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Graphical Abstract

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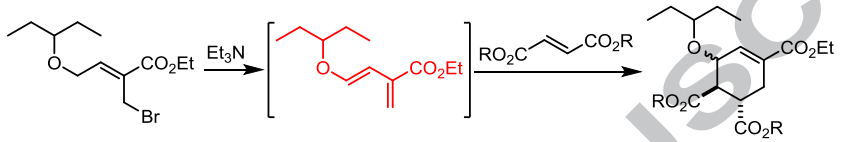

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Diels–Alder reactions of an elusive 1,3-butadiene bearing 2-carboxy and 4-alkoxy substituents

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ABSTRACT

A reactive diene, ethyl 2-methylene-4-(pent-3-oxy)but-2-enoate, bearing electron-withdrawing carboxy and electron-donating pentoxy substituents is prepared and trapped *in situ* by a variety of dienophiles to form [4+2] cycloaddition products. Diels–Alder reaction of this diene with fumarate esters gives multiply substituted cyclohexenes that are useful for building the scaffold of oseltamivir.

For more than four decades, Diels–Alder reaction is one of the most powerful transformations in synthetic organic chemistry.[1] Diels–Alder reaction is a concerted [4+2] cycloaddition reaction of diene with alkene to give a cyclohexene product. Not only does this strategy construct two new C–C σ-bonds in one step, but it also forms a cyclohexene system up to four contiguous stereocenters with good regio- and stereoselectivity. Diels–Alder reactions are particularly useful for the total synthesis of pharmacologically active compounds and natural products such as terpenoids, alkaloids, and polyketides.[2, 3] The structural modification for the dienes and dienophiles plays a crucial role in the development of Diels–Alder reactions. Using heteroatom-substituted electron-rich dienes usually promotes the normal electron-demand Diels–Alder reactions in a highly regioselective fashion. An example of such reactive diene is *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene, also known as Danishefsky's diene.[4–8] Diels–Alder reaction of Danishefsky's diene with unsymmetrical dienophile is facilitated by the electron-donating methoxy and silyloxy substituents to give a regioselective adduct, which is readily subjected to hydrolysis along with elimination of a methanol molecule under acidic condition to furnish an α,β-unsaturated cyclohexenone compound. Other variations of Danishefsky's diene include 1,3-alkoxy-1-trimethylsiloxy-1,3-butadienes (Brassard's diene)[8, 9] and 1-dialkylamino-3-trimethylsiloxy-1,3-butadienes (Rawal's diene),[10] which also bear both electron-donating groups at the C1 and C3 positions of the diene framework.

Tamiflu, the phosphate salt of oseltamivir (**1**), is a popular anti-influenza drug in clinical use.[11, 12] Diels–Alder reactions using 1,3-butadiene,[13] 1-trimethylsilyoxy-1,3-butadiene (**2**),[14, 15] furan,[16] *N*-Boc-pyrrole[17] and 1-Cbz-1,2-dihydropyridine[18, 19] have been successfully applied to react with appropriate dienophiles for construction of the cyclohexene core structure of oseltamivir.[20–26] In one of Shibasaki's syntheses of oseltamivir (Scheme 1),[15] the active diene **2** is used to react with dimethyl fumarate **3** to form a cyclohexene dicarboxylate **4a**, which is hydrolyzed to dicarboxylic acid **4b** and then treated with diphenylphosphoryl azide (DPPA) to give the corresponding diacyl azide for the subsequent Curtius rearrangement in *t*-BuOH. Under the reaction conditions (80 °C, 13 h), the resulting C4 isocyanate group is trapped intramolecularly by the C3 hydroxy group, and the C5 isocyanate group is trapped intermolecularly by *t*-BuOH. The acetylated product **5** is subjected to a palladium-catalyzed allylic substitution reaction with acetoxymalononitrile, as the latent carboxylate group at the C1 position. The 3-pentoxy group is then installed to culminate in the total synthesis of oseltamivir. Although the silyloxydiene **2** is labile in acid conditions, its asymmetric Diels–Alder reaction can be carried out by the catalysis of Ba(O*i*-Pr)$_2$ with a chiral multidentate ligand F$_2$-FujiCAPO.[15]

Inspired by Shibasaki's work, we are interested in exploring the Diels–Alder reaction of diene **6** (Scheme 2) that bears 3-pentoxy and ester substituents existing in the multiply substituted cyclohexene framework of oseltamivir. In contrast to the 1,3-butadienes that may contain electron-donating substituents to promote Diels–Alder reactions, diene **6** that contains both electron-withdrawing carboxy group and electron-donating alkoxy group has not yet investigated.

