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Dynamic kinetic resolution of α-chloro β-keto esters and phosphonates: hemisynthesis of Taxotere® through Ru-DIFLUORPHOS asymmetric hydrogenation

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Dedicated to Professor Henry Kagan on the occasion of his 80th birthday

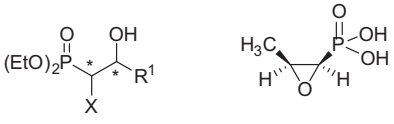
ABSTRACT

The dynamic kinetic resolution (DKR) of racemic α-chloro β-ketoesters and α-chloro β-ketophosphonates through ruthenium-mediated asymmetric hydrogenation is reported. The corresponding α-chloro β-hydroxyesters and α-chloro β-hydroxyphosphonates were obtained in good to high enantio- and diastereomeric excesses using, in particular, the atropisomeric ligand DIFLUORPHOS. This methodology allowed an efficient preparation of the *anti* phenylisoserine side chain of Taxotere® which has been used for the hemisynthesis of the cancer therapeutic agent itself. In addition, ^{13}C NMR in chiral oriented solvents was used to investigate the DKR effect.

1. Introduction

Dynamic kinetic resolution (DKR) is an efficient method for the obtention of enantiomerically pure compounds from racemic substrates. Indeed, DKR allows the formation of a single isomer out of four stereoisomers by combining kinetic resolution with an in situ equilibration of the configurationally labile stereogenic center.[1] By using this method, enantiomerically pure compounds can be synthesized in a single step with theoretical yields of 100% in a highly stereocontrolled manner. Ruthenium-mediated hydrogenation has been widely used in the DKR of β-ketoesters,[2] the first examples being reported by Noyori et al.[3] and Genet et al.[4] We report herein the dynamic kinetic resolution of an α-chloro β-ketoester through ruthenium-mediated asymmetric hydrogenation and its application to the hemisynthesis of Taxotere®. The DKR of α-chloro β-ketophosphonates leading to the corresponding enantioenriched α-chloro β-hydroxyphosphonates is described as well.

Owing to their biological activities as enzyme inhibitors or drug candidates[5], optically active hydroxy phosphonates have attracted significant attention over the years. In particular, α-halo β-hydroxyphosphonates **1** constitute an interesting class of compounds as precursors of various 1,2-epoxyalkylphosphonates,[6] analogous of fosfomycin **2**,[7] a low molecular weight antibiotic of unusual structure, originally isolated from the fermentation broth of *Streptomyces fradiae* or *Pseudomonas syringae* (Scheme 1).



1 (X = halogen) **2**: fosfomycin

Scheme 1.

Various methods have been reported for the asymmetric synthesis of hydroxyphosphonates.[8] In particular, the enantioselective hydrogenation of β-ketophosphonates into their corresponding β-hydroxyphosphonates or α-acetamido β-hydroxyphosphonates has been described.[9] However, with regard to α-halo β-ketophosphonates, only one example of dynamic kinetic resolution through asymmetric hydrogenation has been previously reported in the literature by Noyori et al.[10] In this study, racemic dimethyl 1-bromo-2-oxopropylphosphonate was hydrogenated in methanol at 25 °C under 4 bar of hydrogen using the [$RuCl_2$\{(*S*)-BINAP\}$(DMF)_n$] complex to give dimethyl (1*R*,2*S*)-1-bromo-2-hydroxypropylphosphonate in 98% ee with a 90:10 *syn*/*anti* selectivity. This most straightforward method for the preparation of enantioenriched β-hydroxy α-bromophosphonates suffers one major limitation which is the formation in a significant 15% yield of the

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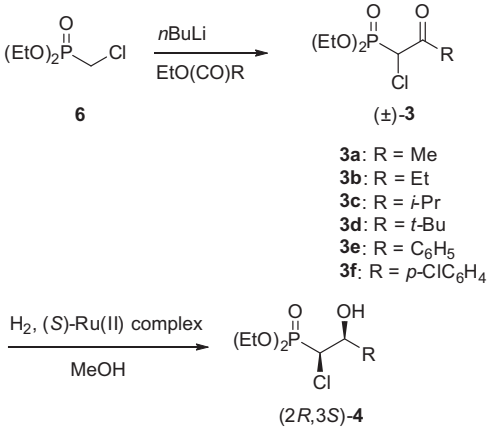
related debrominated compound, resulting from the hydrogenolysis of the carbon–bromide bond. We postulated that the replacement of the bromide atom by a chloride atom would lower this side reaction. Moreover, since the preparation of enantioenriched α-chloro β-hydroxyphosphonates is barely reported in the literature, we were interested in investigating the dynamic kinetic resolution of α-chloro β-ketophosphonates through ruthenium-mediated asymmetric hydrogenation[11] as a practical route to prepare these compounds.

