The Ionic Diels–Alder Reaction of 1-Vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane. Retention of the Ortho Ester Moiety through the Use of the Trioxabicyclo[2.2.2]octanyl Protecting Group

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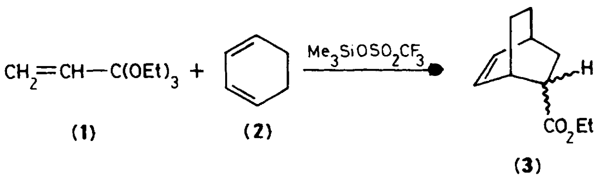
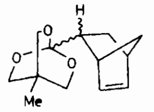
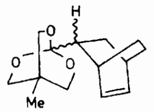
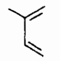
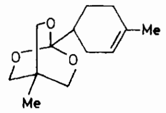
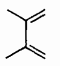
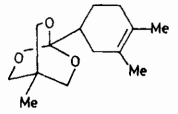
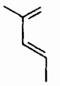
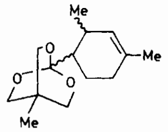
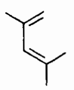
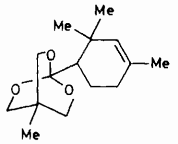
1-Vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane adds to 1,3-dienes at low temperatures under Lewis acid catalysis to give Diels–Alder adducts possessing the intact ortho ester moiety.

Our continued interest in developing high yield, low-temperature ionic Diels–Alder reactions[1] has prompted us to examine in greater detail the addition of vinyl ortho esters to 1,3-dienes. As we previously reported,[1c] triethyl orthoacrylate (**1**) reacts with 1,3-dienes, such as cyclohexa-1,3-diene (**2**), in the presence of trimethylsilyl trifluoromethanesulphonate (triflate) at low temperature to yield the *unprotected* adduct, (**3**) (Scheme 1).[2] Literature precedent[3] for the fate of the



Scheme 1

Table 1. Yields and conditions for the ionic Diels–Alder addition of (**4**) to 1,3-dienes in the presence of boron trifluoride–diethyl ether.

1,3-Diene	Product	Yield/%	Temp./°C	Time/h
		74[a]	−72 to 0	2.50
		74[b]	−78 to 25	4.00
		73	−72 to 0	2.50
		85	−78 to 0	2.25
		75[c]	−70 to 25	2.75
		55[d]	−74 to 0	2.50

[a] The ratio of *endo* to *exo* addition was 2.6 : 1. [b] The ratio of *endo* to *exo* addition was 2.7 : 1. [c] The ratio of *cis* to *trans* adducts was 8.3 : 1. [d] In addition to 55% of the [2π + 4π] adduct, 18% of a 2 : 1 mixture of two [2π + 2π] adducts was formed.

intermediate diethoxy substituted cation suggested that (**3**) should be obtained and not the corresponding ortho ester. In an attempt to design a dienophile in which the carboxylic acid would remain protected as an ortho ester, the use of 1-vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**4**)[4] was explored. We now report that (**4**) adds to 1,3-dienes under catalysis by boron trifluoride–diethyl ether to provide synthetically useful yields of Diels–Alder adducts having an ortho ester as their major functional group.

The protection of the carboxylic acid group as an ortho ester has been shown to have a variety of advantages in synthesis.[4,5] In addition, one of the general methods of synthesis of ortho esters required the intermediacy of a dialkoxy cation.[6] Thus, we felt that (**4**) would be an excellent precursor of a dialkoxy substituted allyl cation, which should be a powerful low temperature dienophile. The advantage of using (**4**) is that, in its open cationic form (**7**), it contains a tethered nucleophile which will regenerate the ortho ester after the Diels–Alder reaction occurs.

In a typical procedure, (**4**)[4]† (1.10 mmol) was combined with cyclohexa-1,3-diene (2.20 mmol) in methylene chloride (5 ml) at −78 °C under nitrogen and boron trifluoride–diethyl ether (0.55 mmol) was added. The reaction mixture was allowed to warm to 25 °C over 4 h and quenched by the addition of an excess of triethylamine, and the products were isolated by chromatography on silica gel to give a 74% yield of a 2.6 : 1 mixture of the *endo* and *exo* isomers of (**5**), respectively (Scheme 2).‡ As shown in Table 1, the reaction is quite general and works equally well for both cyclic and acyclic 1,3-dienes. Yields with six dienes varied from 55 to 85%. In addition to detailed spectroscopic and analytical evidence for the assigned structures,‡ chemical evidence for the structure of (**5**) was obtained through hydrolysis of (**5**) to (**6**) using aqueous hydrochloric acid followed by aqueous lithium hydroxide.

