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Highly Enantioselective Approach to Geminal Bisphosphonates by Organocatalyzed Michael-Type Addition of β-Ketoesters

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Abstract: A valuable organocatalyzed protocol has been developed for the asymmetric synthesis of bisphosphonate derivatives, a class of pharmaceutically important molecules. Cheap and commercially available dihydroquinine effectively catalyzed conjugate additions of cyclic β-ketoesters to ethylidenebisphosphonate esters, leading to optically active geminal bisphosphonates, bearing an all-carbon substituted quaternary stereocenter, in high yields and enantioselectivities of up to 99% *ee*. Further elaborations of Michael adducts to the corresponding bisphosphonic acids or vinyl phosphonates have also been successfully performed, with conservation of optical purity.

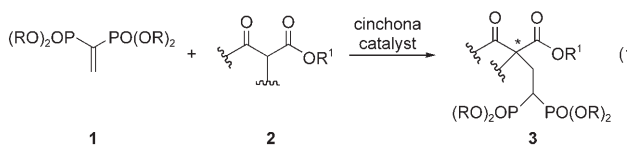
Keywords: asymmetric catalysis · bisphosphonates · ketoesters · Michael addition · organocatalysis

Introduction

Geminal bisphosphonates are structural and stable analogues of naturally occurring pyrophosphates and constitute an important class of pharmacologically active molecules. A significant number of these compounds are currently being used for the treatment of several bone disorders such as Paget's disease, myeloma, bone metastases and osteoporosis,[1] as well as in some childhood diseases.[2] Recently, bisphosphonate drugs have also been found to have activity against the in vitro proliferation of several protozoan parasites, including *Trypanosoma brucei* which causes African trypanosomiasis or sleeping sickness in human and animals.[3] Consequently, the well-proven clinical utility of bisphosphonates has fostered the development of several methodologies for the preparation of novel derivatives; structure–activity studies have actually indicated that bioactivity is highly dependent on the nature of substituents linked to the bisphosphonic skeleton.[4] Different synthetic strategies have been proposed based on the alkylation of tetraalkyl methylene bisphosphonate,[5] reaction of phosphorus electrophiles with enolates,[6] Diels–Alder reaction,[7] palladium catalysis[8] and radical chemistry.[9] Among these, the Michael-type addition to ethylidene bisphosphonate esters is a common and effective procedure affording methylene bisphosphonate derivatives. Carbon nucleophiles,[10] as well as nitrogen,[3,11] oxygen,[11,12] sulphur[11,13] and phosphorus[14] nucleophiles undergo the Michael reaction in good yields. Surprisingly, despite the importance of enantiomerically pure compounds in the pharmaceutical industry, to our knowledge, only the report of Alexakis and co-workers presenting the conjugate addition of aldehydes to vinyl phosphonates, which has been published concurrently with the preparation of the present manuscript, deals with the synthesis of geminal bisphosphonate-based molecules, in an asymmetric fashion.[15]

In this paper we wish to report a highly enantioselective Michael-type addition of β-ketoesters to vinylidene bisphosphonate **1** promoted by cinchona alkaloids as chiral-base catalysts. The efficient and operationally simple protocol developed affords the corresponding bisphosphonate derivatives bearing an all-carbon substituted quaternary stereocenter with high enantioselectivities (up to >99% *ee*) [Eq. (1)]. Importantly, the addition products belong to the class of carbonyl-containing bisphosphonate esters which are potent anti-inflammatory and antiarthritic agents.[10b,c]

Nowadays, the use of prochiral β-ketoesters in organocatalyzed asymmetric Michael additions[16] is a valuable strat-



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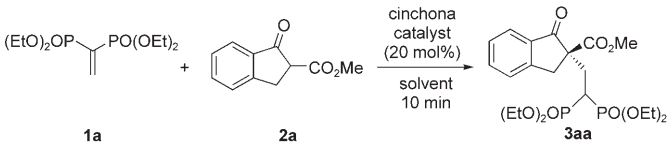
egy for the enantioselective construction of quaternary stereogenic centers which still remains a great challenge to the synthetic chemist. Moreover, the replacement of metal-based catalysts with readily available and inexpensive organocatalysts[17] offers an environmentally-friendly approach for the stereocontrolled synthesis of chiral molecules.

Results and Discussion

The feasibility of our organocatalytic asymmetric approach to the bisphosphonate Michael adducts was first explored employing 1-oxoindan-2-carboxylate **2a** (see Figure 2) as model nucleophile for the addition to tetraethyl ethylidenebisphosphonate **1a** (Table 1) in presence of a catalytic amount of cinchona alkaloid derivatives (Figure 1).

The reaction was initially carried out in CH_2Cl_2 (0.5 M) at −20 °C and the representative results of the catalyst screening are summarized in Table 1, entries 2–6. Although the addition of **2a** to **1a** occurred quantitatively in less than 10 min at room temperature without any catalyst (entry 1), we were pleased to find that cinchona alkaloids were able to promote chiral induction affording the addition product **3aa**

Table 1. Organocatalytic asymmetric addition of model substrate **2a** to **1a**: Screening of catalysts and reaction conditions.[a]



1a **2a** **3aa**

Entry	Catalyst[b]	Solvent (c [M])[c]	T [°C]	Yield[d] [%]	ee[e] [%]
1	–[f]	CH_2Cl_2 (0.5)	RT	86	–
2	**I**	CH_2Cl_2 (0.5)	−20	80	48
3	**II**	CH_2Cl_2 (0.5)	−20	72	24
4	**III**	CH_2Cl_2 (0.5)	−20	84	56
5	**IV**	CH_2Cl_2 (0.5)	−20	76	2
6	**V**	CH_2Cl_2 (0.5)	−20	78	38
7	**III**	toluene (0.5)	−20	82	60
8	**III**	CH_3CN (0.5)	−20	79	40
9	**III**	THF (0.5)	−20	80	54
10	**III**	toluene (0.5)	RT	84	40
11	**III**	toluene (0.5)	−60	82	78
12	**III**	toluene (0.1)	−60	76	87

[a] The reactions were performed using **1a** (0.2 mmol), **2a** (0.22 mmol) and the catalyst (0.04 mmol). [b] Structures of catalysts are reported in Figure 1. [c] In brackets is reported the concentration of the reaction mixture calculated on the basis of mmoles of **1a**. [d] Isolated yields after FC on silica gel. [e] The *ee* was determined by CSP-HPLC analysis. [f] Reaction performed without catalyst.

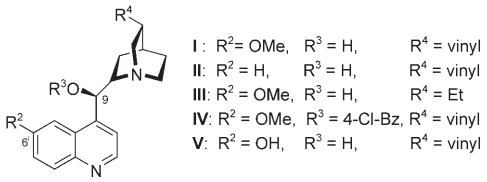
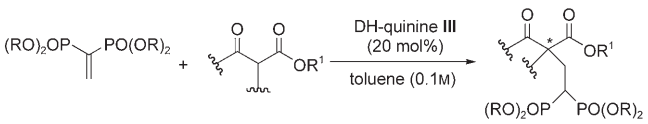


Figure 1. Screened cinchona alkaloid catalysts.

with full conversion at the same reaction times. Quinine **I** catalyzed the conjugate addition with higher enantioselectivity compared with cinchonidine **II** (entries 2, 3). However, further explorations of other catalysts based on quinine skeleton clearly demonstrated the importance of the not protected C9-OH and the presence of methoxyl group on C6[I] to induce high levels of stereoselectivity, since catalysts **IV** and **V** gave **3aa** with poor enantiomeric excess (entries 5, 6). The commercially available dihydroquinine **III** proved to be the most promising catalyst affording the addition product with moderate enantioselectivity (entry 4). Further screening of temperatures, solvents and concentrations (entries 7–12) indicated that toluene is the solvent of choice; moreover, the decrease of both the temperature to −60 °C and the concentration reaction to 0.1 M improved significantly the enantioselectivity to 87 % *ee*, still maintaining short reaction times.