2. Results and discussion

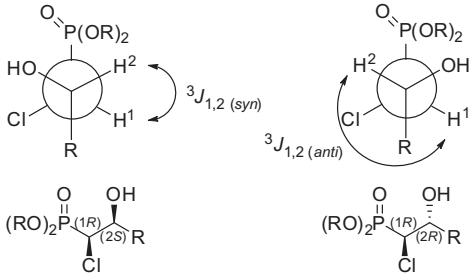
A series of α-chloro β-ketophosphonates **3a**–**3f** was first conveniently synthesized by acylation of diethyl 1-chloromethylphosphonate **6**.[12] Asymmetric hydrogenation promoted by ruthenium catalysts containing the atropisomeric ligands MeO-BIPHEP or SYNPHOS[13] and DIFLUORPHOS,[14] developed in our group, provided the corresponding α-chloro β-hydroxyphosphonates **4a**–**4f** (Scheme 2). As a starting point, we examined the dynamic kinetic resolution of compound **3a** (Scheme 3, Table 1). The hydrogenation reaction was first conducted in methanol at 25 °C under 70 bar of hydrogen for 24 h using 1 mol % of the complex [Ru{(*S*)-SYNPHOS}Br_2], generated in situ from commercially available [Ru(COD)(2-methylallyl)$_2$].[15]

Under these conditions, (1*R*,2*S*)-**4a** was obtained with a moderate 62:38 diastereomeric ratio but with excellent enantioselectivity (99% ee, entry 1) together with 22% of the dechlorinated starting material **5a**. By lowering the hydrogen pressure to 10 bar, the formation of **5a** was limited to 6% at 50 °C, while the diastereomeric ratio was slightly improved (dr = 68:32, entry 2). Pleasingly, when the hydrogenation was run under the same conditions but using the preformed complex [{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2],[16] hydrogenolysis of the carbon–chloride bond was not observed and only the desired compound **4a** was obtained with the same dr as mentioned above and with excellent enantioselectivity (ee >99%, entry 3). The hydrogenation reaction was then performed with [{RuCl((*S*)-DIFLUORPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2] and [{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2] complexes and afforded slightly lower dr (entries 4 and 5) than with [{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]. It should be noted that when the reaction was conducted in dichloromethane at 80 °C and 100 bar of hydrogen, the corresponding α-chloro β-hydroxyphosphonate **4a** was obtained with a slight diastereoselectivity this time in favor of the *anti* isomer (dr = 47:53, entry 6).

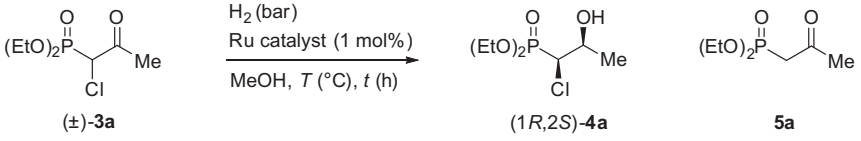


Scheme 2.

The relative configurations of compounds **4** were established on the basis of their coupling constants $^3J_{1,2}$ which bear significantly distinct values for the *syn* and *anti* diastereoisomers (Scheme 4).



Scheme 4.



Scheme 3.

Table 1
DKR of racemic **3a** through ruthenium-assisted hydrogenation[a]

Entry	Ru catalyst	Conditions			Products[b] (%)		dr[c] (%) for (1*R*,2*S*)-**4a**	ee[c] (%) for (1*R*,2*S*)-**4a**
		H_2 (bar)	*T* (°C)	*t* (h)	**5a**	(1*R*,2*S*)-**4a**		
1	[Ru{(*S*)-SYNPHOS}Br_2]	70	25	24	22	78	62:38	>99
2	[Ru{(*S*)-SYNPHOS}Br_2]	10	50	24	6	94	68:32	>99
3	[{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	10	50	24	—	100	67:33	>99
4	[{RuCl((*S*)-DIFLUORPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	10	50	24	—	100	62:38	>99
5	[{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2]	10	50	24	—	100	59:41	>99
6[d]	[Ru{(*S*)-MeO-BIPHEP}Br_2]	100	80	14	6	94	47:53	>99

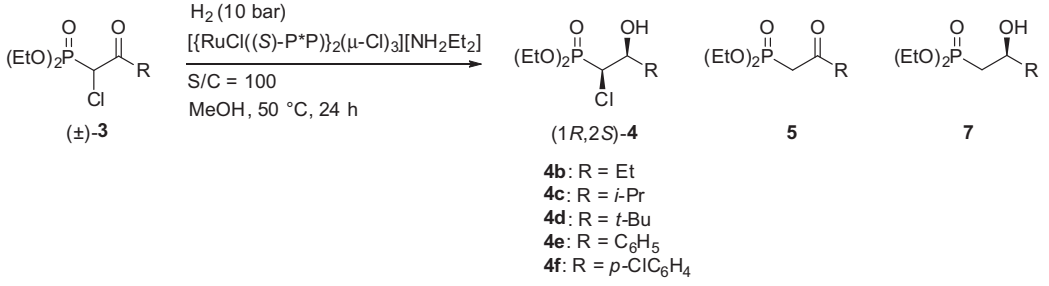
[a] All reactions were performed on 1 mmol at 0.5 M.
[b] Conversion rates were determined by ^{1}H NMR (300 MHz) of the crude reaction mixture.
[c] The diastereo- and enantiomeric excesses were determined by HPLC on the corresponding benzoyl esters **4a**′ (Chiralpak AS-H column).
[d] The reaction was conducted in dichloromethane.

