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Hetero Diels–Alder reactions of acyl phosphonates: synthesis of glycosyl type phosphonates

Sidika Polat-Cakir [a,b], Ayhan S. Demir [b,*]

[a] Department of Chemistry, Nevşehir University, 50300 Nevşehir, Turkey
[b] Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

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ABSTRACT

We have prepared glycosyl type phosphonates via hetero Diels–Alder (HDA) reactions of acyl phosphonates with electron rich dienes. HDA reactions of acyl phosphonates with Danishefsky's diene required thermal activation to yield the desired dihydropyranones in good yield (70–91%). The reactions with Brassard's diene involved Lewis acid promotion to yield the corresponding lactones, though in moderate yield (33–69%).

1. Introduction

The hetero Diels–Alder (HDA) reaction is a potent reaction for the construction of the pyranosyl unit of many biologically active compounds. There are primarily two types of HDA reactions: (a) electron rich dienes with aldehydes and (b) enal dienes (α,β-unsaturated aldehydes) with dienophiles. The first HDA reaction is a normal electron demand, while the second is an inverse. In both cases high pressure and temperature, or Lewis acid catalysis are required to promote the reaction.

Acyl phosphonates ($R_1COPO(OR_2)_3$) are compounds with phosphorous directly attached to a carbonyl group and represent a particular class of functional organophosphorous compounds. They can be considered as synthetic equivalents of aldehydes with enhanced chemical stability. α,β-Unsaturated acyl phosphonates are used in hetero Diels–Alder cycloaddition reactions with electron rich alkenes where the α,β-unsaturated acyl phosphonates serve as the diene.[1] To the best of our knowledge the use of acyl phosphonates in hetero Diels–Alder reactions as the dienophile is not reported elsewhere. Our current interest in acyl phosphonate chemistry[2] has led us to employ acyl phosphonates in hetero Diels–Alder reaction as dienophile partner.

Hetero Diels–Alder cycloaddition reactions of acyl phosphonates with electron rich dienes form glycosyl type phosphonates. Glycosyl phosphates are known as biological glycosyl donors and take part in the glycosylation process.[3] The phosphorous group at the anomeric carbon is considered to be a stable analogue of glycosyl phosphates that may act as competitive inhibitors of glycosyltransferases and may be used in inhibition studies.

2. Results and discussion

Herein, we present the first hetero Diels–Alder (HDA) reactions of acyl phosphonates with electron rich dienes where the acyl phosphonate serves as dienophile. This reaction produces glycosyl type phosphonates as the HDA product in good yield. When electron rich Danishefsky diene was used, the cycloaddition reaction was activated by temperature, while Lewis acid instead of thermal activation was needed in the case of Brassard's diene.

The required aryl and alkyl acyl phosphonates for the hetero Diels–Alder reaction **1a**–**m** were easily prepared in good yield (over 90%) according to a literature procedure.[4] The procedure involved addition of trimethyl phosphites into aryl or alkyl substituted acyl chlorides at 0 °C (the Michaelis–Arbuzov reaction).

The first trial of the HDA reaction of benzoylphosphonate **1a** with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) was thermally activated. When the reaction was heated to 60 °C, no formation of HDA product was observed. The temperature was increased to 100 °C and then the desired glycosyl type phosphonate **2a** was obtained in 89% yield. To investigate this reaction we used a series of aryl and alkyl substituted acyl phosphonates (entries 2–12 in Table 1). The electronic features of the aromatic moieties did not significantly affect the product yield. For instance, benzoyl substrates with electron-donating –OCH_3 (entry 2) and an electron-

* Corresponding author. Tel.: +90 312 2103242; fax: +90 312 2103200; e-mail address: asdemir@metu.edu.tr (A.S. Demir).