With the optimized reaction conditions in hand, we then studied the effect of modifying the ester group of the 2-carboxylate 1-indanone moiety on the enantioselectivity (Table 2, entries 1–4). As expected, the bulkiness of the ester substituent had a pronounced influence on the enantiocontrol,[18] since with the bulkier *tert*-butyl ester **2d** the enantioselectivity was remarkably enhanced to 97 % *ee* (entry 4) compared with analogous methyl, benzyl and isopropyl esters **2a**–**c** (entries 1–3). Importantly, the use of "pseudoenantiomer" dihydroquinidine allowed access to the

Table 2. Enantioselective Michael-type addition of β-ketoesters **2a**–**m** to **1a**,**b**.[a]



1a,b **2a-m** **3**

1a: R = Et; **1b**: R = Bn

Entry	VBP[b]	Nu[c]	t [h]	T [°C]	Product	Yield[d] [%]	ee[e] [%]
1	**1a**	**2a**	0.8	−60	**3aa**	76	−87
2	**1a**	**2b**	0.8	−60	**3ab**	80	−84
3	**1a**	**2c**	0.6	−60	**3ac**	70	−87
4	**1a**	**2d**	0.6	−60	**3ad**	75	−97
5[f]	**1a**	**2d**	0.25	−60	*ent*-**3ad**	94	+96
6	**1a**	**2e**	0.2	−60	**3ae**	90	−97
7[g]	**1a**	**2f**	0.6	−60	**3af**	97	−98
8	**1a**	**2i**	24	−40	**3ai**	60	+84
9	**1b**	**2f**	6	−60	**3bf**	84	−92
10	**1a**	**2g**	6	−60	**3ag**	83	−98[h]
11[f]	**1a**	**2h**	60	−40	**3ah**	75	−84
12	**1a**	**2j**	8	−30	**3aj**	98	> −99
13	**1a**	**2k**	1	−60	**3ak**	93	−99
14	**1a**	**2l**	2	−60	**3al**	95	> −99
15	**1a**	**2m**	0.25	−60	**3am**	72	−54

[a] The reactions were performed using **1** (0.2 mmol), **2** (0.22 mmol) and the catalyst (0.04 mmol), unless otherwise specified. [b] Vinyl bisphosphonate (VBP) structures are indicated in the Scheme above. [c] Structures of nucleophiles **2** are reported in Figure 2. [d] Isolated yields after FC on silica gel. [e] The *ee* was determined by CSP-HPLC analysis. [f] Reaction performed with dihydroquinidine. [g] The reaction was scaled-up using 1 mmol of **1a**. [h] The *ee* was not directly determined for **3ag**, see derivatization into **5** (Scheme 1).

opposite enantiomer of **3d** with comparable enantioselectivity and in shorter reaction time (entry 5).

We subsequently investigated the scope of the reaction performing a systematic study with variously functionalized

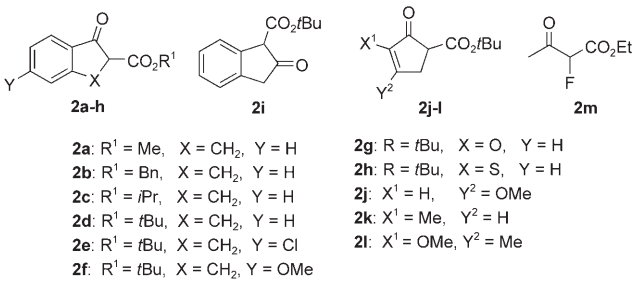
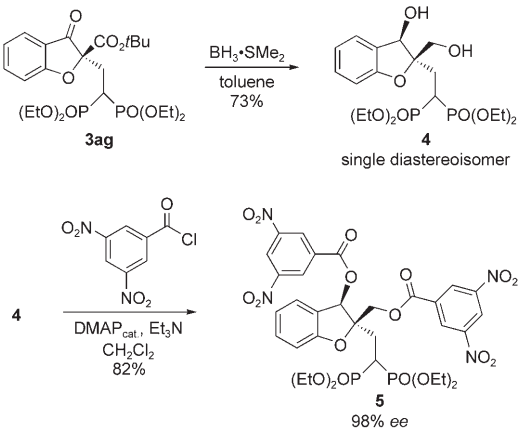


Figure 2. β-Ketoesters used in the Michael-type addition to **1a**,**b**.

indanone structures as well as with different ester groups on the electrophile. Experiments carried out with **1a** and 5-substituted indanones **2e** and **f** revealed that the enantioselectivity is not influenced by electronic effects, since either with electron-withdrawing or electron-donating substituents in the aromatic ring, such as chlorine and methoxyl groups, respectively, excellent enantioselectivities were achieved as well (entries 6, 7). The addition of 2-indanone **2i** bearing a *tert*-butyloxy carbonyl group at C-1 to **1a** was slower compared with analogous 1-indanones **2a–f**, affording the adduct **3ai** after 24 h at −40 °C[19] in acceptable yield and good enantioselectivity (entry 8).

The prospect of more complex conjugates, which would arise from the linkage between a free hydroxyl group of the phosphonate moiety and an organic unit, prompted us to extend our protocol also to tetrabenzyl ethylidenebisphosphonate **1b**, in view of the possibility to remove selectively only one benzyl group from the diphosphonate ester.[20] The study of Michael addition performed with the indanone derivative **2f** as nucleophile demonstrated that the tetrabenzylated addition product **3bf** can be obtained without considerable loss of enantioselectivity (entry 9), compared with tetraethyl ester **3af** (entry 7), while at the same time taking advantage of a more versatile protecting group.

It seemed also interesting to test the reactivity of heteroatom-substituted indanone nucleophiles in the organocatalyzed addition to **1a**, using the benzofuranone **2g** and the novel benzothiophenone **2h**. In these cases, the corresponding addition products **3ag** and **3ah** could be isolated after prolonged reaction times with good levels of enantioselectivities (entries 10, 11). However, for the benzofuranone derivative **3ag** we were not able to determine directly the enantiomeric excess by chiral stationary phase-HPLC analysis. Therefore, considering also the importance of polyhydroxylated dihydrobenzofuran skeleton in certain natural compounds,[21] we envisaged the possibility to transform **3ag** into corresponding diol. The reduction of both carbonyl and *tert*-butoxycarbonyl groups, performed with an excess of borane/methylsulfide complex, afforded diol **4**, derived from the attack of the borane from the opposite side of the *tert*-butoxycarbonyl group, in complete diastereoselectivity. Subsequent benzoylation of both hydroxyl functions allowed us to determine the value of 98% *ee* for the derivative **5** (Scheme 1).



Scheme 1. Reduction of bisphosphonate β-ketoester **3ag** to diol **4** and subsequent benzoylation to **5**.

The absolute configuration of the optically active diol **4** was established to be (1*R*), (2*R*) by X-ray analysis (Figure 3).[22]

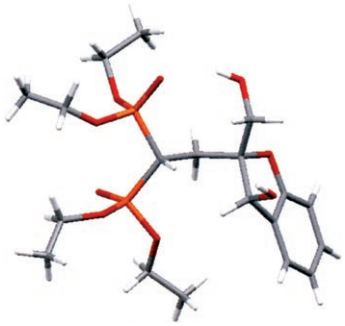


Figure 3. X-ray crystal structure of compound **4** (C gray, H white, O red, P orange).

