13
2							PhMe, BHT (0.2 equiv)	200	1.5	83	13	86:14
3							DMF, BHT (0.2 equiv)	153	1	66	14	83:17
4							DMSO, BHT (0.2 equiv)	200	1	40	0	100:0[c]
5							DCM, Et_2AlCl (1 equiv)	−30→rt	15	33	0	100:0[c]
6	**10**	**17**	H	H	H	CO_2Me	PhMe, BHT (0.2 equiv)	200	2	74	18	80:20
7	**11**	**18**	H	H	H	H	PhMe, BHT (0.2 equiv)	200	1	81	7	92:8
8	**12**	**19**	CH_2OMe	H	CO_2Et	H	PhMe, BHT (0.2 equiv)	200	1	72	11	87:13
9	**13**	**20**	$CH{=}CH_2$	H	CO_2Et	H	PhMe, BHT (0.2 equiv)	200	1.3	40	—	—[c]
10	**14**	**21**	H	CH_3	CO_2Et	H	PhMe, BHT (0.2 equiv)	220	110	60	20	75:25
11	**15**	—	H	CH_3	H	CO_2Me	PhMe, BHT (0.2 equiv)	220	72	—	—	—[c]

[a] Fumarate: fumaric acid monoethyl ester/DCC/DMAP/DCM; Maleate: maleic anhydride/NEt_3, then CH_2N_2; Acrylate: acryloyl chloride/NEt_3/DCM.

[b] All reactions performed at 0.1 M; entries 2 and 6–11 performed in a sealed tube.

[c] Entries 4,5,9: most degradation was observed; entry 9: comparable results were observed at 110 °C over longer reaction times; entry 11: complete degradation.

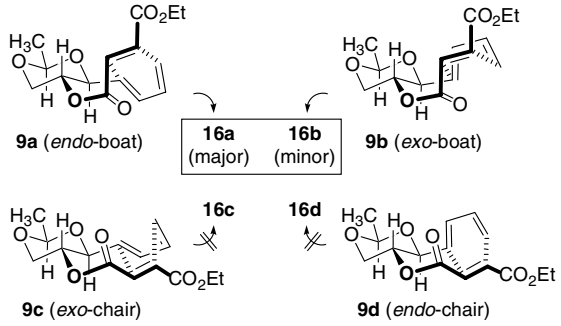
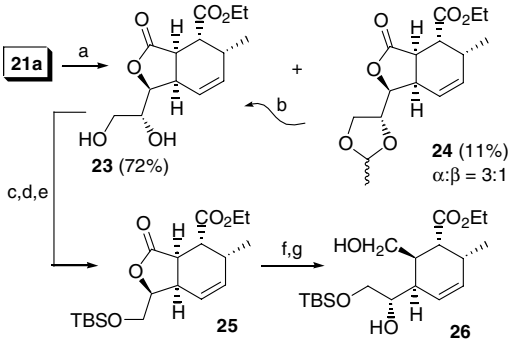


Figure 2.



Scheme 2. Reagents and conditions: (a) H_2O/TFA 1:1, 80 °C, 30 min; (b) HCl, H_2O, acetone; (c) $NaIO_4$, MeOH, H_2O, rt; (d) $NaBH_4$, MeOH, rt; (e) TBSCl, imidazole, DMAP, CH_2Cl_2, reflux (79%, three steps); (f) L-Selectride, THF, −78 °C; (g) $NaBH_4$, MeOH, rt.

and **9d** were not isolated. Indeed, *endo*-boat transition states such as **9a** have often been put forward in the literature[11] to explain the selectivity of this reaction, and considering the constraints fixed by the chiral dioxane tether, the main cycloadducts could not result from a chair-like conformation.

Such a reliable stereoselective IMDA strategy strongly supported our planned synthesis of hainanolide. Further progress consisted in the unraveling of the dioxane tether (Scheme 2). Cycloadduct **21a**[12] was therefore unraveled in acidic medium (TFA/H_2O), leading to acetal hydrolysis. Concomitant ring contraction gave the five-membered lactone **23** along with some recyclable dioxolane **24** (dr 3:1) whose crystallographic analysis of the major isomer (α-**24**, see Fig. 3) confirmed the conservation of epimerizable centers. Sequential diol cleavage/aldehyde reduction/silylation gave the bicyclic compound **25**. Complete reduction of the lactone ring was possible by the successive action of L-Selectride and $NaBH_4$, thus delivering the advanced intermediate **26**.