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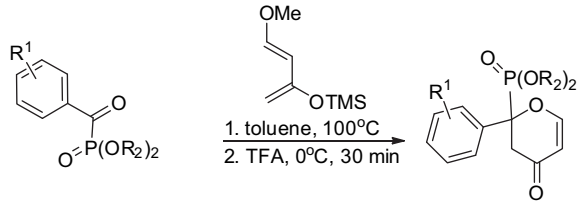
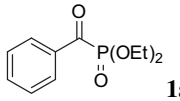
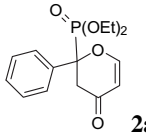
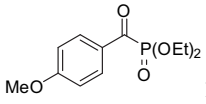
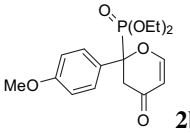
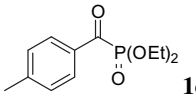
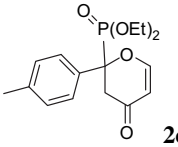
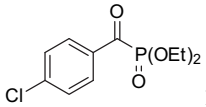
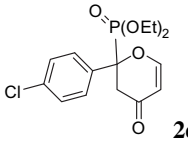
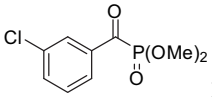
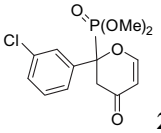
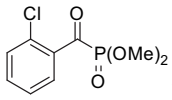
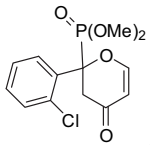
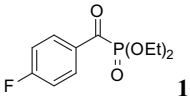
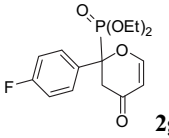
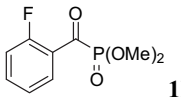
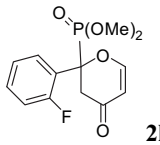
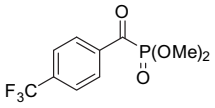
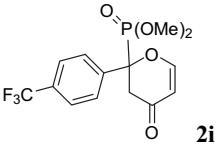
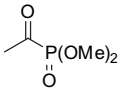
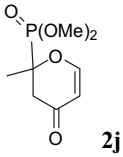
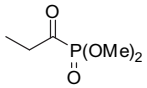
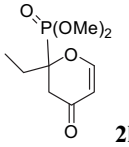
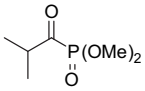
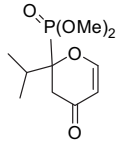
Table 1
Reactions of acyl phosphonates with Danishefsky's diene



Entry	Acyl phosphonate	Reaction conditions and yield[a] (%)	Product
1	 **1a**	18 h, 89	 **2a**
2	 **1b**	18 h, 88	 **2b**
3	 **1c**	16 h, 90	 **2c**
4	 **1d**	14 h, 80	 **2d**
5	 **1e**	14 h, 74	 **2e**
6	 **1f**	16 h, 90	 **2f**
7	 **1g**	14 h, 89	 **2g**
8	 **1h**	6 h, 70	 **2h**

(*continued on next page*)

Table 1 (*continued*)

Entry	Acyl phosphonate	Reaction conditions and yield[a] (%)	Product
9	 **1i**	14 h, 74	 **2i**
10	 **1j**	16 h, 90	 **2j**
11	 **1k**	16 h, 91	 **2k**
12	 **1l**	16 h, 81	 **2l**

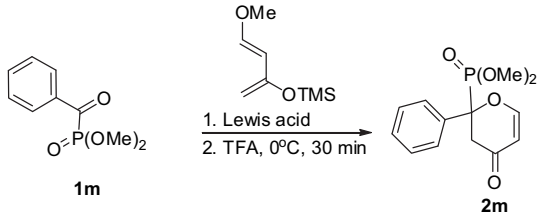
[a] Yields refer to purified compounds.

withdrawing $-CH_3$ groups on the *para* position both resulted in similar yields (entry 2 with 88% yield and entry 3 with 90% yield).

When the electron-withdrawing –Cl group was used in benzoylphosphonates at three different positions (*ortho*, *meta* and *para*), the yield of HDA product (entries 4–6) did not change considerably between these three positions. When –F substituted benzoylphosphonates **1g** and **1h** was employed, glycosyl type phosphonates **2g** and **2h** were attained in 89% and 70% yields, respectively. Acyl phosphonate **1i** (entry 9) resulted in the corresponding HDA product **2i** in 74% yield. We also explored alkyl phosphonates in the HDA reactions. The corresponding glycosyl phosphonates were obtained in good yields (entries 10–12 in Table 1).

As listed in Table 2, we tested three different Lewis acids as catalysts for the HDA reactions of benzoylphosphonate **1m** with Danishefsky's diene. We found that the cycloaddition reaction is efficiently activated by $ZnCl_2$ and the desired compound **2m** was

Table 2
Lewis acid screening of benzoylphosphonate **1a** with Danishefsky's diene

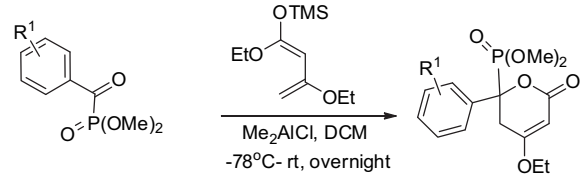


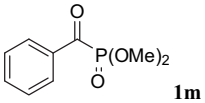
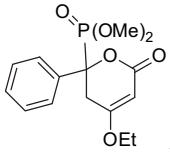
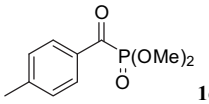
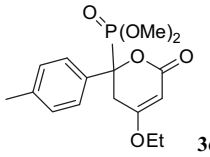
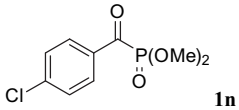
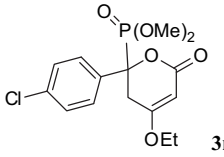
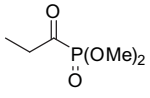
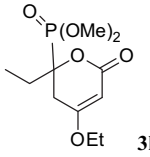
1m **2m**