Based on the absolute configuration of the product formed and taking into account the role of the various groups in the catalyst, we proposed the intermediate involved and its approach to the bisphosphonate, as outlined to the left in Figure 4, to account for the enantioselectivity observed in the reaction. In the less-favored intermediate, to the right in Figure 4, steric repulsion between the aromatic part of the catalyst and the enolate of the β-ketoester is proposed to disfavour this reaction path.

Moreover, we found that addition products **3** could be useful precursors of synthetically valuable vinyl phosphonate derivatives.[23] Indeed, by Horner–Wadsworth–Emmons olefination of **3ag**, it was possible to isolate in good yields the vinyl phosphonate **6**, even if with a slight erosion of

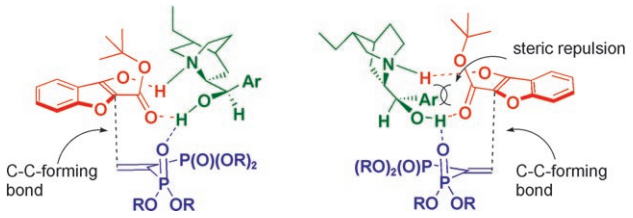
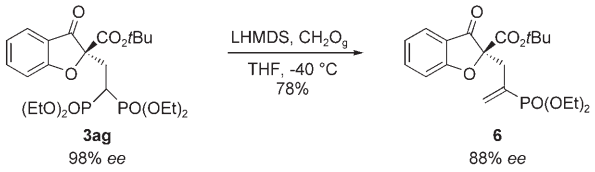


Figure 4. Proposed approach of the intermediates to the bisphosphonate. On the left, the reaction path leading to the observed configuration and on the right, the less-favored reaction path having steric repulsion.

enantiopurity, due to a inevitable partial retro-Michael reaction under basic conditions (Scheme 2).

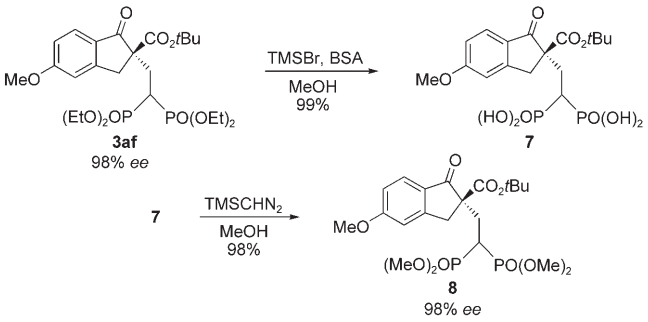


Scheme 2. HWE reaction for the synthesis of vinyl phosphonate **6**.

Next, in light of the considerable importance of cyclopentenone-bearing compounds in anticancer drug design,[24] we desired to study the reactivity and the enantioselective behavior of cyclic five-membered ring β-ketoesters in the organocatalyzed addition to **1a**. We focused on three novel differently functionalized *tert*-butyl esters of cyclopentenone **2j**, **k** and **l**, bearing a cyclic protected 1,3-diketone, a β-susbstituted cyclopentenone and a cyclic protected 1,2-diketone derivatives respectively.[25] With our satisfaction, the addition products **3aj**, **ak** and **al** were isolated in very high yields and excellent enantioselectivities (entries 12–14), providing a valuable class of molecules that might contribute to the development of novel therapeutic bisphosphonate derivatives.

Also the acyclic α-fluorinated β-ketoester **2m** was tested in the organocatalyzed addition to **1a**, but unfortunately, although dihydroquinine catalyzed the reaction quantitatively in only 15 min, only moderate enantioselectivity was achieved (entry 15). Change of catalyst and/or replacement with a bulkier *tert*-butyl ester produced lower enantiomeric excess.

After having demonstrated the feasibility of our asymmetric approach leading to optically active bisphosphonate ester derivatives, we have finally deemed it important to optimize a procedure aimed to convert the bisphosphonic ester products into the corresponding bisphosphonic acids, due to the large applications of the latter in the therapy of most bone diseases.[1] To this purpose, the tetraethyl ester **3af**, chosen as model substrate, was treated with bromotrimethylsilane in presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA).[26] Successive methanolysis of the silyl esters afforded bisphosphonic acid **7** quantitatively. We were able to demonstrate that this transformation occurs without any loss of enantioselectivity, as confirmed by the same value of *ee* measured for the tetramethyl bisphosphonate **8**, obtained in turn by esterification of **7** with trimethylsilyldiazomethane in quantitative yield (Scheme 3).



Scheme 3. Hydrolysis of the tetraethyl ester **3af** to bisphosphonic acid **7** and subsequent esterification to **8**.

Conclusion

In summary, we have developed the first example of asymmetric addition of β-ketoesters to vinyl bisphosphonate esters, catalyzed by cheap and commercially available dihydroquinine. High yields and enantioselectivities were achieved under simple conditions for a wide range of indanone-based β-ketoesters, as well as various unprecedented 5-*tert*-butyloxycarbonyl cyclopentenones. Furthermore we have demonstrated that the bisphosphonate adducts can be conveniently elaborated to other interesting derivatives and can also be easily hydrolyzed to the corresponding acids. Therefore, our protocol allows access to a class of new optically pure geminal bisphosphonates, opening attractive prospects in the field of asymmetric synthesis targeted to bisphosphonate derivatives.

Experimental Section

General methods: NMR spectra were acquired running at 400, 100 and 160 MHz for ^{1}H, ^{13}C and ^{31}P NMR, respectively. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$) for ^{1}H NMR, relative to the central resonance of $CDCl_3$ ($\delta = 77.0$) for ^{13}C NMR and relative to external H_3PO_4 85% ($\delta = 0.00$) for ^{31}P NMR, unless otherwise noted. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded using electrospray (ES^+) ionization techniques. Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates and visualized by ultraviolet irradiation or $KMnO_4$ dip. Optical rotations were measured on a Perkin–Elmer 241 polarimeter and reported in $deg\,cm^3\,g^{-1}$; concentrations are reported in $g\,cm^{-3}$. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD or Chiralcel OD columns). Absolute configuration of the bisphosphonate derivative **4** was established by single-crystal X-ray analysis. The same approach of the nucleophile to ethylidene bisphosphonates **1a** and **b** was assumed for assigning the absolute configuration for the rest of the compounds.

Materials: Analytical grade solvents and commercially available reagents were used without further purification, unless otherwise noted. Tetrahydrofuran and trimethylsilylbromide were freshly distilled before use. Chromatography was carried out by flash chromatography (FC) using

Merck silica gel 60, 230–400 mesh. The reactions were carried out in not inert conditions, unless otherwise specified. Tetraethyl ethylidenebisphosphonate (**1a**) and tetrabenzyl ethylidenebisphosphonate (**1b**) were prepared according to literature procedure.[10g,20] *tert*-Butyl β-ketoesters **2f** and **i** were prepared from the corresponding methyl esters by Bu_2SnO-catalyzed transesterification with *t*BuOH in refluxing toluene; *tert*-butyl β-ketoesters **2j–l** were prepared from the corresponding cyclopent-2-enones by acylation with 1-(*tert*-butoxycarbonyl)-imidazole.[27] Racemic samples were prepared using Et_3N as catalyst.

General procedure of addition of β-ketoesters 2a–m to ethylidenebisphosphonate esters 1a,b: A cooled (−60 °C) solution of ethylidene bisphosphonate **1** (0.2 mmol) in toluene (0.5 mL) was added dropwise to a stirred cooled (−60 °C, unless otherwise specified) solution of β-ketoester **2** (0.22 mmol) and DH-quinine (13 mg, 0.04 mmol) in toluene (1.5 mL). The resulting clear solution was stirred until **1** was completely consumed as indicated by TLC analysis. The reaction mixture was directly subjected to FC (pentane/EtOAc 2:8) to give the desired addition product **3**.