The vicinal coupling constants $^3J_{1,2}$ indicate very clearly the relative configuration of the coupling protons, their contribution depending on the dihedral angle φ, enclosed by the C*H* bonds, according to the Karplus equation.[17] Previously reported ^{1}H NMR studies[18] of racemic α-chloro β-hydroxyphosphonic derivatives showed the coupling constant $^3J_{1,2}$ was low (<2.5 Hz) for the *syn* diastereoisomer compared to the higher value (>7 Hz) observed for the *anti* isomer. The absolute configuration of the hydroxyl-bearing C-2 stereocenter is determined by the chirality of the diphosphine ligand and was attributed on the basis of the general rule established for the BINAP-assisted hydrogenation,[19] and which can be extended to other atropisomeric ligands.

The formerly established hydrogenation conditions were then applied to compounds **3b**–**3f** using the complex [{RuCl((*S*)-P*P)}$_2$(μ-Cl)$_3$][NH_2Me_2] containing MeO-BIPHEP, SYNPHOS, or DIFLUORPHOS as the diphosphines (Scheme 5, Table 2). Thus, the dynamic kinetic resolution of compound **3b** bearing an ethyl substituent delivered the expected alcohol **4b** with comparable dr as observed in the reaction of **3a**, and with no dechlorinated product (dr = 57:43–59:41, entries 1–3). On the other hand, under the standard conditions, the hydrogenation of substrate **3d** bearing a more sterically demanding *tert*-butyl substituent failed to afford the corresponding alcohol **4d**. In this case, only the recovered starting material and the related dechlorinated product were obtained (entries 4 and 5). Switching the hydrogenation conditions to 70 bar of hydrogen and 25 °C did not allow any improvement either (entry 6).

Nevertheless, when these latter conditions were applied to the isopropyl-substituted compound **3c**, the expected alcohol **4c** was obtained with a good diastereomeric ratio and excellent enantioselectivity (*dr* = 92:8, >95% *ee*, entry 7) together with a small amount of the dechlorinated product **7c**. Pleasingly, the dynamic kinetic resolution of compounds **3e** and **3f** bearing, respectively, phenyl and *para*-chlorophenyl substituents, led to the expected α-chloro β-hydroxyphosphonates with good diastereomeric ratios and moderate to high enantioselectivities (dr = 85:15–91:9, 42–90% ee, entries 8–13). For this family of compounds, a ligand effect has been observed since with the (*S*)-MeO-BIPHEP ligand, moderate *ee* were obtained (42–45% ee, entries 8 and 11), while the (*S*)-SYNPHOS diphosphine led to higher enantioselectivities (61–70% ee, entries 9 and 12). Pleasingly, the (*S*)-DIFLUORPHOS ligand afforded high ee in the DKR of **3e** and **3f** (84–90%, entries 10 and 13). The above-mentioned results indicate that the dynamic kinetic resolution of α-chloro β-ketophosphonates through ruthenium-mediated hydrogenation is substrate dependent both in terms of conversion and selectivities. In most cases, standard hydrogenation conditions have been established which allowed the preparation of *syn* α-chloro β-hydroxyphosphonates with moderate to good diastereoselectivities while suppressing the formation of the related dechlorinated compounds.

In connection with our ongoing program directed toward the synthesis of biologically relevant active molecules,[20] we envisaged the hemisynthesis of Taxotere®,[21] an analogue of Taxol®,[22] both remarkable broad-spectrum cancer therapeutic agents, through the dynamic kinetic resolution of an α-chloro β-keto ester. Toward this end, we were interested in pursuing an efficient preparation of the C-13 side chain of Taxotere®. Since the C-13 side chain of Taxotere® is essential for its potent antitumor activity, the development of an efficient process for its preparation in enantiopure form has been the focus of many investigations.[23,24] Only one example of



Scheme 5.

