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Article

Facial Synthesis of Versatile Chiral Norbornenes as Leukotriene D4 Antagonists from D-glucose

Yoongho Lim[1] and Dongsoo Koh*

Department of Applied Chemistry, Dongduk Women's University, Seoul 136-714, Korea

[1]Bio/Molecular Informatics Center, Department of Applied Biology and Chemistry, Konkuk University, Seoul 143-701, Korea

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Chiral dienophile 5 was synthesized from D-glucose by consecutive diisopropylidenation, partial deprotection, diol cleavage, and Wittig reactions. Under thermal conditions, asymmetric Diels-Alder reaction between chiral dienophile and cyclopentadiene gave four possible chiral norbornenes stereoisomers whose absolute configurations were determined through CADD and NMR.

Key words: *Asymmetric reaction,* Chiral Dienophiles*, Diels-Alder reaction, Stereochemistry.*

As a programmed project for the development of leukotriene D4 receptor antagonists for use as anti-asthmatic agents, extracts from higher plants were screened to evaluate the properties of leukotriene D4 receptor antagonists,[1-7] and, after activity-guided fractionation, two final candidates were isolated from *Sanguisorba officinalis* and *Bupueurum falcatum*. Both candidates contained sugar moiety as a potential component in the molecules.[6,7] Optically pure norbornenes have been focused as antagonists for prostaglandines, thromboxanes and leukotrienes which are chemical mediators derived from phospholipids cascade.[8-10] We attempted to synthesize optically pure norbornenes which have sugar moiety as leukotriene D4 receptor antagonists. Here, we report the facial synthesis of chiral norbornenes from the readily available D-glucose.

D-Glucose was transformed into hydroxy aldehyde **4** through a three-steps pathway of diisopropylidenation, partial deprotection, and diol cleavage. Wittig reaction between hydroxy aldehyde **4** and $Ph_3P=CHCO_2CH_3$ was performed to give chiral dienophile **5**. Asymmetric Diels-Alder reaction between chiral dienophile and cyclopentadiene under thermal condition, afforded a mixture of four diastereoisomeric norbornenes **7-10**. Separation of the four pure norbornene derivatives was made by flash column chromatography and their absolute configurations were assigned through NMR and CAMM

Materials and Methods

General methods. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter at 25°C unless otherwise noted. Melting points were determined using a Thomas-Hoover Unimelt apparatus. ^{1}H- and ^{13}C-NMR spectra were recorded using a Bruker Avance 400 spectrometer system (9.4 T) at 298°K. Splitting patterns are designated as: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet.

TLC was performed on precoated glass plates of Silica Gel 60_F-254 (E. Merck), and compounds on the plate were detected by spraying with 10% *aq* H_2SO_4 solution with subsequent heating or irradiation of UV-light. Flash-column chromatography was performed on 230-300 mesh silica gel as described in the literature.[11]

Synthesis of monoacetone glucose 3. Diacetone-D-glucose[12] **2** (2 g, 7.68 mmol) was dissolved in 50% aqueous acetic acid (20 m*l*) and stirred at room temperature for 10 h. The aqueous solvent was evaporated in vacuo to give a white residue. The residue was partitioned into methylenechloride (70 m*l*) and water (20 m*l*), and the aqueous layer was washed with methylenechloride (30 m*l*). The combined organic layers were successively washed with saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. Filtration and evaporation gave a white solid of monoacetone glucose **3**, (1.75 g, 87.5%). mp 158-159°C, (lit[13] mp 160-161°C). $[\alpha]_D$; −12.7°, (*c* 1.2, H_2O), ^{1}H-NMR (400 MHz, CD_3OD); δ 5.76 (d, 1H, *J* 3.7 Hz), 4.37 (d, 1H, *J* 3.7 Hz), 4.10 (d, 1H, *J* 2.6 Hz), 3.92 (dd, 1H, *J* 8.5, 2.6 Hz), 3.78 (m, 1H), 3.68 (dd, 1H, *J* 11.5, 3.1 Hz), 3.50 (dd, 1H, *J* 11.6, 6.0 Hz), 1.35 (s, 3H), 1.19 (s, 3H), ^{13}C-NMR (100 MHz, CD_3OD); δ 112.8, 106.5, 86.6, 81.4, 75.7, 70.5, 65.3, 27.1, 26.5

