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Short Communication

Stereoselective Asymmetric Diels-Alder Reaction of Chiral Lactone Derived from D-Glucose with Cyclopentadiene

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In a previous paper, we reported versatile chiral norbornenes as leukotriene D4 antagonists.[1] The chiral norbornenes were synthesized through asymmetric Diels-Alder reaction between cyclopentadiene and chiral dienophile derived from D-glucose. The chiral dienophile used in the previous study had *trans* double bond, which eventually gave only *trans* relative configurations at newly formed chiral carbons in norbornenes products (**A-D**) (Fig. 1).

Therefore, it is desirable to synthesize chiral dienophile with *cis*-configuration to expand the diversities of chiral norbornenes (**E-H**) which would show improved activities as leukotriene D4 antagonism (Fig. 2).[2-6]

In this communication, facial synthesis of *cis* lactone as a chiral dienophile from D-glucose and its application in asymmetric Diels-Alder reaction in high stereoselective manner will be discussed.

Chiral aldehyde **1** is conveniently prepared by a simple three-step reaction from D-glucose.[1] When Wittig reaction was applied to chiral aldehyde **1** with $Ph_3P=CHCO_2Me$ at room temperature, crude mixture of *trans* (J = 15.8 Hz) and *cis* (J = 11.6 Hz) dienophile (**2**) was obtained as a *trans* major product (*trans* : *cis* = 4 : 1). However, Horner-Emmons alkenation of chiral aldehyde **1** with bis(2,2,2-trifluroethyl) (methoycarbonylmethyl)phosphonate[7] gave dienophile with *cis* major (*trans* : *cis* = 1 : 4). The *cis-trans* mixture **2** was treated with silica gel in MeOH solution, which smoothly transformed *cis* isomer into lactone **3**. Due to difficulty in separation of the *cis* isomer from *cis-trans* mixture of **2**, the resulting chiral lactone made the separation very convenient.

Diels-Alder reaction between chiral lactone **3** and cyclopentadiene under thermal conditions gave only two *Si*-face attacked stereoisomeric norbonenes with isomeric ratio (major : minor = 11 : 1) out of four possible stereoisomers. The relative configurations at the newly formed carbons at C-5 and C-6 were assigned by ^{1}H COSY NMR.

Discrimination between *endo* products (**4** or **5**) and *exo* products (**6** or **7**) is relatively easy. The *endo* products (**4** or **5**) have two protons (H5 and H6) in *exo* mode, which show relatively low-field chemical shifts in ^{1}H-NMR spectra.[8] The

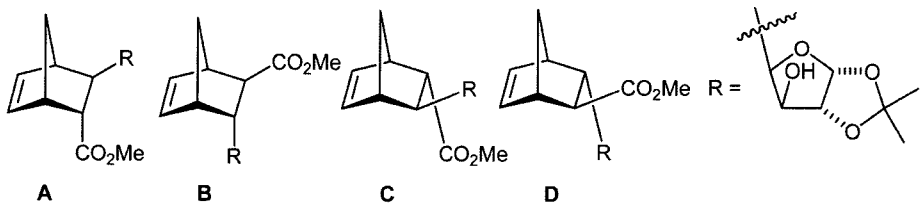

Fig. 1. Enantiomerically pure norbornenes with *trans* relationship substituents from D- glucose.[1]

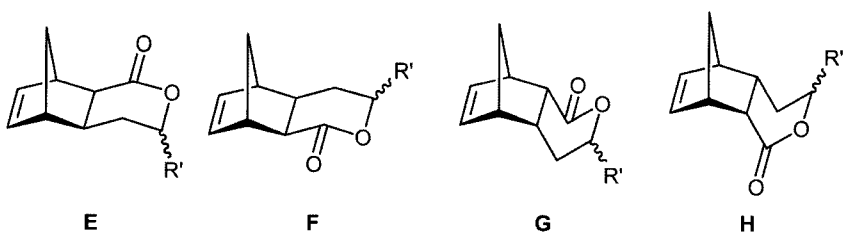

Fig. 2. Enantiomerically pure norbornenes with *cis* relationship substituents.

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Abbreviations: NMR, nuclear magnetic resonance; NOE, nuclear Overhauser enhancement; NOESY, nuclear Overhauser and exchange spectroscopy; TMS, tetramethylsilane.