According to the previously reported procedure,[27] 3-pentanol was subjected to allylation, followed by oxidative cleavage of the C=C double bond, to give alkoxyaldehyde **7** (Scheme 2). The Morita–Baylis–Hillman reaction of aldehyde **7** with ethyl

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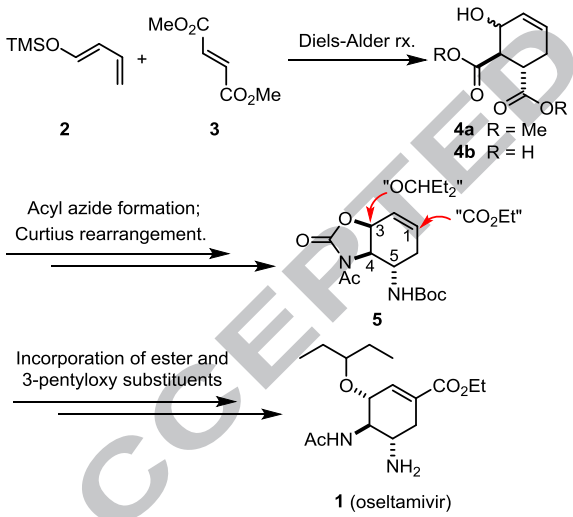
acrylate **8** was promoted by a base DABCO to afford the addition product **9**. Methanesulfonyl chloride was added to **9** at 0 °C, followed by slow addition of triethylamine *via* syringe pump to give the mesylation product **10** in a moderate yield (40%). Mesylate **10** was unstable in basic conditions. For example, treatment of mesylate **10** with DBU at room temperature gave a dimeric compound **12** in low yield (23%) along with other unidentified side products, but no starting material **10** remained. Compound **12** was isolated as a diastereomeric mixture (70:30) by flash chromatography, and the structure was determined by spectral methods including MS, IR, ^{1}H- and ^{13}C-NMR. The ESI–HRMS of **12** showed the protonated molecular ion at *m*/*z* 425.2906, conforming to the molecular formula ($C_{24}H_{40}O_6$) for dimerization of the putative diene **6** ($C_{12}H_{20}O_3$). The regiochemistry of **12** was assigned because its C3 proton (at δ 4.36) appeared as a doublet (J = 3.4 Hz) by coupling with the C2 vinyl proton (at δ 6.89). Thus, Diels–Alder dimerization of the elusive diene **6** abides by the *para* regioselectivity, which is in agreement with a previous study[28] on treatment of methyl 3-hydroxy-2-methylenepentanoate with MsCl/DABCO/DMAP to render *in situ* Diels–Alder dimerization. The facile Diels–Alder dimerization of 1,3-butadiene derivatives bearing an electron-withdrawing group at the C2 position is known as early as 1953.[29] The mechanism of *para* regioselectivity has been predicted by frontier molecular orbital (FMO) theory.[30–32] A recent study[33] also indicates that a regioselective Diels–Alder dimerization is related to the biosynthesis of paracaseolide A, a secondary metabolite isolated from mangrove plant *Sonneratia paracaseolaris*.