(*R*)-Methyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3aa): The title compound was obtained from **1a** and **2a** according to the general procedure after 50 min as a colorless oil (77 mg, 76%). $[\alpha]_D^{20} = -45.1$ ($c = 1.0$, $CHCl_3$, 87% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.71$ (d, $J = 7.3$ Hz, 1H), 7.59 (t, $J = 7.3$ Hz, 1H), 7.45 (d, $J = 7.3$ Hz, 1H), 7.35 (t, $J = 7.3$ Hz, 1H), 4.20–4.01 (m, 8H), 3.74 (A of AB, $J = 17.6$ Hz, 1H), 3.65 (s, 3H), 3.51 (B of AB, $J = 17.6$ Hz), 2.94–2.80 (m, 1H), 2.68 (tt, $J = 24.1$ Hz, $J = 5.1$ Hz), 2.49–2.32 (m, 1H), 1.37–1.20 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.7$, 170.0, 152.9, 135.1, 134.3, 127.3, 125.9, 124.3, 62.5–62.2 (m), 59.5 (t, $J = 4.6$ Hz), 52.3, 36.4, 32.4 (t, $J = 132.7$ Hz), 29.6 (t, $J = 4.6$ Hz), 15.9–15.8 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.4$, 23.2 ppm; HRMS: *m/z*: calcd for $C_{21}H_{32}NaO_9P_2$: 513.1419, found: 513.1437 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 43.6$ min, $\tau_{major} = 50.0$ min (87% *ee*).

(*R*)-Benzyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3ab): The title compound was obtained from **1a** and **2b** according to the general procedure after 50 min as a colorless oil (91 mg, 80%). $[\alpha]_D^{20} = -48.3$ ($c = 1.0$, $CHCl_3$, 84% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.68$ (d, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.40 (d, $J = 7.6$ Hz, 1H), 7.31 (t, $J = 7.4$ Hz, 1H), 7.25–7.15 (m, 5H), 5.07 (A of AB system, $J = 12.6$ Hz, 1H), 5.02 (B of AB system, $J = 12.6$ Hz, 1H), 4.10–3.98 (m, 8H), 3.70 (A of AB system, $J = 17.7$ Hz, 1H), 3.50 (B of AB system, $J = 17.7$ Hz, 1H), 2.93–2.79 (m, 1H), 2.73–2.58 (m, 1H), 2.46–2.30 (m, 1H), 1.25–1.18 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.0$, 169.0, 154.0, 135.2, 127.5, 126.2, 124.6, 82.0, 62.9–62.6 (m), 60.8 (t, $J = 4.6$ Hz), 37.1, 33.0 (t, $J = 132.7$ Hz), 29.5 (t, $J = 4.6$ Hz), 27.7, 16.3–16.2 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.3$, 23.1 ppm; HRMS: *m/z*: calcd for $C_{27}H_{36}NaO_9P_2$: 589.1732, found: 589.1750 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{major} = 55.0$ min, $\tau_{minor} = 64.2$ min (84% *ee*).

(*R*)-Isopropyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3ac): The title compound was obtained from **1a** and **2c** according to the general procedure after 40 min as a colorless oil (72 mg, 70%). $[\alpha]_D^{20} = -47.2$ ($c = 1.0$, $CHCl_3$, 87% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.69$ (d, $J = 7.7$ Hz, 1H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.33 (t, $J = 7.6$ Hz, 1H), 4.98–4.88 (m, 1H), 4.18–4.03 (m, 8H), 3.65 (A of AB system, $J = 17.8$ Hz, 1H), 3.53 (B of AB system, $J = 17.8$ Hz, 1H), 2.91–2.76 (m, 1H), 2.68–2.53 (m, 1H), 2.46–2.31 (m, 1H), 1.31–1.23 (m, 12H), 1.10 ppm (t, $J = 6.5$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 201.5$, 169.5, 153.6, 135.3, 134.8, 127.5, 126.2, 124.6, 69.2, 62.8–62.5 (m), 60.0–59.9 (m), 36.8, 32.7 (t, $J = 132.7$ Hz), 29.6 (t, $J = 4.4$ Hz), 21.4, 21.3, 16.2–16.1 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.6$, 23.1 ppm; HRMS: *m/z*: calcd for $C_{23}H_{36}NaO_9P_2$: 541.1732, found: 541.1732 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 26.2$ min, $\tau_{major} = 31.4$ min (87% *ee*).

(*R*)-*tert*-Butyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3ad): The title compound was obtained from **1a** and **2d** according to the general procedure after 40 min as a colorless oil (80 mg, 75%). $[\alpha]_D^{20} = -61.2$ ($c = 1.0$, $CHCl_3$, 97% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.72$ (d, $J = 7.7$ Hz, 1H), 7.59 (t, $J = 7.6$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 4.21–4.06 (m, 8H), 3.65 (A of AB system, $J = 17.6$ Hz, 1H), 3.55 (B of AB system, $J = 17.6$ Hz, 1H), 2.92–2.77 (m, 1H), 2.69–2.54 (m, 1H), 2.43–2.30 (m, 1H), 1.34–1.26 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.0$, 169.0, 154.0, 135.2, 127.5, 126.2, 124.6, 82.0, 62.9–62.5 (m), 60.8–60.7 (m), 37.1, 33.0 (t, $J = 131.6$ Hz), 29.5 (t, $J = 4.1$ Hz), 27.7, 16.4–16.2 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.7$, 23.2 ppm; HRMS: *m/z*: calcd for $C_{24}H_{38}NaO_9P_2$: 555.1889, found: 555.1899 $[M+Na]^+$. The *ee* was determined by HPLC using two Chiralpak AD columns combined in series (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 35.1$ min, $\tau_{major} = 43.3$ min (97% *ee*).

(*R*)-*tert*-Butyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (*ent*-3ad): The title compound *ent*-**3ad** (enantiomer of **3ad**) was obtained from **1a** and **2d** according to the general procedure after 15 min, using dihydroquinidine, as a colorless oil (100 mg, 94%). Spectral data were identical to compound **3ad**. $[\alpha]_D^{20} = +61.0$ ($c = 1.0$, $CHCl_3$, 96% *ee*). The *ee* was determined by HPLC using two Chiralpak AD columns combined in series (hexane/*i*PrOH 98:2); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 35.5$ min, $\tau_{major} = 43.3$ min (96% *ee*).

(*R*)-*tert*-Butyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-5-chloro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3ae): The title compound was obtained from **1a** and **2e** according to the general procedure after 10 min as a colorless oil (102 mg, 90%). $[\alpha]_D^{20} = -59.6$ ($c = 1.0$, $CHCl_3$, 97% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.63$ (d, $J = 8.1$ Hz, 1H), 7.45 (s, 1H), 7.32 (d, $J = 8.1$ Hz), 4.20–4.06 (m, 8H), 3.62 (A of AB system, $J = 17.9$ Hz, 1H), 3.52 (B of AB system, $J = 17.9$ Hz, 1H), 2.90–2.76 (m, 1H), 2.70–2.54 (m, 1H), 2.39–2.67 (m, 1H), 1.33–1.26 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.5$, 168.6, 155.4, 141.8, 133.3, 128.3, 126.4, 125.6, 82.3, 62.9–62.5 (m), 61.1–61.0 (m), 36.9, 33.0 (dd, $J = 131.2$ Hz, 133.8 Hz), 27.7, 16.3–16.2 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.5$, 23.1 ppm; HRMS: *m/z*: calcd for $C_{24}H_{37}ClNaO_9P_2$: 589.1499, found: 589.1511 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 21.6$ min, $\tau_{major} = 26.6$ min (97% *ee*).