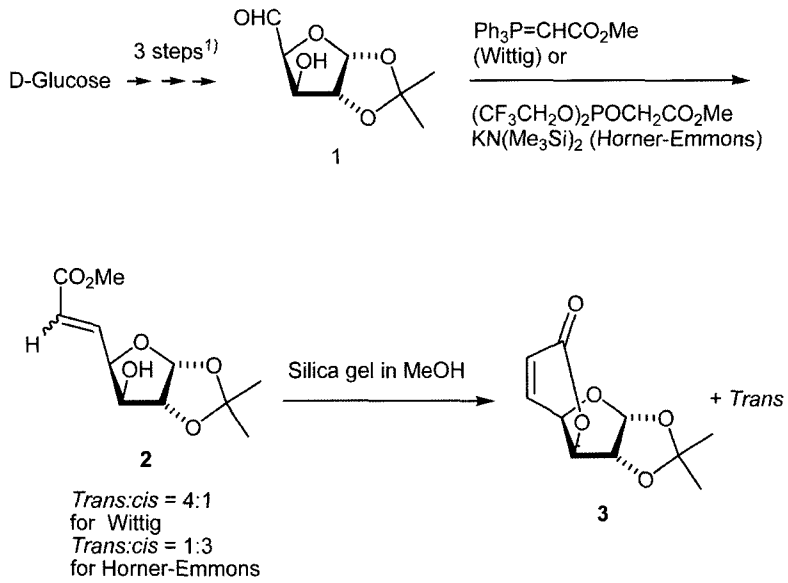

Fig. 3. Synthetic methods for chiral *cis* dienophile 3 from D- glucose.

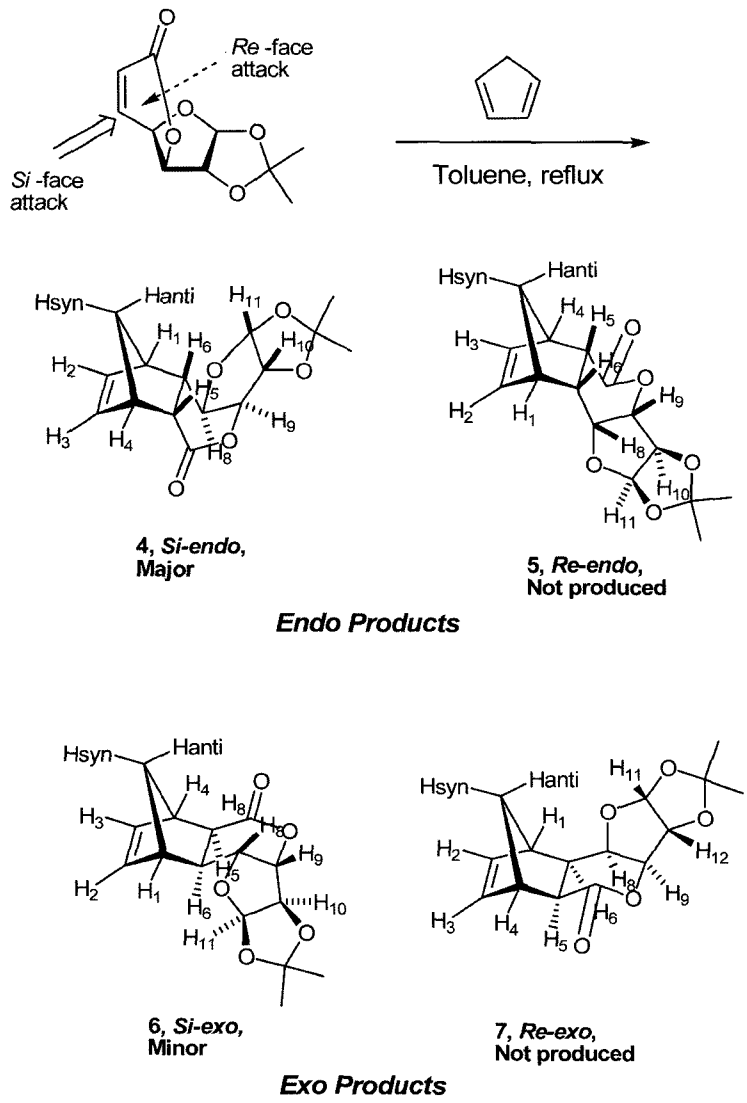

Fig. 4. Asymmetric Diels-Alder reaction between chiral *cis* dienophile 3 and cyclopentadiene.

major stereoisomeric norbonene shows chemical shifts of H-5 at 3.09 ppm and H-6 at 2.91 ppm, indicating it is one of the *endo* norbonenes (**4** or **5**). On the other hand, the minor stereoisomeric norbonene shows relatively high-field chemical shifts of H-5 at 2.46 ppm and H-6 at 2.22 ppm, indicating it is one of the *exo* norbonenes (**6** or **7**). Additional supporting evidence that the major isomer is an *endo* product was obtained from NOESY spectrum, in which strong NOE signals of H-5/ $H\text{-}7_{anti}$ and H-6/ $H\text{-}7_{anti}$ were observed.