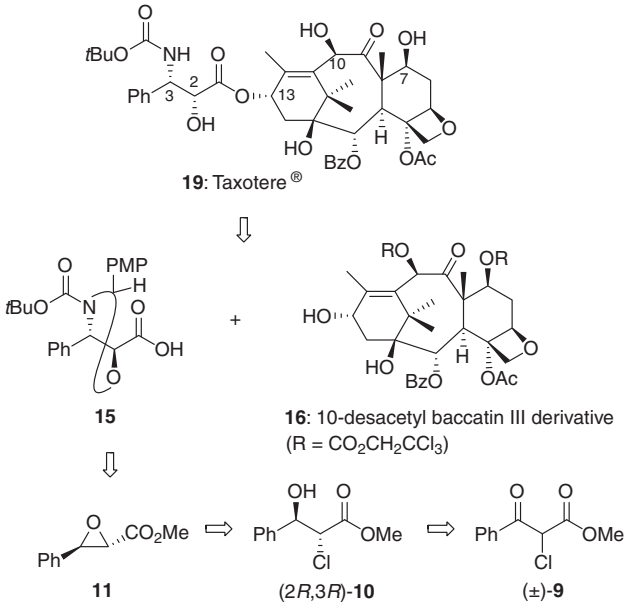
Table 2
DKR of racemic **3** through ruthenium-catalyzed hydrogenation[a]

Entry	Substrate	Ruthenium complex	Products[b]				dr (%) for (1*R*,2*S*)-**4**	ee (%) for (1*R*,2*S*)-**4**
			3	**5**	**7**	(1*R*,2*S*)-**4**		
1	**3b**	[{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	57:43[c]	>99[c]
2	**3b**	[{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	57:43[c]	>99[c]
3	**3b**	[{RuCl((*S*)-DIFLUORPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	59:41[c]	>99[c]
4	**3d**	[{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2]	46	54	—	—	—	—
5	**3d**	[{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	56	44	—	—	—	—
6[d]	**3d**	[{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	70	30	—	—	—	—
7[d]	**3c**	[{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2]	4	—	8	88	92:8[e]	>95[e]
8	**3e**	[{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	88:12	42
9	**3e**	[{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	91:9	61
10	**3e**	[{RuCl((*S*)-DIFLUORPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	86:14	84
11	**3f**	[{RuCl((*S*)-MeO-BIPHEP)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	87:13	45
12	**3f**	[{RuCl((*S*)-SYNPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	89:11	70
13	**3f**	[{RuCl((*S*)-DIFLUORPHOS)}$_2$(μ-Cl)$_3$][NH_2Me_2]	—	—	—	100	85:15	90

[a] All reactions were performed on 1 mmol at 0.5 M.
[b] Conversion rates were determined by ^{1}H NMR (300 MHz) of the crude reaction mixture.
[c] The diastereo- and enantiomeric excesses were determined by HPLC on the corresponding benzoyl esters **4'** (Chiralpak AS-H column).
[d] The hydrogenation was conducted at 25 °C under 70 bar of hydrogen for 100 h.
[e] The diastereo- and enantiomeric excesses were determined by ^{31}P NMR of the corresponding *O*-acetyl-(L)-lactic ester **4″**

the ruthenium-promoted asymmetric hydrogenation of α-chloro β-ketoester into the *syn* α-chloro β-hydroxyester, carried out with ethyl 2-chlorobenzoyl acetate, has been reported so far with a good level of *syn* diastereoselectivity in MeOH/εCH_2Cl_2 (66–90% de).[25]

We report in this paper the efficient DKR of an α-chloro β-ketoester into the corresponding *anti* α-chloro β- hydroxyester and the successful application to the hemisynthesis of Taxotere®. The chosen strategy was based on the observation by Greene et al.[26] that *anti* (2*S*,3*S*) phenylisoserine side chain derivatives could be directly used for the crucial esterification step with baccatine III, since complete epimerization occurred at the C-2 hydroxyl-bearing stereocenter, leading to the required *syn* (2*R*,3*S*) configuration for Taxotere®. Hence, the retrosynthetic scheme relies on the esterification of **15** with a 10-desacetyl baccatin III derivative **16** which would deliver Taxotere® after global deprotection (Scheme 6).

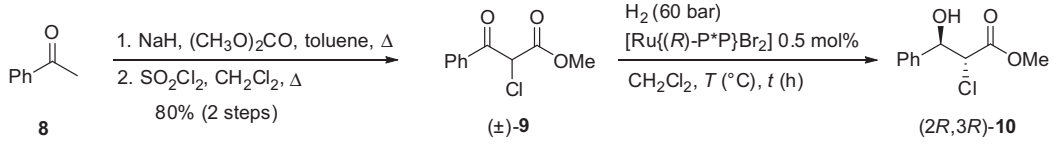


Scheme 6.

The *anti* phenylisoserine derivative **15** would result from regioselective cleavage of (2*S*,3*R*)-3-phenylglycidate **11** by a nitrogen nucleophile. Compound **11** would in turn be obtained from racemic **9** via (2*R*,3*R*)-**10**, by dynamic kinetic resolution through asymmetric hydrogenation.

