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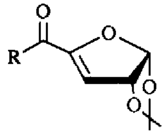
Synthesis of a Highly Substituted Cyclopentane: Completely Exo- and Face-Selective Diels-Alder Reaction of Cyclopentadiene with Cyclic Sugar Dienophiles

Kwan Soo Kim,* In Haeng Cho, Yung Hyup Joo, In Young Yoo, Jung Hoon Song, and Jun Hyung Ko

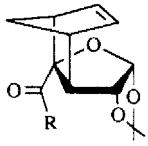
Department of Chemistry, Yonsei University, Seoul 120-749, Korea

Abstract: Diels-Alder reaction of cyclic sugar dienophiles with cyclopentadiene and cyclohexadiene occurred in totally *exo*- and face-selective manner to afford single stereoisomers, one of which was transformed into a highly substituted cyclopentane.

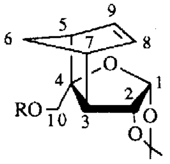
Recent years, Diels-Alder reactions of sugar dienes and dienophiles have been recognized as an important synthetic methodology for the synthesis of carbocyclic rings in optically pure form,[1] and have been applied for the synthesis of certain complex natural products such as olivin,[2] actinobolin,[3] and forskolin.[4] Most of sugar diens or dienophiles have shown usual *endo* selectivities except a few cases, which show slight or moderate *exo* selectivities.[1b,5] Although there are many Diels-Alder reactions which do not follow the *endo* addition rule, it has been generally accepted that the rule is obeyed at least in the addition of cyclic dienes to cyclic dienophiles.[6] However, the term "cyclic dienophile" should be defined more precisely. The cyclic dienophiles referred to in various literatures have been implying the activated cyclic dienophiles in the rigid *s-trans* conformation such as maleic anhydride. There might be two more types of cyclic dienophiles; one containing the exocyclic double bond in the rigid *s-cis* conformation such as itaconic anhydride, and another in the flexible conformation such as compounds **1** or **2**. Recent studies revealed that Diels-Alder reaction of certain rigid cyclic *s-cis* dienophiles afforded predominantly *exo* cycloadducts.[7] On the other hand, there have been scattered reports on Diels-Alder reactions of cyclic dienophiles in flexible conformations and the results are not consistent.[5,8]



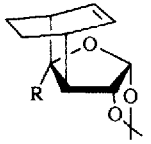
1 R = H
2 R = CH_3



3 R = H
6 R = CH_3

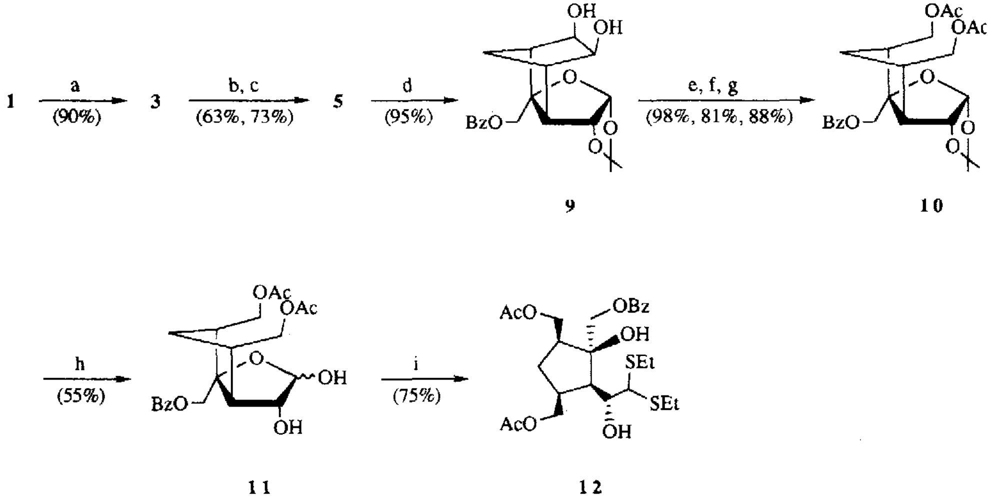


4 R = H
5 R = Bz



7 R = CH=O
8 R = CH_2OBz

Herein we report the synthesis of an asymmetrically substituted cyclopentane employing totally *exo*- and face-selective Diels-Alder reactions of cyclic dienes, namely cyclopentadiene and cyclohexadiene with cyclic sugar dienophiles in flexible conformations, **1**[9] and **2**.[10] Reaction of enal **1** with 1.2 equivalents of cyclopentadiene in methylene chloride at room temperature for 16hr followed by chromatography gave compound **3** as a single stereoisomer in 90% yield.[11] Stereochemistries at C-3 and C-4 of **3** indicate that the reaction occurred exclusively from the convex surface of **1** and was entirely *exo* selective. None of three other possible stereoisomers was found in the reaction mixture. Reaction temperature and addition of Lewis acids such as tin chloride, diethyl aluminum chloride, or titanium tetrachloride did not affect the yield and the composition of products although the reaction time was shortened a little at higher temperature. Compound **3** was transformed into benzoate **5** by two step sequence as shown in Scheme 1: (i) reduction of **3** by $LiAlH_4$, (ii) benzoylation of **4** with benzoyl chloride in pyridine.