Entry	Lewis acid	Reaction conditions	Yield[a] (%)
1	Me_2AlCl (1.1 equiv)	DCM, −78 °C, 30 min	No formation of **2m**
2	$BF_3{\cdot}OEt_2$ (1.1 equiv)	DCM, −78 °C, 30 min	No formation of **2m**
3	$ZnCl_2$ (1.1 equiv)	DCM, −78 °C, 30 min	41
4	Me_2AlCl (1 equiv)	Toluene, 0 °C, 2 h	34
5	Me_2AlCl (1 equiv)	DCM, 0 °C, 2 h	44
6	$ZnCl_2$ (1 equiv)	Toluene, 0 °C, 2 h	81

[a] Yields refer to purified compounds. In all cases 2 equiv of Danishefsky's diene was used except for in entry 1.

Table 3
Reactions of acyl phosphonates with Brassard's diene



Entry	Acyl phosphonate	Yield[a] (%)	Product
1	 **1m**	69	 **3m**
2	 **1c**	52	 **3c**
3	 **1n**	65	 **3n**
4	 **1k**	33	 **3k**

[a] Yields refer to purified compounds.

obtained in 81% yield. We tried an un-optimized asymmetric synthesis of compound **2m** using a bisoxazolidine type ligand with Cu $(OTf)_2$ (*t*-Bu-BOX-Cu^{II}) that produced only 33% ee.[6]

In Table 3, we have summarized our results regarding the HDA reactions of acyl phosphonates with Brassard's diene.[5] Thermal activation of the reaction between benzoylphosphonate **1m** and Brassard's diene did not afford the expected compound. Based on our experience through the results obtained from Lewis acid screening of Danishefsky's diene, we utilized both $ZnCl_2$ and Me_2AlCl to activate the cycloaddition reaction of benzoylphosphonate **1m** with Brassard's diene. We found that Me_2AlCl was an efficient catalyst to promote the cycloaddition reaction. Before testing Brassard's diene with different acyl phosphonates, we performed a solvent screening. Dichloromethane resulted in high yield of HDA product **3m**. Non-chlorinated solvents, such as toluene and THF provided the HDA product, albeit in low yields. Several substituted aryl and alkyl phosphonates were also examined in the HDA reaction with Brassard's diene in acceptable yields (entries 2–4 in Table 3).

3. Conclusion

In summary, we disclose the first hetero Diels–Alder reactions of acyl phosphonates with activated dienes where acyl phosphonates serve as dionophile. The present work provides a synthesis of glycosyl type phosphonates via the thermal hetero Diels–Alder reaction of acyl phosphonates with Danishefsky's diene. The desired glycosyl type phosphonates are obtained in good yields (70–91%). Although the main objective of the current work was to employ acyl phosphonates as dienophile in hetero Diels–Alder reactions, a new method for the syntheses of glycosyl type phosphonates is also reported. Efforts towards the asymmetric syntheses of these glycosyl type phosphonates are currently in progress.

4. Experimental section

4.1. General methods

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on 400 and 100 MHz spectrometers. Chemical shifts in proton and carbon NMR spectra are reported in parts per million and tetramethylsilane was used as an internal reference unless otherwise noted. Spin multiplicities in proton NMR spectra are indicated by the following symbols: s (singlet), t (triplet), dd (doublet of doublet), m (multiplet). Flash column chromatography was performed using 230–400-mesh silica gel using ethyl acetate/hexane mixture as eluting solvent. Reactions sensitive to air and moisture were performed under argon. The progress of all reactions was monitored by thin layer chromatography (TLC), which was carried out on Merck silica gel plates with fluorescent indicator. TLC plates were initially visualized by UV light source, and then dipped into an ethanolic solution of phosphomolybdic acid. All commercially available reagents were used as received unless otherwise reported. Tetrahydrofuran and toluene were distilled from Na/benzophenone and methylene chloride was freshly distilled from calcium hydride and freshly distilled prior to use. Acyl phosphonates were easily prepared according to the published procedure[4] and used freshly in the cycloaddition reactions. Brassard's diene for HDA reactions was also prepared by following the literature procedure[5] and used freshly in each experiment. The enantiomeric excess (ee) of the **2m** was determined by HPLC using Chiralcel OC column with hexane/IPA as the eluent.

4.2. General procedure for the HDA reactions of acyl phosphonates with Danishefsky's diene under thermal conditions (2a–l)

A 10-mL vial was charged with acyl phosphonate (200 mg, 1 equiv) and freshly distilled toluene (2 mL) under argon and then Danishefsky's diene (2 equiv) was added to the above solution. After passing with argon, the vial was then sealed with a cap and heated at 100 °C for the time indicated in the Table 1. The reaction mixture was cooled to room temperature and then TFA was added slowly to the reaction mixture at 0 °C and stirred for 30 min. The reaction mixture was directly purified by flash column chromatography to afford the corresponding product.