The synthesis of the target compound **15** began with the crucial hydrogenation step of α-chloro β-ketoester **9**, which was readily prepared from acetophenone via a two-step sequence in 80% yield (Scheme 7). The dynamic kinetic resolution of **9** was first carried out using conditions that were previously established for the related compound, ethyl 3-phenyl-3-oxopropanoate (Scheme 7, Table 3).[27]

Thus, the asymmetric hydrogenation of **9** was conducted in dichloromethane at 80 °C under 60 bar of hydrogen using 0.5 mol % of the [Ru((*R*)-P*P)Br_2] complex, generated in situ from commercially available [Ru(COD)(2-methylallyl)$_2$].[15] Under these conditions, the reaction afforded the corresponding α-chloro β-hydroxyester (2*R*,3*R*)-**10** with complete conversion and good diastereo- and enantioselectivities (69–82% de, 76–90% ee, entries 1–3) using (*R*)-MeO-BIPHEP, (*R*)-SYNPHOS, or (*R*)-BINAP as ligands. With the (*R*)-DIFLUORPHOS diphosphine, 80% conversion was attained after 26 h (entry 4) whereas full conversion could be achieved after a prolonged reaction time of 36 h, albeit a lower diastereomeric excess was observed (61% de, entry 5). In an attempt to increase the enantio- and diastereoselectivities, the hydrogenation was then performed at a lower temperature and for a longer reaction time (50 °C, 48 h, entries 6–9). Using these conditions, moderate to good conversions were obtained while a drop in diastereoselectivity was observed for (*R*)-SYNPHOS, (*R*)-MeO-BIPHEP, and (*R*)-BINAP (26–67% de, entries 6–8). In sharp contrast, the results obtained with the (*R*)-DIFLUORPHOS ligand showed a significant increase in both the enantio- and diastereoselectivities (96% de, 92% ee vs 61% de, 82% ee, entries 9 and 5) although a lower 58% conversion was achieved. In order to increase the conversion rate in the case of the (*R*)-DIFLUORPHOS diphosphine, a screening of solvents was carried out. Thus, under the previously established hydrogenation conditions, various solvents were examined (Scheme 8, Table 4). Dioxane and chloroform proved inappropriate since poor conversions were obtained in these solvents (<5% conversion, entries 1 and 2).

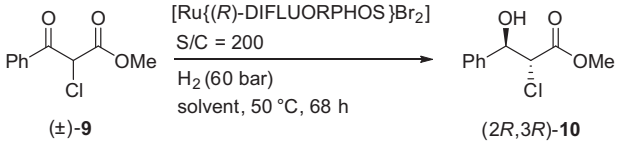


Scheme 7.

Table 3
Dynamic kinetic resolution of racemic **9**[a]

Entry	Ru catalyst	*T* (°C)	*t* (h)	Conversion[b] (%)	de[c] ((2*R*,3*R*)-**10**,%)	ee[c] ((2*R*,3*R*)-**10**,%)
1	[Ru((*R*)-MeO-BIPHEP)Br_2]	80	26	100	69	87
2	[Ru((*R*)-SYNPHOS)Br_2]	80	26	100	75	90
3	[Ru((*R*)-BINAP)Br_2]	80	26	100	82	76
4	[Ru((*R*)-DIFLUORPHOS)Br_2]	80	26	80	87	82
5	[Ru((*R*)-DIFLUORPHOS)Br_2]	80	36	100	61	82
6	[Ru((*R*)-SYNPHOS)Br_2]	50	48	90	26	90
7	[Ru((*R*)-MeO-BIPHEP)Br_2]	50	48	89	57	nd
8	[Ru((*R*)-BINAP)Br_2]	50	48	88	67	73
9	[Ru((*R*)-DIFLUORPHOS)Br_2]	50	48	58	96	92

[a] All reactions were performed on 1 mmol at 0.5 M.
[b] Conversion rates were determined by ^{1}H NMR (300 MHz) of the crude reaction mixture.
[c] The diastereo- and enantiomeric excesses were determined by HPLC (Chiralcel OJ column).



Scheme 8.

In toluene or tetrahydrofuran, low conversions were equally observed (21–25%, entries 3 and 4). The α-chloro β-hydroxyester **10** was obtained with higher conversions in ether and hexane (73–75% conversions, entries 5 and 6) although in these solvents the related dechlorinated compound was also formed. 1,2-Dichloroethane led to results comparable to those obtained with dichloromethane in terms of both enantio- and diastereoselectivities (94% de, 93% ee) albeit a low conversion was obtained (36% conversion, entry 7). Finally, the most suitable solvent for the hydrogenation reaction appears to be dichloromethane, which offers the best compromise between conversion and selectivity. Furthermore, the reaction could be easily scaled up in this solvent on a 20 mmol scale using (*R*)-DIFLUORPHOS as a ligand. Thus, under 60 bar of hydrogen at 50 °C, (2*R*,3*R*)-**10** was obtained with reproducible conversion and selectivities working on this larger scale (58% conversion, 55% isolated yield, 96% de, 92% ee).