Scheme 1

(a) cyclopentadiene, CH_2Cl_2; (b) $LiAlH_4$, THF, 0°C to r.t.; (c) BzCl, pyridine;(d) OsO_4, $NaIO_4$(cat.), $EtOH$-H_2O, then $NaClO_3$, 70% EtOH, 45-50°C; (e) $NaIO_4$, 80% EtOH; (f) $NaBH_4$, MeOH; (g) Ac_2O, pyridine; (h) 80% AcOH; (i) C_2H_5SH, BF_3•Et_2O(cat.), CH_2Cl_2.

Stereochemistries at newly generated stereocenters of **3** were established by determining the stereochemistries at those of more stable benzoate **5**[12] on the basis of its NMR spectroscopic data. The evidence for *exo*-addition comes from the value $J_{3,7}$ = 4.0 Hz which can be accomodated only by a relationship between H_3 and H_7 in the *exo*-cycloadduct, **5**. That the addition had occurred exclusively from the convex surface of **1** was apparent from the value $J_{2,3}$ = 0 Hz of **5** which indicated a *trans* relationship between the hydrogens concerned. The NOE experiment further confirmed the stereochemistries at C-3 and C-4: upon irradiation of H-2, NOE was observed on the olefinic protons, H-8 and H-9. Exclusive *exo*- and face-selectivity was also observed with α,β-unsaturated keto sugar **2** as a dienophile. Thus, Diels-Alder reaction of **2** with cyclopentadiene afforded a single stereoisomer **6** in 98% yield. When the diene was changed from cyclopentadiene to cyclohexadiene, the selectivity was not affected: a single cycloadduct **7** was obtained in 54% yield from the reaction of **1** with cyclohexadiene. The stereochemistries at the newly generated stereocenters of **6**[13] and **8**[14] were determined on the basis of the 2D ^{1}H NMR COSY and NOESY spectroscopic data.

Direct cleavage of the double bond of **5** with $NaIO_4$ and OsO_4 was not satisfactory probably because of the high stability of the cyclic osmate. When **5** was treated with $NaIO_4$ and a catalytic amount of OsO_4 in ether-water solvents, the stable cyclic osmate was isolated as a yellowish green solid in quantitative yield. The crude osmate was hydrolyzed by $NaClO_3$ in 70% EtOH at 45 - 50°C to afford diol **9** in 95% yield.[15] Direct dihydroxylation of **5** without isolation of cyclic osmate required a prolonged reaction time, while dihydroxylation of **5** employing $KMnO_4$ in $CHCl_3$-H_2O at pH 11-12 in the presence of Adogen 464® at 0°C afforded diol **9** in 5 min but the yield was 65%. The dihydroxylation of **5** was totally stereoselective and the stereochemistries at C-8 and C-9 was readily determined on the basis of $J_{5,9}$ = 0 Hz and $J_{7,8}$ = 0 Hz. Cleavage of diol **9** was performed with $NaIO_4$ in 80% EtOH at room temperature and the resulting dialdehyde was reduced with $NaBH_4$ followed by acetylation of the diol with acetic anhydride to give rise to diacetate **10**. The isopropylidene group of **10** was hydrolyzed with 80% acetic acid at 40°C for 3 days to provide hemiacetal **11**. Reaction of **11** with EtSH in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ in methylene chloride at room temperature afforded a cyclopentane derivative 12 in 75% yield.[16]

The facial selectivity of the Diels-Alder reaction in the present work can be readily explained on the basis of a huge steric congestion of the concave side of **3** while the origin of the complete *exo* selectivity is unclear as yet. Steric, conformational, and/or stereoelectronic effect might play in the role. The present work indicates that compounds **1**, **2**, and their derivatives might be used as valuable starting materials for the synthesis of various optically pure carbocyclic rings.

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10. Bonjouklian, R.;Ganem, B. *Carbohydr. Res.* **1979**, *76*, 245-251. Compound **3** in the present work was prepared by a different method from the known one: addition of CH_3MgBr to **1** and oxidation of the resulting allylic alcohol with NiO_2-Al_2O_3 afforded **3** in 90% overall yield. For oxidation with NiO_2-Al_2O_3, see: Kim, K. S.; Cho, S. B.; Hahn, C. S. *Bull. Korean Chem. Soc.* **1991**, *12*, 115-116.