(*R*)-*tert*-Butyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3af): The title compound was obtained from **1a** and **2f** according to the general procedure after 40 min as a colorless oil (103 mg, 92%). $[\alpha]_D^{20} = -71.6$ ($c = 1.0$, $CHCl_3$, 97% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.63$–7.60 (m, 1H), 6.89–6.83 (m, 2H), 4.20–4.04 (m, 8H), 3.84 (s, 3H), 3.59 (A of AB system, $J = 18.1$ Hz, 1H), 3.50 (B of AB system, $J = 18.1$ Hz, 1H), 2.92–2.74 (m, 1H), 2.70–2.53 (m, 1H), 2.37–2.22 (m, 1H), 1.38–1.21 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 199.8$, 169.2, 165.7, 157.1, 128.0, 126.2, 115.8, 109.0, 81.8, 62.8–62.4 (m), 61.1–61.0 (m), 55.5, 37.0, 33.1 (t, $J = 131.7$ Hz), 29.6, 27.7, 16.3–16.2 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.5$, 23.3 ppm; HRMS: *m/z*: calcd for $C_{25}H_{40}NaO_{10}P_2$: 585.1994, found: 585.1994 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 30.1$ min, $\tau_{major} = 39.5$ min (97% *ee*).

(*S*)-*tert*-Butyl 1-(2,2-bis(diethoxyphosphoryl)ethyl)-2-oxo-2,3-dihydro-1*H*-indene-1-carboxylate (3ai): The title compound was obtained from **1a** and **2i** according to the general procedure, at −40 °C after 24 h as a colorless oil (64 mg, 60%). $[\alpha]_D^{20} = +20.0$ ($c = 1.0$, $CHCl_3$, 84% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33–7.16 (m, 4H), 4.12–3.86 (m, 8H), 3.67 (A of AB system, $J = 21.9$ Hz, 1H), 3.59 (B of AB system, $J = 21.9$ Hz, 1H), 3.17–3.02 (m, 1H), 2.85–2.74 (m, 1H), 2.28–2.09 (m, 1H), 1.32–1.16 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 211.1$, 169.0, 139.4, 139.2, 128.4, 127.2, 125.1, 124.3, 82.5, 65.6–65.5 (m), 62.7–62.4 (m), 43.5, 32.3 (t, $J = 135.7$ Hz), 27.4, 26.5, 16.3–16.1 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.7$, 22.8 pppm; HRMS: *m/z*: calcd for $C_{24}H_{38}NaO_9P_2$: 555.1889, found: 555.1893 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 33.2$ min, $\tau_{major} = 26.9$ min (84% *ee*).

(*R*)-*tert*-Butyl 2-(2,2-bis-(bisbenzyloxyphosphoryl)ethyl)-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (3bf): The title compound was obtained from **1b** and **2f** according to the general procedure after 6 h as a colorless oil (136 mg, 84%). $[\alpha]_D^{20} = -29.6$ (c = 1.0, $CHCl_3$, 92% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.55$ (d, $J = 8$ Hz, 1H), 7.32–7.26 (m, 20H), 6.84–6.82 (d, $J = 8$ Hz, 1H), 6.74 (s, 1H), 5.07–4.92 (m, 8H), 3.85 (s, 3H), 3.48 (A of AB system, $J = 18$ Hz, 1H), 3.37 (B of AB system, $J = 18$ Hz, 1H), 3.07–2.79 (m, 2H), 2.54–2.41 (m, 1H), 1.30 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.1$, 169.6, 165.9, 157.2, 136.3, 128.7–128.2, 126.6, 116.0, 109.4, 82.2, 68.7–68.5 (m), 68.4–68.3 (m), 61.2–61.1 (m), 55.9, 37.3, 34.0 (t, $J = 131.0$ Hz), 29.7, 27.9 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.5$, 23.2 ppm; HRMS: *m*/*z*: calcd for $C_{45}H_{48}NaO_{10}P_2$: 833.2620, found: 833.2635 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 70:30); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 21.4$ min, $\tau_{major} = 49.3$ min (92% *ee*).

(*S*)-*tert*-Butyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (3ag): The title compound was obtained from **1a** and **2g** according to the general procedure after 6 h as a colorless oil (89 mg, 83%). $[\alpha]_D^{20} = -33.1$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.65$–7.61 (m, 2H), 7.18 (d, $J = 8.8$ Hz, 1H), 7.10 (t, $J = 8.8$ Hz, 1H), 4.23–4.00 (m, 8H), 3.05–2.90 (m, 1H), 2.77–2.51 (m, 2H), 1.40 (s, 9H), 1.35–1.17 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 195.6$, 172.2, 164.0, 138.2, 124.7, 122.5, 119.6, 113.3, 89.4–89.3 (m), 83.8, 63.0–62.6 (m), 31.7 (t, $J = 133.7$ Hz), 28.4, 27.6, 16.3–16.0 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 22.5$, 22.3 ppm; HRMS: *m*/*z*:calcd for $C_{23}H_{36}NaO_{10}P_2$: 557.1681, found: 557.1672 $[M+Na]^+$.

(*S*)-*tert*-Butyl 2-(2,2-bis(diethoxyphosphoryl)ethyl)-3-oxo-2,3-dihydrobenzo-[*b*]thiophene-2-carboxylate (3ah): The title compound was obtained from **1a** and **2h** (2 equiv) according to the general procedure after 60 h at −40 °C, using dihydroquinidine, as a colorless oil (89 mg, 75%). $[\alpha]_D^{20} = -83.7$ (c = 1.0, $CHCl_3$, 84% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.73$ (d, $J = 7.7$ Hz, 1H), 7.53 (t, $J = 7.7$ Hz, 1H), 7.38 (d, $J = 7.7$ Hz, 1H), 7.21 (t, $J = 7.7$ Hz), 4.23–3.93 (m, 8H), 3.14–3.00 (m, 1H), 2.98–2.83 (m, 1H), 2.65 (tt, $J = 24.4$ Hz, $J = 4.8$ Hz, 1H), 1.35–1.29 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 197.4$, 167.2, 151.0, 135.6, 130.2, 126.9, 125.2, 123.9, 83.2, 67.3–67.0 (m), 63.0–62.3 (m), 33.4 (t, $J = 134.0$ Hz), 28.0, 27.4, 16.4–16.0 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.4$, 22.4 ppm; HRMS: *m*/*z*: calcd for $C_{23}H_{36}NaO_9P_2S$: 573.1453, found: 573.1458 $[M+Na]^+$. The *ee* was determined by HPLC using two Chiralpak AD columns combined in series (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{major} = 42.4$ min, $\tau_{minor} = 48.5$ min (84% *ee*).

(*S*)-*tert*-Butyl 1-(2,2-bis(diethoxyphosphoryl)ethyl)-4-methoxy-2-oxocyclopent-3-enecarboxylate (3aj): The title compound was obtained from **1a** and **2j** according to the general procedure, at −30 °C after 8 h as a colorless oil (100 mg, 98%). $[\alpha]_D^{20} = -58.8$ (*c* = 1.0, $CHCl_3$, > 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.18$ (s, 1H), 4.19–4.08 (m, 8H), 3.82 (s, 3H), 3.12 (A of AB system, $J = 18.1$ Hz, 1H), 3.03 (B of AB system, $J = 18.1$ Hz), 2.86–2.68 (m, 2H), 2.15–1.98 (m, 1H), 1.38–1.26 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.3$, 191.3, 168.5, 101.0, 81.9, 62.8–62.4 (m), 59.7, 58.8, 38.9, 33.5 (t, $J = 133.4$ Hz), 29.9, 27.7, 16.4–16.2 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.4$, 23.3 ppm; HRMS: *m*/*z*: calcd for $C_{21}H_{38}NaO_{10}P_2$: 535.1838, found: 535.1832 $[M+Na]^+$. The *ee* was determined by HPLC using two Chiralpak AD columns combined in series hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 67.1$ min, $\tau_{major} = 60.1$ min (> 99% *ee*).