4.2.1. Diethyl (4-oxo-2-phenyl-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2a***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.49 (m, 2H), 7.40–7.24 (m, 3H), 7.32 (dd, J=6.1, 1.6 Hz, 1H), 5.36 (dd, J=6.1, 1.0 Hz, 1H), 4.15–3.91 (m, 4H), 3.43 (dd, J=16.7, 11.1 Hz, 1H), 3.29 (ddd, J=16.7, 5.4 and 1.0 Hz, 1H), 1.25 (q, J=7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2 (d, J_{C-P}=12 Hz), 159.4 (d, J_{C-P}=12 Hz), 133.0, 128.6 (d, J_{C-P}=2.2 Hz), 128.2 (d, J_{C-P}=2.1 Hz), 126.8 (d, J_{C-P}=4.3 Hz), 108.2, 83.3 (d, J_{C-P}=173.6 Hz), 63.9 (br s, $(CH_3CH_2O)_2P$), 40.6, 16.0 (d, J=5.1 Hz, $(CH_3CH_2O)_2P$); ^{31}P NMR (161 MHz, $CDCl_3$): 16.45; IR (ATR technique, cm^{-1}): 2983, 1735, 1677, 1242, 1013; HRMS: calculated for $C_{15}H_{19}O_5P$ 310.0970 and found 310.0977.

4.2.2. Diethyl (2-(4-methoxyphenyl)-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2b***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (dd, J=9.0, 2.2 Hz, 2H), 7.28 (d, J=1.0 Hz, 1H), 6.89 (d, J=9.0 Hz, 2H), 5.36 (dd, J=6.1, 1.0 Hz, 1H), 4.16–3.94 (m, 4H), 3.8 (s, 3H), 3.39 (dd, J=16.7, 10.9 Hz, 1H), 3.25 (ddd, J=16.7, 4.8 and 1.0 Hz, 1H), 1.25 (q, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.6 (d, J_{C-P}=12 Hz), 159.8 (d, J_{C-P}=2.5 Hz), 159.4 (d, J=12.7 Hz), 128.4 (d, J=4.2 Hz), 128.4, 113. 7 (d, J_{C-P}=2.0 Hz), 108.2, 83.0 (d, J_{C-P}=176.1 Hz), 63.9 (br s, $(CH_3CH_2O)_2P$), 55.0, 40.5, 16.1 (d, J=4.9 Hz, $(CH_3CH_2O)_2P$); ^{31}P NMR (161 MHz, $CDCl_3$): 16.65; IR (ATR technique, cm^{-1}): 2981, 2923, 1681, 1599, 1510, 1250, 1014; HRMS: calculated for $C_{16}H_{21}O_6P$ 340.1076 and found 340.1081.

4.2.3. Diethyl (4-oxo-2-p-tolyl-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2c***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 (dd, J=8.4, 2.2 Hz, 2H), 7.22 (dd, J=6.1, 1.6 Hz, 1H), 7.11 (d, J=7.8 Hz, 2H), 5.28 (dd, J=6.1, 1.0 Hz, 1H), 4.08–3.86 (m, 4H), 3.34 (dd, J=16.6, 11.0 Hz, 1H), 3.19 (ddd, J=16.6, 4.9 and 1.0 Hz, 1H), 2.26 (d, J=1.6 Hz, 3H), 1.19 (q, J=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.3 (d, J_{C-P}=13 Hz), 159.3 (d, J_{C-P}=12.6 Hz), 138.5 (d, J=2.9 Hz), 130.6, 128.9 (d, J_{C-P}=2.2 Hz), 126.7 (d, J_{C-P}=4.3 Hz), 108.1, 83.1 (d, J_{C-P}=174.6 Hz), 63.1 (br s, $(CH_3CH_2O)_2P$), 40.5, 20.7, 16.0 (d, J=5.3 Hz, $(CH_3CH_2O)_2P$); ^{31}P NMR (161 MHz, $CDCl_3$): 16.56; IR (ATR technique, cm^{-1}): 2982, 1678, 1599, 1248, 1013; HRMS: calculated for $C_{16}H_{21}O_5P$ 324.1127 and found 324.1127.