At this stage, taking into account the moderate conversion observed, one may wonder whether a dynamic kinetic resolution has really been taking place or if only kinetic resolution has occured. In order to establish the DKR effect, it was necessary to measure the ee of the initial β-keto ester that has not been consumed during the reaction in order to determine whether the mixture is still racemic or enantioenriched in *S*-isomer. Preliminary HPLC analysis failed to separate the enantiomers of **9**. Although the specific rotation of the mixture prior to and after the hydrogenation step remains mainly equal to zero, these experimental facts do not constitute concluding evidence since the absolute value of rotation of each enantiomer can be very weak.

To definitely answer this question, we turned our attention to NMR in chiral liquid crystals (CLC) prepared with concentrated organic solutions ($CHCl_3$ or DMF) of polypeptides (PBLG).[28–30] This efficient method relies on the ability of the CLC to orient in average differently two optical isomers relative to the magnetic field B_o. Advantageously, the *R*/*S* orientational ordering difference can be spectrally revealed through any order-sensitive NMR interactions, such as the shift anisotropy (CSA), or the dipolar (D) and quadrupolar (Q) interactions that are not anymore averaged to zero at the NMR time scale as in isotopic solvents.[28] Another interest of the method lies in the possibility to observe any magnetically active nuclei in the molecule, including dilute atoms such as carbon-13 or deuterium at natural abundance level.[30] Considering the structure of **9**, ^{13}C NMR in CLC was chosen.[32,33] In proton-decoupled ^{13}C NMR (^{13}C–{^1H}), the *R*/*S* discrimination is detected via a difference of ^{13}C CSA, leading to two resonances, one for each enantiomer and the other for each equivalent carbon site of the molecule.

As the parameters governing the strength of the ^{13}C CSA mainly increase with the electronegativity of the substituents and the hybridization state of the carbons $\Delta\sigma$ (sp) > $\Delta\sigma$ (sp^2) > $\Delta\sigma$ (sp^3),[29–31] we could expect to obtain a significant chiral discrimination on the benzenic or carbonyl carbons of **9**. In practice, the *ortho* and *meta* aromatic sites are the most suitable carbon sites for accurately evaluating the ee for two reasons: (i) 2 equiv carbons contribute to signal, (ii) the proton-to-carbon NOE transfer exists for these sites.

Figure 1b presents the ^{13}C–{^1H} signals of the *ortho* and *meta* aromatic carbons of **9** before the hydrogenation reaction, and recorded in the PBLG/$CHCl_3$ mesophase at 300 K. Compared to isotopic ^{13}C–{^1H} spectrum (Fig. 1a), two ^{13}C resonances are observed for the *ortho* and *meta* carbons, thus clearly indicating the enantiodiscrimination of these sites. The chemical shift differences ($\Delta\delta = |\delta_R - \delta_S|$) for *ortho* and *meta* carbons are of 0.06 ppm. As expected, spectral discriminations were also detected on the *ipso* and *para* carbons and carbonyl sites (Figure 1d). Not surprisingly, the ee of the sample is equal to zero within the experimental error, and therefore the starting mixture is effectively racemic.

As seen in Figure 1c, the ^{13}C–{^1H} 1D spectrum of the α-chloro β-keto-ester, not consumed during the hydrogenation reaction, can be fully superimposed on the spectrum corresponding to the sample of β-keto-α-chloro ester prior to hydrogenation. The integration of signal surfaces (confirmed also by deconvolution of peaks) shows that enantiomeric excess is still zero within the experimental errors, thus confirming unambiguously the results obtained by the optical method. Conclusively, the solution of α-chloro β-hydroxy ester remains racemic all along the reaction, and so the hydrogenation of precursor is, as initially suspected, under the control of a dynamic kinetic resolution.

Having in hand the diastereo- and enantiomerically enriched α-chloro β-hydroxy ester **10**, we next turned our attention to the hemisynthesis of Taxotere®. Thus, compound **10** was converted into the corresponding epoxide **11** in an excellent 98% yield by treatment with DBU in dichloromethane (Scheme 9). Refluxing **11** with sodium azide and ammonium chloride in an acetone-water mixture allowed the regio- and stereoselective cleavage[34] of the epoxide to afford α-hydroxy β-azidoester **12** in 80% yield. Subsequent hydrogenation of the azide with Pd/C under hydrogen pressure (1 atm) in the presence of di-*tert*-butyldicarbonate[35] yielded **13**, which was converted into oxazolidine **14** by refluxing with *p*-(methoxyphenyl)dimethoxymethane and a catalytic amount of PPTS. Hydrolysis of **14** provided the corresponding carboxylic acid **15** as the *anti* protected phenylisoserine side chain of Taxotere®. Esterification of the 7,10-bis-trichloroethoxycarbonyl derivative of 10-desacetyl baccatin III **16** with **15** using previously reported conditions[26] provided the Taxotere® precursor **17** in 60% yield, and with complete epimerization at the C-2 stereocenter as