11. Compound **3**: TLC(SiO_2, 1:1 hexane/ethyl acetate) $R_f = 0.53$; $[\alpha]_D^{21}$ -2.40°(c 2.0, $CHCl_3$), ^{1}H NMR (60MHz, CCl_4) δ 1.26(s,3H), 1.46(s, 3H), 1.54-1.90(m, 2H), 2.85-3.16(m, 3H), 4.19(d, J = 3.9Hz, 1H), 5.52(d, J = 3.9Hz, 1H), 6.26-6.36(m, 2H), 9.82(s, 1H).
12. Compound **5**: TLC(SiO_2, 8:2:3 hexane/ethyl acetate/chloroform) $R_f = 0.30$; $[\alpha]_D^{21}$ -17.45° (c 4.0, $CHCl_3$), ^{1}H NMR (300MHz, $CDCl_3$) δ 1.25(s, 3H), 1.49(s, 3H), 1.60(t, J = 1.5Hz, 2H), 2.76(d, J = 4.0Hz, 1H), 3.02-3.05(m, 1H), 3.13-3.16(m, 1H), 4.27(d, J = 3.5Hz, 1H), 4.63 and 4.68(ABq, J = 11.8Hz, 2H), 5.55(d, J = 3.5Hz,1H), 6.25-6.32(m, 2H), 7.41-7.62(m, 3H), 8.09-8.17(m, 2H); ^{13}C NMR($CDCl_3$) δ 26.3, 27.7, 44.3, 48.8, 49.9, 54.5, 69.8, 83.2, 97.9, 108.7, 111.9, 128.2, 129.8, 130.1, 132.7, 135.0, 138.4, 166.6. All new compounds gave satisfactory spectroscopic and/or microanalytical data.
13. Compound **6**: TLC(SiO_2, 1:1 hexane/ethyl acetate) $R_f = 0.62$; $[\alpha]_D^{21}$ +4.0°(c 1.40, $CHCl_3$),^{1}H NMR (300MHz, $CDCl_3$) δ 1.25(s,3H), 1.40(s, 3H), 1.51(d, J = 8.5Hz, 1H), 1.78(d, J = 8.5Hz, 1H), 2.41(s, 3H), 2.96(brs, 1H), 3.04(brs, 1H), 3.19(d, J = 4.0Hz, 1H), 4.24(d, J = 3.9Hz, 1H), 5.60(d, J = 3.9Hz, 1H), 6.28(m, 1H), 6.32(m, 1H).
14. Compound **8**: TLC(SiO_2, 8:2:3 hexane/ethyl acetate/chloroform) $R_f = 0.4$; m.p. 117-118.5°C; $[\alpha]_D^{25}$ -57.36° (c 0.5, $CHCl_3$), ^{1}H NMR(300MHz, $CDCl_3$) δ 1.27(s, 3H), 1.53(s, 3H), 1.27-1.68(m, 4H), 2.15 (d, J = 2.7Hz, 1H), 2.73-2.80(m, 1H), 3.07-3.14(m, 1H), 4.32(d, J = 3.4Hz, 1H), 4.53 and 4.57 (ABq, J = 11.1Hz, 2H), 5.60(d, J = 3.4Hz, 1H), 6.25(m, 1H), 6.37(m,1H), 7.42-7.59(m, 3H), 8.06-8.18(m, 2H).
15. Compound **9**: TLC(SiO_2, 1:1 hexane/ethyl acetate) $R_f = 0.15$; m.p.94.5-96.0°C; $[\alpha]_D^{25}$ -3.12°(c 0.86, $CHCl_3$), ^{1}H NMR(300MHz, $CDCl_3$) δ 1.28(s, 3H),1.50(s, 1H), 1.53(s, 3H), 1.94(s, 1H), 2.39 (d, 4.8Hz, 1H), 2.47(d, J = 4.8Hz, 1H), 2.51(s, 1H), 3.78(d, J = 5.4Hz, 1H), 4.32(d, J = 5.4Hz, 1H), 4.35 and 4.49 (ABq, J = 11.8Hz, 2H), 4.64(d, J = 3.2Hz, 1H), 5.72(d, J = 3.2Hz, 1H),7.41-7.60(m, 3H), 8.04-8.11(m, 2H).
16. Compound **12**: TLC(SiO_2, 1:1 hexane/ethyl acetate) $R_f = 0.56$; $[\alpha]_D^{25}$ +2.7° (c 0.5, $CHCl_3$), ^{1}H NMR (80MHz, $CDCl_3$) δ 1.20(t, J =7.3Hz, 3H), 1.26(t, J = 7.3Hz, 3H), 1.29-1.52(m, 4H), 2.02(s, 3H), 2.04 (s, 3H), 2.25-2.77(m, 7H), 3.73-4.44(m, 8H), 7.42-7.53(m, 3H), 7.98-8.10(m, 2H).

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