The absolute configuration of the major product **4**, differentiating it from the other possible *endo* isomer **5**, could also be established through NOESY spectrum. Weak NOE signals were shown between H-2, H-3 (both protons have the same chemical shift at 6.28 ppm) and H-9 (4.38 ppm), H-8 (4.28 ppm), which are relatively close to each other in three dimensional model. No NOE between H-6 and H-9 was detected in NOESY spectrum of major product **4**, which indicates that H-5 and H-6 are in opposite direction to H-8 and H-9 in the lactone plane. If major *endo* isomer were **5**, it would show strong NOE between H-6 and H-9 and insensible NOE signals between H-2, H-3 and H-8, H-9.A similar discrimination between two possible minor *exo* isomers **6** and **7** was made through NOESY spectrum. Two strong NOE signals (H-2/H-6 and H-3/H-5) indicate the minor product is an *exo* isomer. A large NOE signal between H6 and H11 rules out the possibility of structure **7**, thus permitting assignment of the minor product **6**.

It is noteworthy that the large coupling constant between H-5 and H-6, which are attached to the newly formed carbons C-5 and C-6 respectively ($J_{5,6}$= 9.2 Hz in major **4**, $J_{5,6}$= 8.6 Hz in major **6**) shows that H5 and H6 are in the *cis* relationship ($J_{5,6}$ = 4.4-5.2 Hz in the *trans* isomers **A-D**), [1] confirming that *cis*-relationship between H-5 and H-6 was maintained during the Diels-Alder reaction.

These two assignments of absolute configurations revealed that the diene attacks the dienophile **3** exclusively from the *si*-face. *Re* face of the dienophile's δ-lactone ring is strongly shielded by two sugar rings. On this steric ground it is clear that favored attack of diene would be exclusively from the *si*-face of the dienophile, resulting in a very high diastereofacial selectivity.

Dienophile 3.; ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.33 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 4.63 (m, 1H, H_3), 4.82 (m, 2H, H_4, H_5), 6.02 (d, 1H, *J*3.7 Hz, H_6), 6.23 (d, 1H, *J* 9.7 Hz, H_1), 6.96 (dd, 1H, *J* 9.7, 5.6 Hz, H_3), ^{13}C-NMR (100 MHz); δ. 160.8 (C = O), 138.6 (C3), 125.4 (C2), 112.6 (C7), 105.3 (C8), 83.4 (C4), 82.4 (C5), 67.6 (C6), 26.7 (CH_3), 26.2 (CH_3).

4 ; ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.31 (s, 3H, CH_3), 1.48 (d, 1H, $J_{7syn,7anti}$ 8.7 Hz, H_{7syn}), 1.52 (s, 3H, CH_3), 1.58 (dd, 1H, *J* 1.7, 8.7 Hz, H_{7anti}), 2.91 (d, 1H, $J_{5,6}$ 9.2 Hz, 3.4 Hz, H_6), 3.09 (dd, 1H, *J* 4.2, 9.2 Hz, H_5), 3.16 (bs, 1H, H_1), 3.40 (bs, 1H, H_4), 4.28 (bs, 1H, H_8), 4.38 (d, 1H, *J* 2.3 Hz, H_9), 4.60(d, 1H, $J_{10,11}$ 3.8 Hz, H_{10}), 5.78 (d, 1H, *J* 3.8 Hz, H_{11}), 6.28 (m, 2H, $H_{2,3}$) ^{13}C-NMR (100 MHz); δ. 171.2 (C = O), 136.2 (C2), 135.9 (C3), 111.9 (C12), 103.2 (C11), 84.3 (C10), 81.6 (C9), 73.7 (C8), 50.7 (C7), 48.8 (C4), 46.6 (C1), 40.0 (C5), 39.9 (C6), 26.4 (C14), 26.0(C13).

6 ; ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.33 (s, 3H, CH_3), 1.40 (d, 1H, $J_{7syn,7anti}$ 9.6 Hz, H_{7syn}),1.46 (dd, 1H, *J* 1.5, 9.6 Hz, H_{7anti}), 1.54 (s, 3H, CH_3), 2.22 (d, 1H, $J_{5,6}$ 8.6 Hz, H_6), 2.46 (ddd, 1H, *J* 0.8, 1.5, 8.6 Hz, H_5), 2.89 (bs, 1H, H_1), 3.30 (bs, 1H, H_4), 4.41 (t, 1H, *J* 1.9 Hz, H_8), 4.74 (d, 1H, $J_{10,11}$ 3.8 Hz, H_{10}), 4.67 (d, 1H, *J* 2.3 Hz, H_9), 5.83 (d, 1H, *J* 3.8 Hz, H_{11}), 6.25 (dd, 1H, *J* 2.9, 5.5 Hz, H_3), 6.36 (dd, 1H, *J* 3.1, 5.5 Hz, H_2), ^{13}C-NMR (100 MHz); δ. 171.9 (C = O), 139.0 (C2), 136.5 (C3), 112.1 (C12), 103.4 (C11), 84.4 (C10), 81.6 (C9), 74.7 (C8), 50.7 (C4), 45.9 (C1), 44.5 (C7), 40.0 (C5), 39.3 (C6), 26.4 (C14), 26.1 (C13).

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