4.2.4. Diethyl (2-(4-chlorophenyl)-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2d***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.44 (dd, J=8.8, 2.2 Hz, 2H), 7.36 (d, J=8.6 Hz, 2H), 7.30 (dd, J=6.1, 1.6 Hz, 1H), 5.38 (dd, J=6.1, 1.0 Hz, 1H), 4.17–3.96 (m, 4H), 3.42 (dd, J=16.7, 11.1 Hz, 1H), 3.22 (ddd, J=16.7, 5.3 and 1.0 Hz, 1H), 1.27 (dt, J=7.0, 3.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.0 (d, J_{C-P}=12 Hz), 159.3 (d, J_{C-P}=12 Hz), 134.8 (d, J=3.5 Hz), 132.7, 128.5 (d, J_{C-P}=2.1 Hz), 128.3 (d, J_{C-P}=4.3 Hz), 108.4, 82.9 (d, J_{C-P}=174.0 Hz), 64.1 (d, J=6.9 Hz, $(CH_3CH_2O)_2P$), 64.0 (d, J=7.2 Hz, $(CH_3CH_2O)_2P$), 40.6, 16.1 (d, J=5.5 Hz, $(CH_3CH_2O)_2P$); ^{31}P NMR (161 MHz, $CDCl_3$): 15.98; IR (ATR technique, cm^{-1}): 2983, 1681, 1599, 1242, 1011; HRMS: calculated for $C_{15}H_{18}ClO_5P$ 344.0580 and found 344.0584.

4.2.5. Dimethyl (2-(3-chlorophenyl)-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2e***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ7.50–7.49 (m, 1H), 7.38–7.31 (m, 4H), 5.04 (dd, J=6.1, 1.1 Hz, 1H), 3.75 (d, J=10.6, 3H), 3.69 (d, J=10.6, 3H), 3.39 (dd, J=16.7, 11.1 Hz, 1H), 3.20 (ddd, J=16.7, 6.1 and 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.6 (d, J_{C-P}=12.0 Hz), 159.2 (d, J_{C-P}=12.0 Hz), 136.2, 134.7 (d, J=2.8 Hz), 129.7 (d, J_{C-P}=2.3 Hz), 129.1 (d, J=2.8 Hz), 126.9

(d, J_{C-P}=4.2 Hz), 125.1 (d, J=4.2 Hz), 108.5, 83.0 (d, J_{C-P}=173.8 Hz), 54.6 (d, J=7.0 Hz, $(CH_3O)_2P$), 54.5 (d, J=7.2 Hz, $(CH_3O)_2P$), 40.6; ^{31}P NMR (161 MHz, $CDCl_3$): 18.13; IR (ATR technique, cm^{-1}): 2958, 1680, 1258, 1016; HRMS: calculated for $C_{13}H_{14}ClO_5P$ 316.0267 and found 316.0266.

4.2.6. Dimethyl (2-(2-chlorophenyl)-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2f***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59–7.54 (m, 1H), 7.44–7.40 (m, 1H), 7.37 (dd, J=6.0, 1.2 Hz, 1H), 7.35–7.27 (m, 2H), 5.42 (dd, J=6.0, 1.1 Hz, 1H), 3.81 (d, J=10.6 Hz, 3H), 3.74 (d, J=10.6 Hz, 4H), 3.48 (dd, J=16.8, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.3 (d, J_{C-P}=11.8 Hz), 159.3 (d, J_{C-P}=12.2 Hz), 132.8 (d, J=5.0 Hz), 132.7 (d, J=1.9 Hz), 130.8, 130.2, 130.17 (d, J=3.6 Hz), 127.0 (d, J=4.3 Hz), 108.6, 84.9 (d, J_{C-P}=173.8 Hz), 54.5 (d, J=7.1 Hz, $(CH_3O)_2P$), 54.3 (d, J=7.1 Hz, $(CH_3O)_2P$), 41.4; ^{31}P NMR (161 MHz, $CDCl_3$): 18.10; IR (ATR technique, cm^{-1}): 2981, 2923, 1681, 1599, 1510, 1250, 1014; HRMS: calculated for $C_{13}H_{14}ClO_5P$ 316.0267 and found 316.0276.

4.2.7. Diethyl (2-(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2g***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (ddd, J=8.9, 5.0, 2.2 Hz, 2H), 7.30 (dd, J=6.1, 1.5 Hz, 1H), 7.07 (t, J=8.6 Hz, 2H), 5.38 (d, J=6.1, 1H), 4.14–3.97 (m, 4H), 3.42 (dd, J=16.7, 11.0 Hz, 1H), 3.24 (dd, J=16.7, 5.2 Hz, 1H), 1.26 (t, J=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.0 (d, J_{C-P}=12.0 Hz), 162.6 (dd, J=249.0 and 3.2 Hz), 159.2 (d, J_{C-P}=12.2 Hz), 128.8 (dd, J=8.2 and 4.2 Hz), 115.2 (dd, J=21.8 and 2.1 Hz), 108.2, 82.8 (d, J_{C-P}=174.8 Hz), 63.9 (d, J=6.6 Hz, $(CH_3CH_2O)_2P$), 63.8 (d, J=5.8 Hz, $(CH_3CH_2O)_2P$), 40.5, 16.0 (d, J=5.2 Hz, $(CH_3CH_2O)_2P$); ^{31}P NMR (161 MHz, $CDCl_3$): 16.18; IR (ATR technique, cm^{-1}): 2983, 1682, 1602, 1238, 1012; HRMS: calculated for $C_{15}H_{18}FO_5P$ 328.0876 and found 328.0866.