Synthesis of hydroxy aldehyde 4. Monoacetone glucose **3** (1.70 g, 7.73 mmol) was dissolved in MeOH (25 m*l*) to give a clear solution, and the temperature was cooled down to 0°C. Aqueous $NaIO_4$ solution (3.31 g, 15.46 mmol in 25 m*l* H_2O) was added to the above cold solution and stirred for 3 h at room temperature. Precipitate was filtered, and the filtrate was evaporated under reduced pressure. The resulting residue was

*Corresponding author
Phone: +82-2-940-4512; Fax: +82-2-940-4193
Email: dskoh@dongduk.ac.kr

Abbreviations: TLC, thin layer chromatography; NMR, nuclear magnetic resonance; NOESY, Nuclear Overhauser and Exchange Spectroscopy; CAMM, Computer Aided Molecular Modeling.

partitioned into ethyl acetate (50 m*l*) and water (30 m*l*), and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and evaporation afforded syrup of aldehyde **4** (1.01 g, 69.7%), which was used for subsequent reaction without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$); δ 9.56 (s, 1H), 5.99 (dd, 1H, *J* 3.7, 15.8 Hz), 4.55 (m, 1H), 4.26 (m, 1H), 4.14 (m, 1H), 1.50 (s, 3H), 1.31 (s, 3H), ^{13}C-NMR (100 MHz, $CDCl_3$); δ 192.0, 112.2, 105.1, 86.7, 84.6, 83.2, 26.8, 26.6

Synthesis of dienophile 5. Hydroxy aldehyde **4** (1.01 g, 5.37 mmol) and methyl (triphenylphosphoranylidene)acetate (2.69 g, 8.06 mmol) were dissolved in methylene chloride (50 m*l*) and the reaction mixture was stirred for 7 h at room temperature. TLC showed one major (R_f 0.47, 1 : 1 EtOAc-hexanes), one minor (R_f 0.35), and a by-product triphenyl oxide (R_f 0.15). Solvent was removed under reduced pressure. Diethyl ether was added to the residue, and the insoluble by-product triphenylphospine oxide was filtered. Filtration and concentration of the filtrates afforded syrup, which was purified by flash chromatography (1 : 1 EtOAc-hexane), to give syrup of *trans* dienophile **5** (787 mg, 64%). $[\alpha]_D$; −42.2°, (*c* 1.8, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$); δ 6.96 (dd, 1H, *J* 4.4, 15.8 Hz), 6.26 (dd, 1H, *J* 1.9, 15.8 Hz), 5.99 (d, 1H, *J* 3.8 Hz), 4.84 (dd, 1H, *J* 4.5, 2.5 Hz), 4.57 (d, 1H, *J* 3.6 Hz), 4.24 (s, 1H), 3.75 (s, 3H), 2.34 (s, 1H), 1.50 (s, 3H), 1.32 (s, 3H), ^{13}C-NMR (100 MHz, $CDCl_3$); δ 166.8, 141.4, 123.5, 112.1, 104.7, 85.0, 79.7, 76.0, 51.9, 26.8, 26.2

Synthesis of norbornene derivatives 7-10. To a stirred solution of *trans* dienenophile **5** (1.4 g, 5.7 mmol) in toluene (20 m*l*) was added catalytic amount of hydroquinone (5 mg) and cyclopentadiene **6** (freshly distilled from dicyclopentadiene, 3.1 m*l*), and the mixture was refluxed for 15 h. TLC showed that the starting material dienenophile **5** was absent. Solvent was evaporated in vacuo to give a brown syrup, which was charged onto a column of silica gel eluted with 1 : 7 EtOAc-hexane to afford two major products **7** (271 mg, 15.3%) and **9** (672 mg, 38.0%), and two minor products **8** (97 mg, 5.5%) and **10** (62 mg, 3.5%).

Compound 7. R_f 0.48 (1 : 3 EtOAc- hexanes), ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.33 (s, 3H, CH_3), 1.49 (ddd, 1H, *J* 1.5, 1.7, 9.1 Hz, H_{7syn}), 1.51 (s, 3H, CH_3), 1.54 (d, 1H, *J* 9.1 Hz, H_{7anti}), 1.99 (ddd, 1H, *J* 1.4, 4.8, 11.0 Hz, H_6), 2.57 (dd, 1H, *J* 4.8, 8.5 Hz, H_5), 3.09 (m, 1H, H_1), 3.21 (m, 1H, H_4), 3.71 (s, 3H, OCH_3), 3.94 (dd, 1H, *J* 2.1, 11.0 Hz, H_8), 4.14 (m, 1H, H_9), 4.58 (d, 1H, *J* 3.7 Hz, H_{10}), 5.96 (d, 1H, *J* 3.7 Hz, H_{11}), 6.06 (dd, 1H, *J* 2.8, 5.6 Hz, H_3), 6.30 (dd, 1H, *J* 3.2, 5.6 Hz, H_2), ^{13}C-NMR (100 MHz); δ. 176.9, 139.0, 134.4, 111.2, 105.1, 84.8, 84.7, 74.9, 52.6, 48.2, 45.4, 44.6, 44.5, 42.6, 26.8, 26.1.