Table 4
Solvent effect in the DKR of **9**

Entry	Solvent	Conv[a] (%)	Yld (%)	de[b] (%), (2*R*,3*R*)-**10**	ee[b] (%), (2*R*,3*R*)-**10**
1	Dioxane	<5	nd	nd	nd
2	$CHCl_3$	<5	nd	nd	nd
3	Toluene	21	21	83	76
4	THF	25	24	50	86
5	Et_2O	73	57[c]	22	85
6	Hexane	75	55[c]	10	85
7	$Cl(CH_2)_2Cl$	36	27	94	93

[a] Conversion rates were determined by ^1H NMR (300 MHz) of the crude reaction mixture.
[b] The diastereo- and enantiomeric excesses were determined by HPLC (Chiralcel OJ column).
[c] The dechlorinated hydrogenated product was also isolated.

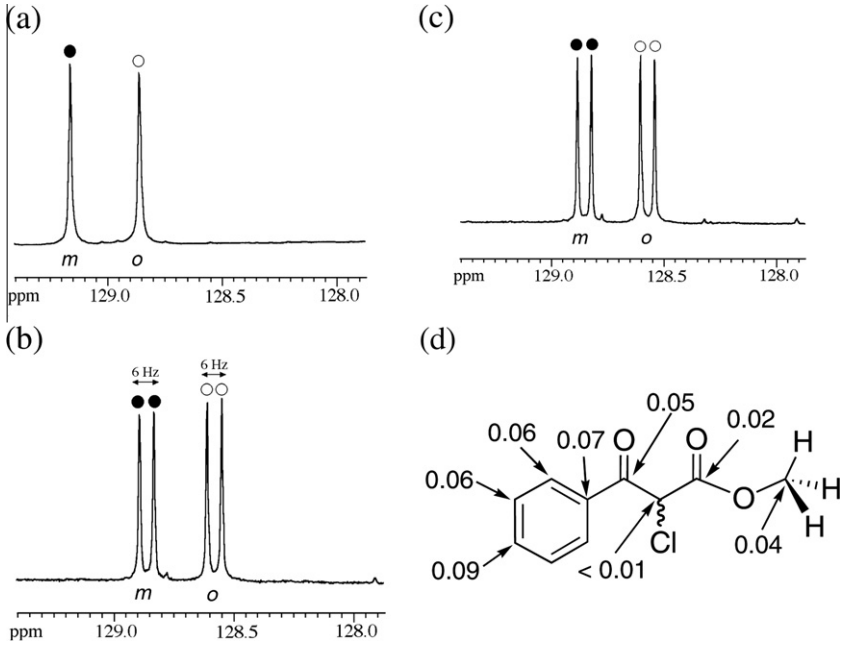


Figure 1. 100 MHz ^{13}C–{^{1}H} spectrum (aromatic region) of **9** in (a) isotopic solvent ($CHCl_3$) and (b) CLC (PBLG/$CHCl_3$) at 300 K. The spectra (b) and (c) correspond to a mixture prior to and after the hydrogenation step. The small variations of δ ^{13}C in (b) and (c) compared to (a) result from the solvent effect (CLC) and ^{13}C CSA as well. For each trace, 1000 scans were added and the recycling delay is around 3 s. The PBLG samples were prepared with 100 mg of **9**, 140 mg of PBLG (D.P. = 463) and 350 mg of $CHCl_3$, (see Ref. 27). On Figure 1d are reported the spectral enantiodifferences (in ppm) measured on each carbon site.

expected. Subsequent cleavage of the oxazolidine moiety[36] was performed using APTS in methanol and furnished **18** in 55% yield (based on recovered starting material). Deprotection of the 2,2,2-trichloroethoxycarbonyl (Troc) groups has been previously reported in the literature using standard procedure to give Taxotere®.[36]

3. Conclusion

In summary, we have shown that the dynamic kinetic resolution of a series of racemic α-chloro β-keto phosphonates through ruthenium-mediated asymmetric hydrogenation allowed the formation of the corresponding *syn* α-chloro β-hydroxy phosphonates. Complete conversions were obtained in methanol, alongside with excellent enantioselectivities (up to >99% ee) and good diastereoselectivities were observed for substrates bearing phenyl or *para*-chlorophenyl substituents (up to 84% de). Moreover, under the standard established conditions, no dechlorinated compounds were observed. The dynamic kinetic resolution has also been extended to the asymmetric hydrogenation of an α-chloro β-keto ester. In particular, the use of the (*R*)-DIFLUORPHOS ligand allowed the formation of the *anti* protected phenylisoserine side chain of Taxotere® in a highly enantio- and diastereoselective fashion. This enantioenriched compound (95% de, 92% ee) was then successfully used in the hemisynthesis of Taxotere®. Finally, we have nicely demonstrated that NMR in CLC was a powerful tool to solve problems related to chirality,[37] thus providing a unique alternative to usual NMR methods.