4.2.8. Dimethyl (2-(2-fluorophenyl)-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2h***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.47 (m, 1H), 7.38–7.31 (m, 2H), 7.18 (t, J=7.6 Hz, 1H), 7.08 (dd, J=12.4, 8.3 Hz, 1H), 5.40 (dd, J=6.1, 1.0 Hz, 1H), 3.78 (d, J=10.6 Hz, 3H), 3.76 (d, J=10.6 Hz, 3H), 3.53 (dd, J=16.5 and 7.0 Hz, 1H), 3.42 (ddd, J=16.5, 10.4, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.3 (d, J_{C-P}=12.1 Hz), 160.4 (dd, J=251.6 and 4.2 Hz), 159.2 (d, J_{C-P}=12.0 Hz), 131.1 (dd, J=8.9, 2.8 Hz), 129.3 (dd, J=3.7, 2.7 Hz), 124.2 (t, J=2.9 Hz), 120.9 (dd, J=10.0, 1.4 Hz), 117.1 (dd, J=24.2, 2.1 Hz), 108.5, 83.0 (dd, J_{C-P}=175.3, 4.2 Hz), 54.5 (d, J=7.0 $(CH_3O)_2P$), 54.4 (d, J=7.1 $(CH_3O)_2P$), 40.8 (d, J=8.6 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): 18.03; IR (ATR technique, cm^{-1}): 2960, 1682, 1599, 1242, 1013; HRMS: calculated for $C_{13}H_{14}FO_5P$ 300.0562 and found 300.0560.

4.2.9. Dimethyl (4-oxo-2-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2i***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (br t, J=10 Hz, 4H), 7.33 (dd, J=6.1, 1.3 Hz, 1H), 5.40 (dd, J=6.1 and 0.8 Hz, 1H), 3.77 (d, J=10.6 Hz, 3H), 3.70 (d, J=10.6 Hz, 3H), 3.47 (dd, J=16.7 and 11.3 Hz, 1H), 3.28 (dd, J=16.7, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.6 (d, J_{C-P}=12.0 Hz), 159.2 (d, J_{C-P}=12.0 Hz), 138.4, 131.2 (dq, J=32.8, 2.9 Hz), 127.4 (d, J=4.1 Hz), 125.5 (t, J=3.2 Hz), 123.7 (dd, J=272.2 and 1.2 Hz), 108.8, 83.4 (d, J=173.9 Hz), 54.8 (d, J=6.8 Hz, $(CH_3O)_2P$), 54.7 (d, J=6.7 Hz, $(CH_3O)_2P$), 40.8; ^{31}P NMR (161 MHz, $CDCl_3$): 17.96; IR (ATR technique, cm^{-1}): 3283, 2969, 2911, 1675, 1178, 1056, 1009; HRMS: calculated for $C_{14}H_{14}F_3O_5P$ 350.0531 and found 350.0532.

4.2.10. Dimethyl (2-methyl-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2j***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, J=6.2 Hz, 1H), 5.44 (d, J=6.2 Hz, 1H), 3.88 (d, J=10.5 Hz, 6H), 3.08 (dd, J=16.7 and 12.1 Hz, 1H), 2.55 (dd, J=16.7 and 11.5 Hz, 1H), 1.65 (d, J=15.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.2 (d, J_{C-P}=9.9 Hz), 159.3 (d, J_{C-P}=9.4 Hz), 105.9, 79.9 (d, J_{C-P}=176.3 Hz), 53.6 (d, J_{C-P}=5.8 Hz), 41.4, 19.2; ^{31}P NMR (161 MHz, $CDCl_3$): 22.08; IR (ATR technique, cm^{-1}): 2961, 1672, 1600, 1309, 1231, 1019, 832; HRMS: calculated for $C_8H_{13}O_5P$ 220.0500 and found 220.0491.

4.2.11. Dimethyl (2-ethyl-4-oxo-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2k***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, J=6.2 Hz, 1H), 5.43 (d, J=6.2 Hz, 1H), 3.86 (d, J=10.6 Hz, 3H), 3.83 (d, J=10.6 Hz, 3H), 2.98 (dd, J=17.0 and 12.0 Hz, 1H), 2.71 (t, J=17.0 Hz, 1H), 2.13–1.98 (m, 2H), 1.06 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 188.9 (d, J_{C-P}=6.6 Hz), 159.8 (d, J_{C-P}=6.6 Hz), 106.2, 83.1 (d, J_{C-P}=171.6 Hz), 53.7 (d, J=6.4 Hz), 53.5 (d, J=6.5 Hz), 39.5, 26.8, 7.48 (d, J_{C-P}=5.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): 22.59; IR (ATR technique, cm^{-1}): 2960, 1675, 1601, 1252, 1228, 1021, 831; HRMS: calculated for $C_9H_{15}O_5P$ 234.0657 and found 234.0649.