Compound 8. R_f 0.27 (1 : 3 EtOAc- hexanes), ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.31 (s, 3H, CH_3), 1.39 (ddd, 1H, *J* 1.6, 1.8, 9.9 Hz, H_{7syn}), 1.50 (s, 3H, CH_3), 1.81 (d, 1H, *J* 8.6 Hz, H_{7anti}), 2.07 (ddd, 1H, *J* 1.7, 4.4, 4.4 Hz, H_6), 2.75 (m, 1H, *J* 1.6 Hz, H_1), 3.22 (m, 1H, H_4), 3.25 (dd, 1H, *J* 4.2, 4.4 Hz, H_5), 3.66 (s, 3H, OCH_3), 4.15 (m, 1H, H_9), 4.17 (dd, 1H, *J* 2.5, 4.4 Hz, H_8), 4.49 (d, 1H, *J* 3.8 Hz, H_{10}), 5.92 (d, 1H, *J* 3.8 Hz, H_{11}), 6.04 (dd, 1H, *J* 2.7, 5.6 Hz, H_3), 6.28 (dd, 1H, *J* 3.1, 5.6 Hz, H_2), ^{13}C-NMR (100 MHz, $CDCl_3$); δ. 177.3, 138.4, 134.7, 111.2, 104.7, 84.7, 83.2, 76.4, 52.1, 48.3, 46.9, 45.4, 46.0, 41.9, 26.7, 26.1.

Compound 9. R_f 0.36 (1 : 3 EtOAc- hexanes), ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.31 (s, 3H, CH_3), 1.38 (dd, 1H, *J* 8.9 Hz, H_{7anti}), 1.45 (s, 3H, CH_3), 1.58 (ddd, 1H, *J* 1.2, 1.8, 8.9 Hz, H_{7syn}), 1.87 (dd, 1H, *J* 1.7, 5.2 Hz, H_5), 2.58 (ddd, 1H, *J* 3.4, 5.2, 10.9 Hz, H_6), 3.11 (dd, 1H, *J* 1.8, 3.4 Hz, H_1), 3.25 (m, 1H, H_4), 3.56 (dd, 1H, *J* 2.2, 10.9 Hz, H_8), 3.77 (s, 3H, OCH_3), 4.03 (m, 1H, H_9), 4.53 (d, 1H, *J* 3.6 Hz, H_{10}), 5.94 (d, 1H, *J* 3.6 Hz, H_{11}), 6.23 (dd, 1H, *J* 1.7, 4.4 Hz, H_3), 6.23 (dd, 1H, *J* 1.8, 4.4 Hz, H_2), ^{13}C-NMR (100 MHz, $CDCl_3$); δ. 177.3, 136.5, 135.9, 111.4, 105.0, 84.9, 84.5, 75.1, 52.8, 48.0, 47.5, 45.6, 44.5, 42.9, 27.0, 26.4.

Compound 10. R_f 0.22 (1 : 3 EtOAc- hexanes), ^{1}H-NMR (400 MHz, $CDCl_3$); δ 1.28 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.44 (ddd, 1H, *J* 1.7, 1.7, 8.6 Hz, H_{7syn}), 1.67 (d, 1H, *J* 8.6 Hz, H_{7anti}), 2.28 (dd, 1H, *J* 1.5, 4.5 Hz, H_5), 2.80 (ddd, 1H, *J* 3.4, 4.5, 9.9 Hz, H_6), 2.94 (m, 1H, H_1), 3.06 (m, 1H, H_4), 3.52 (dd, 1H, *J* 2.6, 9.9 Hz, H_8), 3.70 (s, 3H, OCH_3), 4.03 (m, 1H, H_9), 4.49 (d, 1H, *J* 3.8 Hz, H_{10}), 5.85 (d, 1H, *J* 3.8 Hz, H_{11}), 6.12 (dd, 1H, *J* 2.8, 5.6 Hz, H_2), 6.29 (dd, 1H, *J* 3.3, 5.6 Hz, H_3), ^{13}C-NMR (100 MHz, $CDCl_3$); δ. 176.3, 137.5, 134.8, 111.3, 104.3, 85.4, 83.9, 75.3, 52.1, 48.1, 47.8, 47.4, 44.4, 42.2, 26.6, 26.1.