(*S*)-*tert*-Butyl 1-(2,2-bis(diethoxyphosphoryl)ethyl)-3-methyl-2-oxocyclopent-3-enecarboxylate (3ak): The title compound was obtained from **1a** and **2k** according to the general procedure after 1 h as a colorless oil (92 mg, 93%). $[\alpha]_D^{20} = -37.8$ (*c* = 1.0, $CHCl_3$, 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.34$ (s, 1H), 4.20–4.07 (m, 8H), 3.99 (AB system, $J = 19.4$ Hz, 2H), 2.75–2.55 (m, 2H), 2.19–2.07 (m, 1H), 1.75 (s, 3H), 1.40–1.27 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 204.9$, 168.8, 158.2, 139.3, 81.7, 62.8–62.4 (m), 58.2–58.1 (m), 37.8, 32.9 (t, $J = 133.8$ Hz), 29.6, 27.7, 16.3–16.2 (m), 10.4 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.7$, 23.4 ppm; HRMS: *m*/*z*: calcd for $C_{21}H_{38}NaO_9P_2$: 519.1889, found: 519.1890 $[M+Na]^+$. The *ee* was determined by HPLC using two Chiralpak AD columns combined in series (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 26.2$ min, $\tau_{major} = 27.7$ min (99% *ee*).

(*S*)-*tert*-Butyl 1-(2,2-bis(diethoxyphosphoryl)ethyl)-3-methoxy-4-methyl-2-oxocyclopent-3-enecarboxylate (3al): The title compound was obtained from **1a** and **2l** according to the general procedure after 2 h as a colorless oil (100 mg, 95%). $[\alpha]_D^{20} = -52.6$ (*c* = 1.0, $CHCl_3$, > 99% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 4.14$–4.01 (m, 8H), 3.74 (s, 3H), 2.78 (AB system, $J = 19.1$ Hz, 2H), 2.68–2.53 (m, 2H), 2.13–2.01 (m, 1H), 1.91 (s, 3H), 1.31–1.22 ppm (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 198.3$, 168.8, 155.1, 150.6, 82.0, 63.0–62.7 (m), 58.6–58.4 (m), 57.0–56.0 (m), 38.5, 33.1 (t, $J = 132.1$ Hz), 29.6, 27.9, 16.6–16.4 (m), 14.9 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 23.6$, 23.4 ppm; HRMS: *m*/*z*: calcd for $C_{22}H_{40}NaO_{10}P_2$: 549.1994, found: 549.2007 $[M+Na]^+$. The *ee* was determined by HPLC using two Chiralpak AD columns combined in series (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 23.9$ min, $\tau_{major} = 29.5$ min (> 99% *ee*).

***tert*-Butyl 2-acetyl-4,4-bis(diethoxyphosphoryl)-2-fluorobutanoate (3am)**: The title compound was obtained from **1a** and **2m** according to the general procedure after 15 min as a colorless oil (64 mg, 72%). $[\alpha]_D^{20} = -16.0$ (*c* = 1.0, $CHCl_3$, 54% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 4.28$–4.08 (m, 10H), 2.82–2.55 (m, 3H), 2.28 (d, $J = 4.5$, 3H), 1.31–1.29 ppm (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 200.6$ (d, $J = 28.3$ Hz), 165.7 (d, $J = 25.9$ Hz), 99.2 (d, $J = 202.5$ Hz), 62.9–62.8 (m), 30.6 (t, $J = 133.9$ Hz), 28.6 (d, $J = 21.1$ Hz), 25.6 (d, $J = 3.7$ Hz), 16.2, 13.8 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 22.5$, 22.2 ppm; ^{19}F NMR ($CDCl_3$, 25 °C): $\delta = -166.2$ ppm (dt, $J = 19.1$ Hz, $J = 2.8$ Hz); HRMS: *m*/*z*: calcd for $C_{16}H_{31}FNaO_9P_2$: 471.1325, found: 471.1312 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor} = 16.6$ min, $\tau_{major} = 18.3$ min (54% *ee*).

Reduction of 3ag into the corresponding diol 4: A large excess of borane/methylsulfide complex (1.5 mL, 15.8 mmol) was added dropwise under an argon atmosphere to a stirred solution of bisphosphonate derivative **3ag** (310.5 mg, 0.58 mmol) in anhydrous toluene (1 mL). After stirring for 20 h at RT, the mixture was cooled to 0 °C and quenched with EtOH (4 mL). The solvent was removed under reduced pressure and the crude product (single diasteroisomer in the ^{1}H NMR spectrum) was subjected to FC (MeOH/EtOAc 2:98) to give the desired diol **4** as a white solid (97 mg, 73%).

(2*R*,3*R*)-Tetraethyl 2-(3-hydroxy-2-(hydroxymethyl)-2,3-dihydrobenzofuran-2-yl)ethane-1,1-diyldiphosphonate (4): $[\alpha]_D^{20} = -8.5$ (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.39$ (d, $J = 8.0$ Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 1H), 6.91 (t, $J = 8.0$ Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 5.09 (brs, 1H), 5.04 (s, 1H), 4.44–3.70 (m, 10H), 3.57 (brs), 2.90–2.60 (m, 1H), 2.48–2.24 (m, 1H), 2.23–1.94 (m, 1H), 1.60–0.95 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 158.4$, 130.3, 127.5, 126.5, 121.1, 110.5, 90.3–90.2 (m), 77.6, 63.6–62.4 (m), 59.6, 30.7 (t, $J = 133.3$ Hz), 28.1, 16.2 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 25.5$ (d, $J = 4.9$ Hz), 22.5 ppm (d, $J = 4.9$ Hz); HRMS: *m*/*z*: calcd for $C_{19}H_{32}NaO_9P_2$: 489.1419, found: 489.1429 $[M+Na]^+$.

Benzoylation of diol 4 to the corresponding diester 5: 3,5-Dinitrobenzoyl chloride (92.2 mg, 0.4 mmol) was added to a stirred solution of diol **4** (46.6 mg, 0.1 mmol) in anhydrous CH_2Cl_2 (2 mL), and then Et_3N (0.2 mL) and a catalytic amount of DMAP (2 mg). After stirring for 1 h at RT, the solvent was removed under reduced pressure and the crude product was purified by FC (pentane/EtOAc 3:7) affording the corresponding diester **5** as a yellow oil (70 mg, 82%).

(2*R*,3*R*)-2-(2,2-bis(diethoxyphosphoryl)ethyl)-2-((3,5-dinitrobenzoyloxy)-methyl)-2,3-dihydro-benzofuran-3-yl 3,5-dinitrobenzoate (5): $[\alpha]_D^{20} = -41.0$ (*c* = 1.0, $CHCl_3$, 98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 9.25$–9.10 (m, 2H), 9.05–8.98 (m, 2H), 8.95–8.88 (m, 2H), 7.55–7.30 (m, 2H), 7.10–6.85 (m, 3H), 4.89 (A of AB system, $J = 12.0$ Hz, 1H), 4.84 (B of AB system, $J = 12.0$ Hz, 1H), 4.45–3.95 (m, 8H), 3.00–2.55 (m, 3H), 1.60–1.15 ppm (m, 12H); ^{13}C NMR ($CDCl_3$): $\delta = 162.3$, 161.9, 159.3, 148.7, 148.6, 133.1, 132.7, 132.3, 129.3, 126.6, 123.0, 122.9, 122.8, 122.6, 122.5, 122.2, 110.7, 88.8–88.6 (m), 80.5, 64.9, 63.4–62.6 (m), 31.3 (t, $J = 134.1$ Hz), 29.8, 16.3 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25 °C): $\delta = 22.3$ (d, $J = 3.0$ Hz), 22.2 ppm (d, $J = 3.0$ Hz); HRMS: *m*/*z*: calcd for

$C_{33}H_{36}N_4NaO_{19}P_2$: 877.1347, found: 877.1343 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralcel OD column (hexane/*i*PrOH 50:50); flow rate 0.5 mL min^{-1}; $\tau_{major}=62.9$ min, $\tau_{minor}=84.3$ min (98% *ee*).