Mechanistically, we believe that (**4**) reacts with the boron trifluoride–diethyl ether to produce the ring opened zwitterion (**7**). The cationic centre adjacent to the vinyl group should transform the vinyl group into a powerful dienophile for the Diels–Alder reaction, since a carbocation is the ultimate carbon-based electron-withdrawing substituent.§

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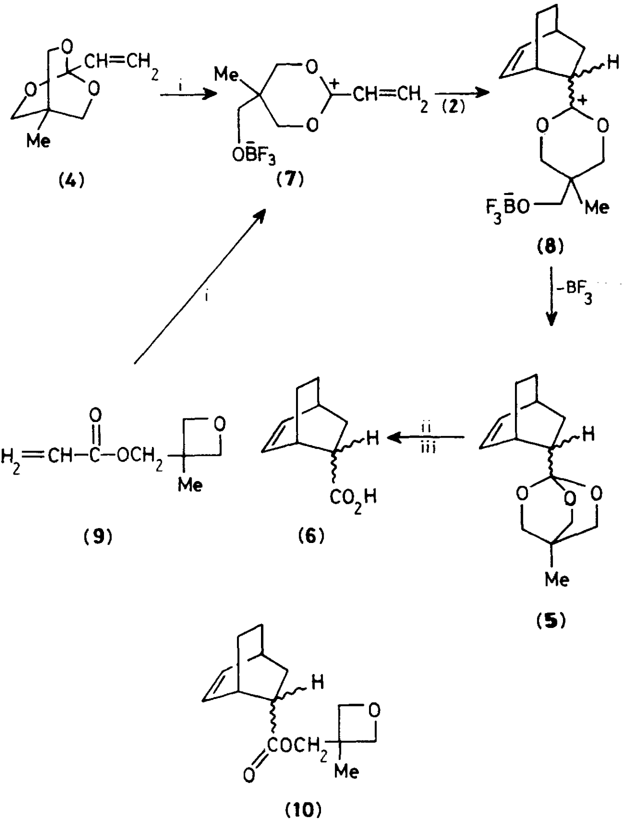
† Although (**4**) had been reported in the literature previously,[4] we chose to prepare (**4**) from triethyl 2-bromo-orthopropionate *via* acid-catalysed exchange of the three ethoxy groups with 1,1,1-tris(hydroxymethyl)ethane, followed by dehydrohalogenation with potassium t-butoxide in dimethyl sulphoxide.

‡ Satisfactory elemental analyses and exact mass molecular weights were obtained on all new compounds. In all cases ^{13}C n.m.r., ^{1}H n.m.r., and i.r. spectral data were consistent with the assigned structures.

§ It should be recognized that extensive charge delocalization should occur in (**7**) [and (**8**)].



Scheme 2. *Reagents and conditions:* i, $BF_3\cdot O(Et)_2$; ii, HCl, H_2O; iii, LiOH, H_2O.

Addition of (**7**) to cyclohexa-1,3-diene should produce (**8**) in either a concerted or a stepwise process.[¶] Reclosure of the third ether bridge with loss of boron trifluoride would then yield (**5**).

An alternative approach to (**7**) involved treatment of the acrylate ester (**9**)[||] with boron trifluoride–diethyl ether. When this reaction was carried out in the presence of cyclohexa-1,3-diene, (**5**) was isolated in 76% yield. We were concerned that (**9**) might have added to the cyclohexa-1,3-diene under boron trifluoride–diethyl ether catalysis to form (**10**) followed by Lewis acid-catalysed conversion of (**10**) into (**5**). This possibility was removed by the demonstration that ethyl acrylate added to cyclohexa-1,3-diene in only 4% yield under conditions where (**9**) added to cyclohexa-1,3-diene to give (**5**) in 74% yield. Thus, the intermediacy of (**10**) is implausible.

In summary, a simple low temperature process has been developed for the Diels–Alder addition of an orthoacrylate to 1,3-dienes with overall retention of the ortho ester protecting group.

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[¶] The formation of small amounts of cyclobutane derivatives from 2,4-dimethylpenta-1,3-diene would be consistent with a stepwise process. However, it is possible that two separate mechanisms were operative in the formation of the $[2\pi + 2\pi]$ adducts *vs.* the $[2\pi + 4\pi]$ adducts.

[||] The synthesis of (**9**) involved the reaction of acryloyl chloride with 3-methyl-3-hydroxymethyloxetane[6,7] in the presence of triethylamine.