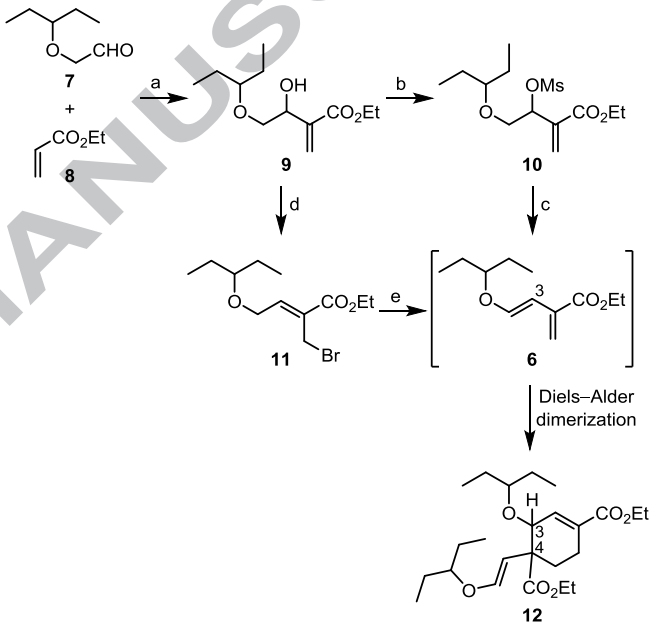


Scheme 1. A previously reported synthesis of oseltamivir **1** starting with Diels–Alder reaction of 1-trimethylsilyloxy-1,3-butadiene (**2**) with dimethyl fumarate (**3**).[15]

Alternatively, alcohol **9** was treated with *N*-bromosuccinimide (NBS) and dimethyl sulfide to give a relatively stable bromo compound **11** *via* an S_N2' reaction. Compound **11** was tentatively assigned to have (*Z*)-configuration because the NOESY spectrum did not show any correlation between the vinyl proton (at δ 7.00) and the bromomethyl protons (in the region of δ 4.29–4.20). Dehydrobromination of **11** under basic conditions also proceeded with a rapid Diels–Alder dimerization of the intermediate diene **6**. This result is consistent with a previous work[34] that demonstrates the facile Diels–Alder dimerization of 1,3-butadiene-2-carboxylate intermediate generated from a base-induced dehydrobromination of *tert*-butyl 2-bromomethyl-2-butenoate.

Nevertheless, the intermediate diene **6** was successfully trapped *in situ* by using activated dienophiles (Scheme 3). Thus, a THF solution of bromo compound **11** and *N*-phenylmaleimide **13** (1 equiv) was heated under reflux in the presence of Et_3N (2 equiv) to afford a [4+2] cycloaddition product of hexahydro-1*H*-isoindole **14**, which contained the *endo* and *exo* isomers in ≥95:5 diastereomeric ratio (d.r.) according to the ^{1}H NMR analysis. The predominant isomer **14**-*endo* was isolated by chromatography, and its structure was rigorously determined by spectral methods and X-ray diffraction analysis. This result is in agreement with a concerted Diels–Alder reaction of diene **6** with dienophile **13** *via* an *endo* transition state to account for the stereochemistry of product **14**-*endo*.

The reaction of bromo compound **11** with 1,4-naphthoquinone **15** (1 equiv) and Et_3N (2 equiv) was performed in refluxing THF to provide 67% yield of anthraquinone **16**,[35] which was presumably derived from the cycloaddition product [**A**] by sequential elimination of a 3-pentanol molecule and oxidative aromatization. The ^{1}H NMR spectrum of **16** displayed 7 aromatic protons and 5 protons for the ethyl ester. The ^{13}C NMR spectrum exhibited the characteristic signals for ester (at δ_C 164.8) and two ketones of anthraquinone (at δ_C 182.3 and 182.1).



Scheme 2. Synthesis of mesylate **10** and bromo compound **11** as the precursors of diene **6**. *Reagents and reaction conditions*: (a) DABCO, 1,4-dioxane/H_2O (1:1), rt, 20 h; 60% for two steps. (b) Et_3N, MsCl, CH_2Cl_2, 0 °C to rt, 30 min; 40%. (c) DBU, CH_2Cl_2, rt, 4 h; giving **12** in 23% yield. (d) NBS, Me_2S, CH_2Cl_2, 0 °C to rt, 18 h; 73%. (e) Et_3N, THF, reflux, 20 h; giving **12** in 71% yield.