Derivatization of 3ag into the corresponding vinyl phosphonate 6 by Horner-Wadsworth-Emmons reaction: In a 2-necked flask a solution of bisphosphonate derivative **3ag** (88 mg, 0.16 mmol) in anhydrous THF (5 mL) was cooled at −40°C under an argon atmosphere. In a separate two-necked flask paraformaldehyde (2 g) was placed under argon and subsequently heated to 200°C to promote paraformaldehyde depolymerization. Formaldehyde gas was collected by cannula to the flask containing the cooled solution of **3ag** until complete saturation, then a solution of LHMDS (0.18 mmol, 1.06 M in THF) was added dropwise over 15 min. After stirring at −40°C for 10 min, the mixture was quenched with water and extracted with diethyl ether (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude mixture by FC (pentane/EtOAc 1:1) afforded the vinyl phosphonate **4** as colorless oil (50 mg, 76%).

(*S*)-*tert*-Butyl 2-(2-diethoxyphosphoryl)allyl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (6): $[\alpha]_D^{20}=-33.0$ ($c=1.0$, $CHCl_3$, 88% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.64$–7.60 (m, 2H), 7.17 (d, $J=8.7$ Hz, 1H), 7.09 (t, $J=7.6$ Hz, 1H), 6.19–6.00 (m, 2H), 4.11–3.94 (m, 4H), 3.36–3.25 (m, 1H), 2.79–2.73 (m, 1H), 1.39 (s, 9H), 1.31 (t, $J=7.1$ Hz, 3H), 1.24 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=$ 195.3, 172.3, 163.8, 138.5, 133.9, 132.4–132.2 (m), 124.8, 122.5, 119.0, 113.4, 90.6, 83.8, 61.9–61.7 (m), 34.4 (d, $J=12.9$ Hz), 27.5, 16.3–16.1 ppm (m); ^{31}P NMR (160 MHz, $CDCl_3$, 25°C): $\delta=18.0$ ppm; HRMS: *m*/*z*: calcd for $C_{20}H_{27}NaO_7P$: 433.1392, found: 433.1392 $[M+Na]^+$. The *ee* was determined by HPLC using a Chiralpak AD column (hexane/*i*PrOH 90:10); flow rate 1.0 mL min^{-1}; $\tau_{minor}=14.4$ min, $\tau_{major}=16.4$ min (88% *ee*).

Hydrolysis of 3af into the corresponding bisphosphonic acid 7: Under argon, freshly distilled TMSBr (0.6 mL) was added dropwise to a stirred solution of tetraethyl bisphosphonate **3af** (0.3 mmol), previously dried-up under vacuum over P_2O_5 for 12 h, in BSA (1.5 mL). The mixture was stirred at RT for 24 h. The residue was first evaporated at reduced pressure, then co-evaporated with *o*-xylene (5 mL) three times. The crude mixture was treated with MeOH (5 mL) and the resulting mixture stirred overnight. Evaporation of the solvent at reduced pressure afforded pure bisphosphonic acid **7** as a white solid (133 mg, 99%).

(*R*)-2-(2-(*tert*-Butoxycarbonyl)-5-methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)ethane-1,1-diyldiphosphonic acid (7):[28] $[\alpha]_D^{20}=-71.1$ ($c=1.0$, MeOH); ^{1}H NMR (400 MHz, CD_3OD, 25°C): $\delta=7.63$ (d, $J=8.5$ Hz, 1H), 7.05 (d, $J=2$ Hz, 1H), 6.96 (dd, $J=8.5$ Hz, $J=2$ Hz, 1H), 3.90 (s, 3H), 3.67 (A of AB system, $J=17.9$ Hz, 1H), 3.58 (B of AB system, $J=$ 17.9 Hz, 1H), 2.98–2.76 (m, 1H), 2.58–2.38 (m, 1H), 2.35 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD, 25°C): $\delta=202.6$, 171.0, 167.8, 159.3, 128.9, 127.2, 117.2, 110.4, 83.1, 62.9–62.7 (m), 56.5, 38.4, 35.6 (t, $J=$ 125.7 Hz), 30.9, 28.1; ^{31}P NMR (160 MHz, CD_3OD, 25°C): $\delta=21.2$, 20.7 ppm; HRMS: *m*/*z*: calcd for $C_{17}H_{24}NaO_{10}P_2$: 473.0742, found: 473.0740 $[M+Na]^+$.

Esterification of bisphosphonic acid 7 to the corresponding tetramethyl ester 8: A solution of $TMSCHN_2$ 2 M in hexane (1.1 mL) was added dropwise to a stirred solution of bisphosphonic acid **7** (0.1 mmol) in MeOH (2 mL). After stirring for 15 min at RT the solvent was evaporated at reduced pressure affording pure tetramethyl bisphosphonate **8** as a colorless oil (49 mg, 98%).

(*R*)-*tert*-Butyl 2-(2,2-bis(dimethoxyphosphoryl)ethyl)-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (8): $[\alpha]_D^{20}=-69.9$ ($c=1.0$, $CHCl_3$, 98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta=7.64$ (d, $J=7.5$, 1H), 6.94–6.85 (m, 2H), 3.87 (s, 3H), 3.84–3.69 (m, 12H), 3.60 (A of AB system, $J=17.6$ Hz, 1H), 3.40 (B of AB system, $J=17.6$ Hz, 1H), 2.90–2.68 (m, 2H), 2.39–2.21 (m, 1H), 1.35 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta=199.7$, 169.1, 165.8, 156.9, 127.9, 126.3, 115.9, 109.1, 82.0, 60.9–60.8 (m), 55.6, 53.6–52.8 (m), 37.3, 32.2 (t, $J=131.4$ Hz), 29.7, 27.7 ppm; ^{31}P NMR (160 MHz, $CDCl_3$, 25°C): $\delta=24.9$, 24.5 ppm; HRMS: *m*/*z*: calcd for $C_{21}H_{32}NaO_{10}P_2$: 529.1368, found: 529.1364 $[M+Na]^+$. The *ee* was determined by HPLC using two Chiralpak AD columns combined in series (hexane/*i*PrOH 80:20); flow rate 0.7 mL min^{-1}; $\tau_{minor}=89.3$ min, $\tau_{major}=95.7$ min (98% *ee*).