Results and Discussion

Partial cleavage of two isopropylidene groups in diacetone glucose **2** was accomplished by treatment with 50% aqueous acetic acid solution, affording monoacetone glucose **3** at 87.5% yield (Fig. 1). Diol in monoacetone glucose **3** was cleaved via sodium periodate[14] oxidation to give hydroxy aldehyde **4**. Wittig olefination was performed through reaction between hydroxy aldehyde **4** and $Ph_3P=CHCO_2CH_3$ as described in the literature.[15] The crude product of Wittig reaction showed *trans* configuration at newly formed C = C double bond (*J* 15.8 Hz) as a major, which was contaminated with *cis* minor (*J* 11.6 Hz) product by NMR. When dichloromethane solvent was used in the reaction, *trans* isomer was obtained as a major product. However when methanol solvent was employed, *cis* isomer was increased to 30% yield. After flash chromatography (1 : 1 EtOAc-hexanes) separation, *trans* dienophile **5** was obtained at 64% yield. Diels-Alder reaction between dienophile **5** and cyclopentadiene **6** under thermal conditions (refluxing toluene) gave all possible four stereoisomers, two major products **7** (271 mg, 15.3%) and **9** (672 mg, 38.0%), and two minor products **8** (97 mg, 5.5%) and **10** (62 mg, 3.5%) (Fig. 2).

For the convenience of discussion, the proton adjacent to the carboxylate group is assigned as H_5, and the proton neighboring the sugar group is assigned as H_6 in all norbornene derivatives. H_{7syn} is in the same side, whereas H_{7anti}

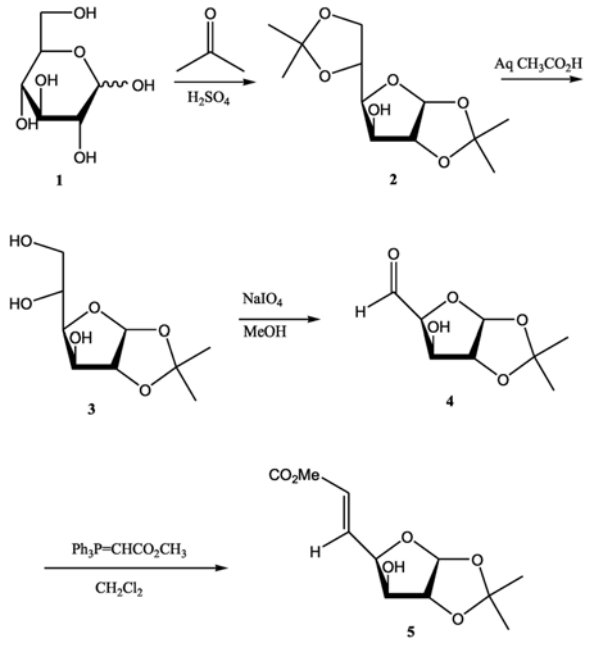

Fig. 1. Synthetic methods for chiral dienophoile 5 from D-glucose.

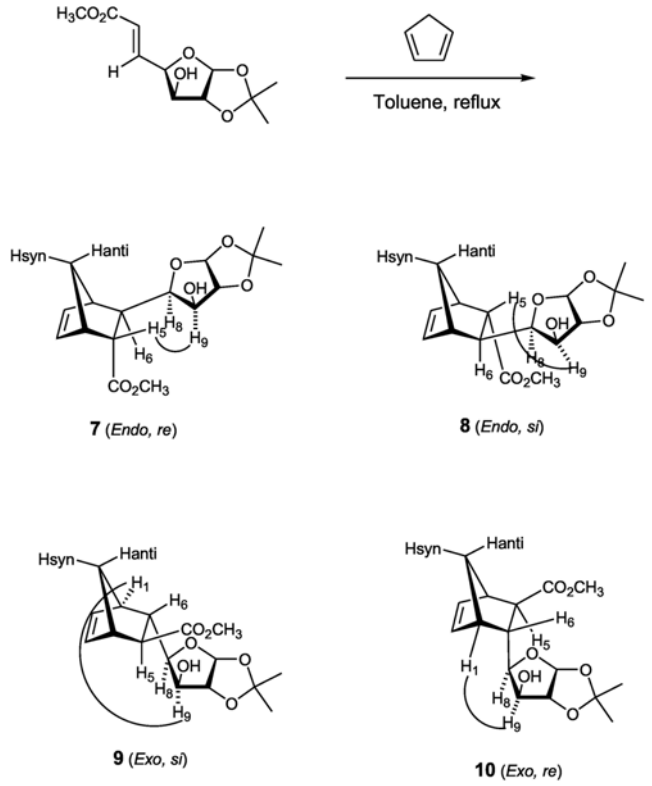

Fig. 2. Asymmetric Diel-Alder reaction and formation of versatile chiral norvornenes.