The IMDA strategy reported herein has been developed for the asymmetric synthesis of a complex diterpene. The need for a readily available asymmetric tether for the construction of 1,3,9-decatrienes led us to choose the chiral dioxane template arising from (1′*R*)-(−)-2,4-*O*-ethylidene-D-erythrose (**1**). This heterocycle which was later destined to be unraveled allowed the diene and the dienophile to be closely oriented for stereoselective cycloaddition. We thus demonstrated that it can be a good conformational activator for stereocontrolled IMDA reactions and that an *endo*-boat transition state can only explain the diastereofacial selectivity. Asymmetric tricyclic systems have thus been elaborated in a

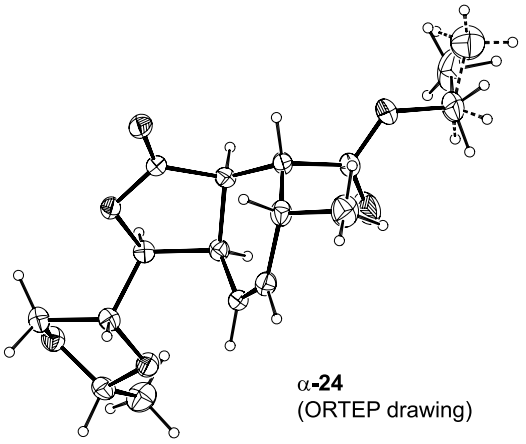


Figure 3.

short time and easy steps, and could serve as valuable intermediates in forthcoming natural product synthesis.

Acknowledgment

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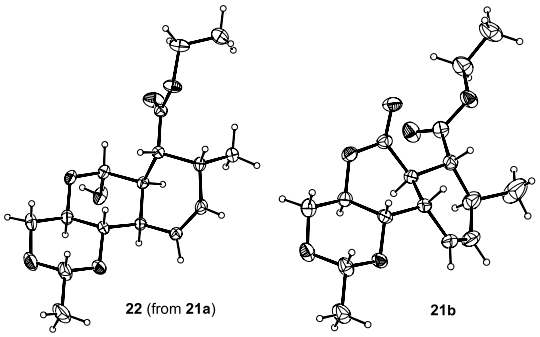
9. Except for products **17a/b** which were separated after hydrogenation, all cycloadducts were separated by simple column chromatography. The structures were determined by NOESY experiments showing transannular correlations in the lactone ring. X-ray analysis (ORTEP drawings shown below) confirmed the stereochemistry for the *endo* product **21a** after L-Selectride reduction into lactol **22** and for the *exo* product **21b** (see also Scheme 2).



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11. See Ref. 6c and references cited therein.
12. Data for compound **21a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 5.80 (m, 1H). 5.66 (m, 1H), 4.75 (q, 5.1 Hz, 1H), 4.33 (dd, 10.5, 5.3 Hz, 1H), 4.23 (m, 3H), 3.56 (dd, 10.5, 10.0 Hz, 1H), 3.43 (dd, 10.1, 3.4 Hz, 1H), 3.29 (dd, 5.4, 3.4 Hz, 1H), 3.23 (t-like dd, 9.2 Hz, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.39 (d, 5.1 Hz, 3H), 1.27 (t, 7.2 Hz, 3H), 1.12 (d, 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 172.3, 171.7, 131.3, 125.6, 99.9, 79.8, 68.0, 67.7, 60.7, 43.6, 38.3, 35.0, 28.1, 20.4, 17.9, 14.4. IR (KBr) ν cm^{-1}: 2978, 2928, 2852 (CH), 1751 (C=O lactone), 1732 (C=O ester), 1184–1072 (C–O). HRMS (ESI+) m/z: Calcd for $C_{16}H_{22}O_6Na$ (MNa^+) 333.1314. Found: 333.1311. $[\alpha]_D^{20}$ −94.1 (CH_3OH, c 1.0).