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[1] For a recent review on the clinical use of bisphosphonates, see: S. Zhang, G. Gangal, H. Uludağ, *Chem. Soc. Rev.* **2007**, *36*, 507–531.
[2] T. Srivastava, U. S. Alon, *Eur. J. Pediatr.* **2003**, *162*, 735–751.
[3] E. Kotsikorou, Y. Song, J. M. W. Chan, S. Faelens, Z. Tovian, E. Broderick, N. Bakalara, R. Docampo, E. Olfield, *J. Med. Chem.* **2005**, *48*, 6128–6139, and references therein.
[4] a) G. H. Ebetino, A. V. Bayless, L. Amburgey, K. J. Ibbotson, S. Dansereau, A. Ebrahimpour, *Phosphorus Sulfur Silicon* **1996**, *109/110*, 217–220; b) E. van Beek, C. Lowik, I. Que, S. Papapoulos, *J. Bone Miner. Res.* **1996**, *11*, 1492–1497.
[5] a) V. Chaleix, M. Lecouvey, *Tetrahedron Lett.* **2007**, *48*, 703–706; b) X. Liu, X. R. Zhang, G. M. Blackburn, *Chem. Commun.* **1997**, 87–88; c) H. J. Cristau, C. Brahic, J. L. Pirat, *Tetrahedron* **2001**, *57*, 9149–9156; d) F. H. Ebetino, C. R. Gegenhardt, L. A. Jamison, D. C. Burdsall, *Heterocycles* **1990**, *30*, 855–862.
[6] Y. Du, K. Y. Jung, D. Wiemer, *Tetrahedron Lett.* **2002**, *43*, 8665–8668.
[7] R. Ruzziconi, G. Ricci, A. Gioiello, H. Couthon-Gourves, J. P. Gourves, *J. Org. Chem.* **2003**, *68*, 736–742.
[8] P. Moreau, M. Maffei, *Tetrahedron Lett.* **2004**, *45*, 743–746.
[9] a) F. Gagosz, S. Z. Zard, *Synlett* **2003**, 387–389; b) J. H. Byers, J. G. Thissel, M. A. Thomas, *Tetrahedron Lett.* **1995**, *36*, 6403–6406.
[10] a) D. G. Piotrwska, *Tetrahedron* **2006**, *62*, 12306–12317; b) H. Couthon-Gourvès, G. Simon, J.-P. Haelters, B. Corbel, *Synthesis* **2006**, 81–88; c) L. Lazzarato, B. Rolando, M. L. Lolli, G. C. Tron, R. Fruttero, A. Gasco, G. Deleide, H. L. Guenther, *J. Med. Chem.* **2005**, *48*, 1322–1329; d) S. H. Szajnman, A. Montalvetti, Y. Wang, R. Docampo, J. B. Rodriguez, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3231–3235; e) S. Inoue, T. Okauchi, T. Minami, *Synthesis* **2003**, 1971–1976; f) M. L. Lolli, L. Lazzarato, A. Di Stilo, R. Fruttero, A. Gasco, *J. Organomet. Chem.* **2002**, *650*, 77–83; g) P. C. Bulman Page, J. P. G. Moore, I. Mansfield, M. J. McKenzie, W. B. Bowler, J. A. Gallagher, *Tetrahedron* **2001**, *57*, 1837–1847; h) S. T. Schlachter, L. A. Galinet, S. K. Shields, D. A. Aspar, C. J. Dunn, N. D. Staite, R. A. Nugent, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1093–1096; i) R. A. Nugent, S. T. Schlachter, M. Murphy, C. J. Dunn, N. D. Staite, L. A. Galinet, S. K. Shields, H. Wu, D. G. Aspar, K. Richard, *J. Med. Chem.* **1994**, *37*, 4449–4454; j) G. Sturtz, J. Guervenou, *Synthesis* **1991**, 661–662.
[11] D. W. Hutchinson, D. M. Thornton, *J. Organomet. Chem.* **1998**, *346*, 341–348.
[12] S. H. Szajnman, G. G. Liñares, P. Moro, J. B. Rodriguez, *Eur. J. Org. Chem.* **2005**, 3687–3696.
[13] G. Bansal, J. E. I. Wright, S. Zhang, R. F. Zernicke, H. Uludag, *J. Biomed. Mater. Res. Part A* **2005**, *74*, 618–628.
[14] L. Delain-Bioton, A. Turner, N. Lejeune, D. Villemin, G. B. Hix, P.-A. Jaffrès, *Tetrahedron* **2005**, *61*, 6602–6609.
[15] S. Sulzer-Mosse′, M. Tissot, A. Alexakis, *Org. Lett.* **2007**, *9*, 3749–3752.
[16] a) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057–4060; b) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244; c) H. Brunner, B. Kimel, *Monatsh. Chem.* **1996**, *127*, 1063–1072; d) N. Kobayashi, K. Iwai, *J. Am. Chem. Soc.* **1978**, *100*, 7071–7072; e) A. Sera, K. Takagi, H. Katayama, H. Yamada, *J. Org. Chem.* **1988**, *53*, 1157–1161; f) R. Alvarez, M.-A- Hourdin, C. Cave, J. D′Angelo, P. Chaminade, *Tetrahedron Lett.* **1999**, *40*, 7091–7094; g) G. Szollosi, M. Bartok, *Chirality*, **2001**, *13*, 614–618; h) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926–3928; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–

3798; i) E. J. Park, M. H. Kim, D. A. Kim, *J. Org. Chem.* **2004**, *69*, 6897–6899; j) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185–9188; k) T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen, *Angew. Chem.* **2006**, *118*, 6071–6074; *Angew. Chem. Int. Ed.* **2006**, *45*, 6551–6554; l) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem.* **2006**, *118*, 961–964; *Angew. Chem. Int. Ed.* **2006**, *45*, 947–950; m) G. Bartoli, M. Bosco, A. Carlone, A. Cavalli, M. Locatelli, A. Mazzanti, P. Ricci, L. Sambri, P. Melchiorre, *Angew. Chem.* **2006**, *118*, 5088–5092; *Angew. Chem. Int. Ed.* **2006**, *45*, 4966–4970; n) T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 441–449.

[17] For books on organocatalysis, see: a) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim (Germany), **2007**; b) A. Berkessel, H. Gröger, Asymmetric Organocatalysis, Wiley-VCH, Weinheim (Germany), **2005**. For reviews on organocatalysis, see: c) J. Seayed, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; e) Special Issue: "Asymmetric Organocatalysis", *Acc. Chem. Res.* **2004**, *37*.

[18] Similar significant effects of changing the ester group of the ketoester have already been observed, see for example refs. [16l,m], and following: a) J. Alemán, B. Richter, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 5611–5615; *Angew. Chem. Int. Ed.* **2007**, *46*, 5515–5519; b) Y. Hamashima, D. Hotta, N. Umebayashi, Y. Tsuchiya, T. Suzuki, M. Sodeoka, *Adv. Synth. Catal.* **2005**, *347*, 1576–1586; c) G. Kumaraswamy, N. Jena, M. N. V. Sastry, M. Padmaja, B. Markondaiah, *Adv. Synth. Catal.* **2005**, *347*, 867–871; d) N. Makoto, S. Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron* **2003**, *59*, 7307–7313; e) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241.

[19] Attempts to improve enantioselectivity decreasing the reaction temperature to −60 °C failed, due to the very low reactivity of **2i** at this temperature.

[20] P. C. B. Page, M. J. McKenzie, J. A. Gallagher, *Synth. Commun.* **2002**, *32*, 211–218, and references therein.

[21] a) B. B. Snider, X. Wu, *Heterocycles* **2006**, *70*, 279–294; b) Y. Zou, M. Lobera, B. B. Snider, *J. Org. Chem.* **2005**, *70*, 1761–1770.

[22] CCDC-656632 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] For a review on synthetic application of vinyl phosphonates, see: T. Minami, J. Motoyoshiya, *Synthesis* **1992**, 333–349.

[24] M. Conti, *Anti-Cancer Drugs* **2006**, *17*, 1017–1022.

[25] For the preparation of **2j–l**, we developed a convenient and efficient procedure starting from the corresponding cyclic enones and employing the commercially available *N-tert*-butoxycarbonyl imidazole as acylating agent. This protocol provided a valid alternative to the use of more common *tert*-butyl cyanoformate.

[26] The use of BSA led to a clean profile of the hydrolysis reaction, while in experiments carried out in absence of this reagent only several by-products were obtained.

[27] For detailed experimental procedures, see Supporting Information.

[28] Chemical shifts (δ) are reported in ppm relative to CD_3OH ($\delta = 4.84$) for ^1H NMR, relative to the central resonance of CD_3OD ($\delta = 49.05$) for ^{13}C NMR and relative to external H_3PO_4 85% ($\delta = 0.00$) for ^{31}P NMR.

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