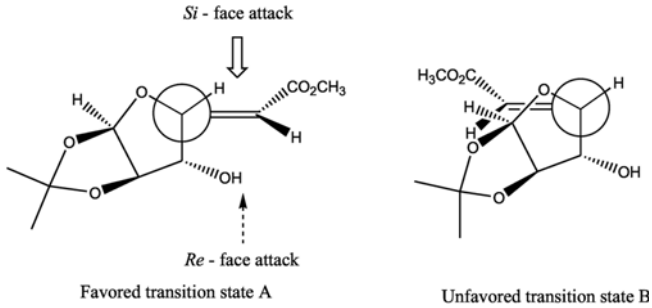

Fig. 3. Two transition states of asymmetric Diel-Alder reaction.

is in the opposite side, of norbornene double bond. Stereochemistry of each norbornene derivative was determined as follow. Discriminations between *endo* products and *exo* could be easily made, because the *endo* products (**7**, **8**) have H_5 in *exo* mode and H_6 in *endo* mode. Therefore, H_5 was in the same direction with H_{7anti}, which showed NOE signals between H_5 and H_7anti. However, H_6 showed NOE signals with H_{7anti} in *exo* products (**9**, **10**). Therefore, norbornenes **7** and **8** were assigned as *endo*, and **9** and **10** were assigned as *exo*. Notably, H_5 in *endo* products showed relative down-field chemical shift compared to H_5 chemical shifts in *exo* products[16] in norbornene system. Good agreements were observed between *endo* products **7** (δ 2.57 ppm, H_5) and **8** (δ 3.25 ppm, H_5), and *exo* products **9** (δ 1.87 ppm, H_5) and **10** (δ 2.28 ppm, H_5).

Distinguishing absolute stereochemistriry between two *endo* **7** and **8**, and *two* exo **9** and **10** was difficult. To discriminate **7** from **8**, distance between H_5 and H_9 was calculated by CAMM. The distances D(H_5-H_9) in norbornenes **7** and **8** are 2.60 and 4.70 Å, respectively. NOESY spectrum of **7** showed a strong NOE between signals H_5 and H_9, whereas that of **8** showed no NOE between signals H_5 and H_9. In the case of differentiation between **9** and **10**, distances between H_1 and H_9 were adopted. The distances D(H_1-H_9) calculated by CAMM of **9** and **10** were 5.09 and 2.91 Å, respectively. NOESY spectrum of **10** showed strong NOE between signals H_1 and H_9, whereas none was observed **9**. Based on the above results, stereoisomers of norbornenes **7** and **8** were assigned as (*endo*, *re*) and (*endo*, *si*), and those of **9** and **10** were assigned as (*exo*, *si*) and (*exo*, *re*), respectively. Sum of the *si* products (**8** + **9**, 43.5%) was higher than that of the *re* products (**7** + **10**, 18.8%). This stereochemical outcome could be rationalized by Trost model.[17] Two transition states are suggested to explain the stereochemical route of the asymmetric Diels-Alder reaction (Fig. 3). Transition state A is considered to be more favorable than transition state B, because in the transition state B, bulky sugar moiety is congested at the double bond where Diels-Alder reaction occurs. Adoptation of the more favorable transition state A affords a less crowded *si*-face attack as opposed to a more crowed *re*-face attack, resulting in *si* products as the major producrs.

The relatively low $J_{5,6}$ coupling constants (4.2-5.2 Hz) in all norbornenes **7**-**10** showed that H_5 and H_6 are in the *trans* relationship ($J_{5,6}$ 9.3 Hz in *cis* norbornene),[18] an indication that the *trans* geometry of the starting dienophile **5** has been preserved in the carbon-carbon bond formations at C5 and C6

where Diels-Alder reaction occurred. No *cis-trans* isomerization occurred in dienophile **5** under the thermal Diels-Alder reaction.

Acknowledgments

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