4.2.12. Dimethyl (2-isopropyl-4-oxo-3,4-dihydro-2H-pyran-2-yl) phosphonate ***2l***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, J=6.2 Hz, 1H), 5.41 (d, J=6.2 Hz, 1H), 3.82 (d, J=10.5 Hz, 3H), 3.79 (d, J=10.7 Hz, 3H), 2.91–2.74 (m, 2H), 2.54–2.39 (m, 1H), 1.09 (d, J=2.0 Hz, 3H), 1.08 (d, J=2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.1 (d, J=3.6 Hz), 160.2 (d, J=3.3 Hz), 106.0, 83.3 (d, J=166.0 Hz), 53.7 (d, J=7.5 Hz), 53.2 (d, J=7.4 Hz), 37.3, 33.4 (d, J=3.2 Hz), 17.0 (d, J=2.7 Hz), 16.9 (d, J=6.7 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): 23.14; IR (ATR technique, cm^{-1}): 2968, 1278, 1602, 1404, 1219, 1028, 1009; HRMS: calculated for $C_{10}H_{17}O_5P$ 248.0814 and found 248.0808.

4.3. General procedure for the HDA reactions of benzoylphosphonate 1m with Danishefsky's diene in the presence of Lewis acids

To a solution of benzoylphosphonate **1m** (200 mg, 1 equiv) in either DCM or toluene (2 mL) was added Lewis acid (either 1.1 equiv or 1.0 equiv) at −78 °C under argon atmosphere. After stirring for 10 min, Danishefsky's diene (2 equiv) was added to the reaction mixture at the same temperature as the time indicated in Table 2. TFA was added slowly to the reaction mixture and stirred for 30 min. The reaction mixture was carefully quenched by adding few drops of water at 0 °C and then filtrated over Celite and concentrated. The crude product was purified by flash column chromatography.

4.3.1. Dimethyl (4-oxo-2-phenyl-3,4-dihydro-2H-pyran-2-yl)phosphonate ***2m***. Yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52–7.49 (m, 2H), 7.41–7.34 (m, 3H), 7.31 (dd, J=6.1 and 1.4 Hz, 1H), 5.37 (d, J=6.1 Hz, 1H), 3.71 (d, J=10.6 Hz, 3H), 3.65 (d, J=10.6 Hz, 3H), 3.43 (dd, J=16.7 and 11.1 Hz, 1H), 3.29 (ddd, J=16.7, 5.6 and 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 188.1 (d, J=12.4 Hz), 159.3 (d, J=12.3 Hz), 133.7, 128.9 (d, J=2.3 Hz), 128.5 (d, J=2.0 Hz), 126.9 (d, J=4.3 Hz), 108.4, 83.5 (d, J=174.5 Hz), 54.5 (t, J=7.4 Hz), 40.6; ^{31}P NMR (161 MHz, $CDCl_3$): 18.07; IR (ATR technique, cm^{-1}): 2959, 1675, 1597, 1243, 1015, 832; HRMS: calculated for $C_{13}H_{15}O_5P$ 282.0657 and found 282.0654. Determination of enantiomeric excess (ee) values for racemic **2m**: Chiralcel OC, hexane/IPA=95:5, flow=1 mL/min t=12.29 and 13.34 min. The asymmetric compound **2m** was prepared according to the procedure in literature (Ref. 6). (*S,S*)-2,2′-Methylenebis(4-*tert*-butyl-2-oxazoline) was used as the ligand. Determination of enantiomeric excess (ee) values for asymmetric **2m**: Chiralcel OC, hexane/IPA=95:5, flow=1 mL/min t=12.11 and 13.80 min.

4.4. General procedure for the HDA reactions of acyl phosphonates with Brassard's diene in the presence of Me_2AlCl (3m, 3c,d and 3k)

To a solution of acyl phosphonate (200 mg, 1 equiv) in DCM (2 mL) was added Me_2AlCl (1.1 equiv) at −78 °C under argon atmosphere. After stirring for 10 min, freshly prepared Brassard's

diene (2 equiv) was added to the reaction mixture at the same temperature and left it overnight. The reaction mixture was carefully quenched by adding few drops of water at 0 °C and then filtrated over Celite and concentrated. The crude product was purified by flash column chromatography to give the desired HDA product.