The bromo compound **11** reacted rapidly with dimethyl acetylenedicarboxylate (**17**) (1 equiv) at room temperature in the presence of Et_3N (2 equiv) to give benzene-1,2,4-tricarboxylate **18**, albeit in low yield (11%) due to a competitive addition reaction of Et_3N to alkyne **17**, giving a side product of dimethyl (*E*)-2-diethylaminobut-2-ene-dioate (56%).[36] The side product was effectivley suppressed by using a bulky base *N*,*N*-diisopropylethylamine (DIPEA) instead of Et_3N. Thus, the reaction of **11** with **17** and DIPEA (2 equiv) in CH_3CN at 70 °C for 21 h afforded the desired product **18** in 64% yield. Under such reaction conditions, the Diels–Alder adduct [**B**] might lose a 3-pentanol molecule to end up with the aromatic product **18**.

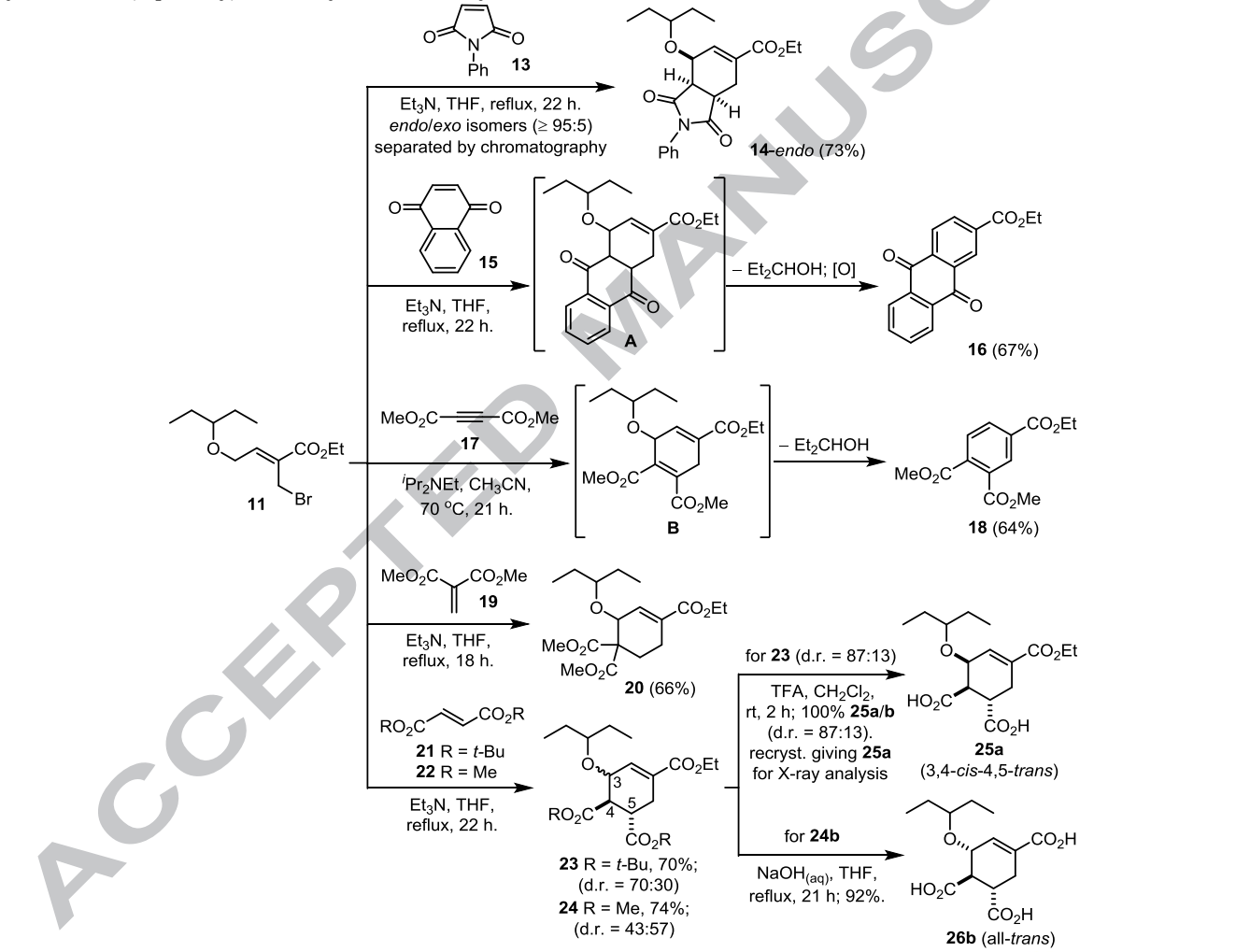
Using dimethyl 2-methylenemalonate **19** (1.5 equiv) as an unsymmetric dienophile, its reaction with bromo compound **11** in the presence of Et_3N (2 equiv) afforded the cyclohexene product **20** in 66% yield. The C3 proton at δ 4.54 (d, J = 4.4 Hz) only coupled with the C2 vinyl proton at δ 7.00, supporting the structure of **20** instead of its regioisomer.