4.4.1. Dimethyl (4-ethoxy-6-oxo-2-phenyl-3,6-dihydro-2H-pyran-2-yl)phosphonate ***3m***. Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57–7.54 (m, 2H), 7.41–7.34 (m, 3H), 5.01 (d, J=1.3 Hz, 1H), 3.85 (d, J=10.5 Hz, 3H), 3.84 (q, J=12.4 Hz, 2H), 3.48 (d, J=10.4 Hz, 3H), 3.46 (ddd, J=17.3, 11.5 and 1.5 Hz, 1H), 3.09 (dd, J=17.3 and 5.2 Hz, 1H), 1.32 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.3 (d, J=17.7 Hz), 164.5 (d, J=11.1 Hz), 136.0, 128.4, 128.4 (d, J=2.1 Hz), 126.0 (d, J=4.0 Hz), 90.6, 80.6 (d, J=171.7 Hz), 64.8, 54.5 (t, J=7.9 Hz), 33.1, 13.6; ^{31}P NMR (161 MHz, $CDCl_3$): 18.50; IR (ATR technique, cm^{-1}): 2955, 1720, 1624, 1229, 1013, 840; HRMS: calculated for $C_{15}H_{19}O_6P$ 326.0919 and found 326.0908.

4.4.2. Dimethyl (4-ethoxy-6-oxo-2-p-tolyl-3,6-dihydro-2H-pyran-2-yl)phosphonate ***3c***. Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (dd, J=8.4 and 2.2 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 5.00 (d, J=1.4 Hz, 1H), 3.85 (d, J=10.4 Hz, 3H), 3.81 (q, J=11.8 Hz, 2H), 3.50 (d, J=10.4 Hz, 3H), 3.43 (ddd, J=17.2, 11.5 and 1.5 Hz, 1H), 3.07 (dd, J=17.3 and 4.8 Hz, 1H), 2.34 (d, J=1.4 Hz, 3H), 1.32 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4 (d, J=18.2 Hz), 164.8 (d, J=11.4 Hz), 138.4 (d, J=3.2 Hz), 133.0, 129.2 (d, J=2.2 Hz), 126.9 (d, J=4.0 Hz), 90.7, 80.6 (d, J=172.8 Hz), 64.8, 54.7 (d, J=7.5 Hz), 54.6 (d, J=7.4 Hz), 33.1, 20.9, 13.7; ^{31}P NMR (161 MHz, $CDCl_3$): 18.68; IR (ATR technique, cm^{-1}): 2957, 1716, 1625, 1221, 1028, 748; HRMS: calculated for $C_{16}H_{21}O_6P$ 340.1076 and found 340.1069.

4.4.3. Dimethyl (2-(4-chlorophenyl)-4-ethoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)phosphonate ***3n***. Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (dd, J=8.8 and 2.2 Hz, 2H), 7.37 (d, J=8.6 Hz, 2H), 5.01 (d, J=1.4 Hz, 1H), 3.86 (d, J=10.5 Hz, 5H), 3.56 (d, J=10.4 Hz, 3H), 3.47 (ddd, J=17.2, 11.4 and 1.5 Hz, 1H), 3.04 (dd, J=17.3 and 5.1 Hz, 1H), 1.32 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2 (d, J=17.6 Hz), 164.3 (d, J=11.0 Hz), 134.8 (d, J=3.6 Hz), 128.7 (d, J=2.3 Hz), 127.6 (d, J=4.2 Hz), 90.6, 80.3 (d, J=172.3 Hz), 65.0, 54.75 (d, J=5.4 Hz), 54.68 (d, J=5.9 Hz), 33.1, 13.7; ^{31}P NMR (161 MHz, $CDCl_3$): 18.10; IR (ATR technique, cm^{-1}): 2958, 1728, 1624, 1239, 1220, 1027, 852; HRMS: calculated for $C_{15}H_{18}ClO_6P$ 360.0530 and found 360.0524.

4.4.4. Dimethyl (4-ethoxy-2-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-yl)phosphonate ***3k***. Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.14 (s, 1H), 4.02–3.95 (m, 2H), 3.85 (d, J=3.3 Hz, 3H), 3.83 (d, J=3.2 Hz, 3H), 2.92 (dd, J=17.8 and 12.7 Hz, 1H), 2.60 (dd, J=19.7 and 17.9 Hz, 1H), 2.14–1.95 (m, 2H), 1.40 (t, J=7.0 Hz, 3H), 1.05 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2 (d, J=8.3 Hz), 164.8 (d, J=5.0 Hz), 89.9, 80.1 (d, J=169.8 Hz), 64.7, 53.8 (d, J=7.2 Hz), 53.7 (d, J=7.4 Hz), 30.7 (d, J=2.8 Hz), 28.8 (d, J=1.4 Hz), 13.8, 7.5 (d, J=5.4 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): 23.04; IR (ATR technique, cm^{-1}): 2958, 2922, 1710, 1628, 1214, 1021; HRMS: calculated for $C_{11}H_{19}O_6P$ 278.0919 and found 278.0909.

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Supplementary data

Supplementary data (the copies of ^{1}H, ^{13}C and ^{31}P NMR spectra of these synthesized compounds are presented) associated with this article can be found online at doi:10.1016/j.tet.2011.02.007. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

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