The reaction of bromo compound **11** with di-*tert*-butyl fumarate (5 equiv) in the presence of Et_3N (2 equiv) afforded product **23** (70%) as a mixture of two diastereomers in a ratio of

70:30. After chromatography, a sample of **23** (d.r. = 87:13) was obtained for the subsequent treatment with TFA in CH_2Cl_2 solution to remove the *tert*-butyl groups. The major isomer **25a** was recrystallized from CH_2Cl_2/hexane and determined to have the 3,4-*cis*-4,5-*trans* configuration by X-ray diffraction analysis.

The similar reaction of **11** with dimethyl fumarate (3 equiv) and Et_3N (2 equiv) gave the [4+2] cycloaddition product **24** as a mixture of two diastereomers (43:57), which could be separated by repeated chromatography on a silica gel column. The major isomer **24b** was treated with $NaOH_{(aq)}$ in refluxing THF to afford the corresponding tricarboxylic acid **26b**. The X-ray diffraction analysis revealed that **26b** has all-*trans* configuration. Interestingly, the ratio of diastereomers in cycloaddition products (2.3:1 in **23** versus 1:1.3 in **24**) is greatly affected by the alkyl groups (*tert*-butyl versus methyl) in fumarate esters.

In conclusion, Morita–Baylis–Hillman reaction of ethyl acrylate with 2-(3-pentoxy)acetaldehyde, followed by conversion of the hydroxyl group to bromine atom with NBS/Me_2S afforded a relatively stable bromo compound **11**. Treatment of **11** with Et_3N generated a reactive diene **6** that contains electron-withdrawing carboxy and electron-donating pentoxy substituents at the 2- and 4-positions. Diene **6** could be trapped *in situ* with activated alkenes, particularly dialkyl fumarate to afford the desired Diels–Alder adducts **23** and **24** bearing multiple substituents on the cyclohexene core structure. The all-*trans* isomer could be elaborated to oseltamivir (in racemic form) *via* a sequence of reactions that comprise acyl azide formation and Curtius rearrangement (Scheme 1) as demonstrated by Shibasaki's team.[14, 15] We are currently investigating the asymmetric Diels–Alder reaction by using either chiral fumarate as the dienophile, or chiral **11** as the precursor of chiral diene, or by using chiral base to promote the cycloaddition.



Scheme 3. Generation of diene **6** from bromo compound **11** for *in situ* Diels–Alder reactions with dienophiles. ORTEP drawing of cycloaddition products (left to right): **14**-*endo*, **25a** (3,4-*cis*-4,5-*trans* isomer) and **26b** (all-*trans* isomer).

Acknowledgments

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Supplementary Material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1484953, 1484956 and 1484958. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK). Supplementary data associated with this article can be found, in the online version, at

Diels–Alder reactions of an elusive 1,3-butadiene bearing 2-carboxy and 4-alkoxy substituents

Highlights:

- An elusive 1,3-butadiene having 2-carboxy and 4-alkoxy substituents is prepared.
- This reactive diene is trapped with dienophiles to give cycloaddition products.
- The cycloadduct from fumarate ester can be elaborated to oseltamivir (Tamiflu).