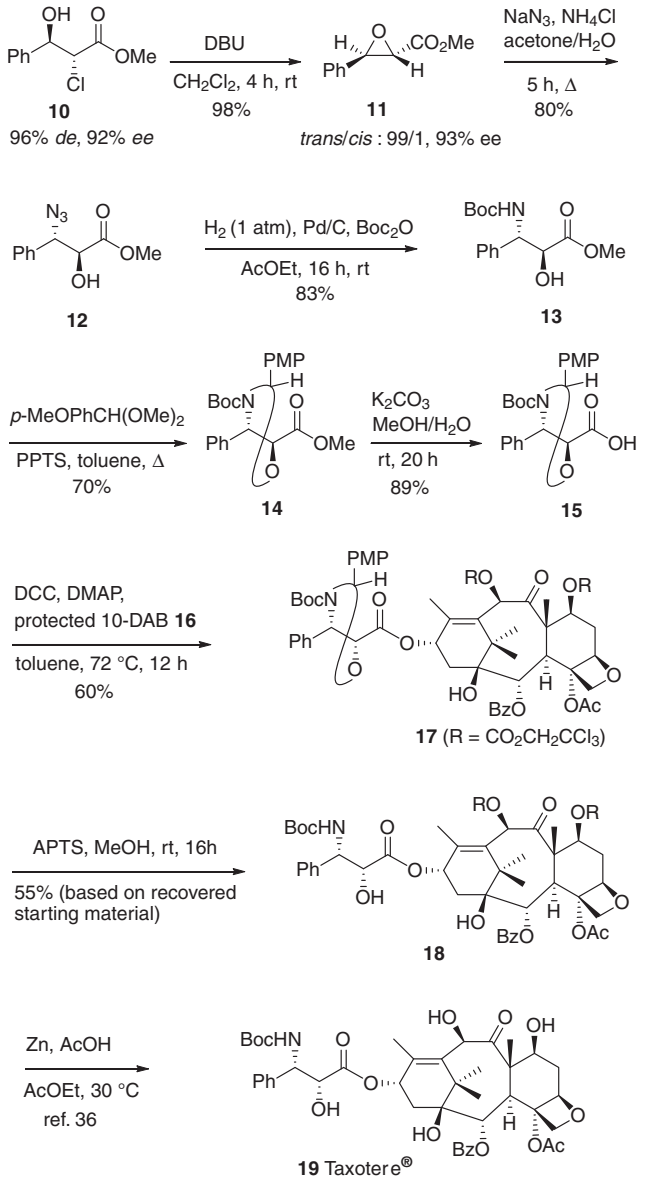
4. Experimental

4.1. General

All air- and/or water-sensitive reactions were carried out under an argon atmosphere. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin layer chromatography carried out on precoated silica gel plates (E. Merck Ref. 5554 60 F254) and revealed with either an ultra-violet lamp (λ = 254 nm) or a potassium permanganate solution. The nuclear magnetic resonance spectra were recorded on a Bruker AC 200, AC 300, or Avance 400 instrument at 200, 300, or 400 MHz, respectively, for ^{1}H and 50, 75, or 100 MHz, respectively, for ^{13}C. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform (7.26 ppm for ^{1}H and 77.1 ppm for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; sept, septuplet; m, multiplet; and br, broad), coupling constants, integration, and assignment. Mass spectra (MS) were recorded by the ENSCP Mass Spectroscopy Service on a Hewlett-Packard HP 5989 A spectrometer. Ionization was obtained either by electronic impact (EI, 70 eV) or chemical ionization with ammonia (CI, NH_3) and data are reported as *m*/*z* (relative intensity). Melting points (mp) were determined on a Kofler melting point apparatus or on a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter or a Jasco P-1010 polarimeter. High resolution mass spectrometric (HRMS) analyses were measured on LTQ-Orbitrap (Thermo Fisher Scientific) at Pierre et Marie Curie University.

4.2. Diethyl 1-chloromethylphosphonate 6

In a 500 mL round-bottomed flask equipped with a mechanical stirrer were introduced 1-chloromethylphosphoryl dichloride (50.2 g; 0.3 mol; 1 equiv) and tetrahydrofuran (100 mL). A solution of triethylamine (67 g; 0.66 mol; 2.2 equiv) in tetrahydrofuran (100 mL) was added dropwise under vigorous stirring, then the reaction mixture was cooled with an ice-bath. Ethanol (31 g or 39.29 mL; 0.66 mol; 2.2 equiv) was added dropwise at such a rate as to maintain the reaction temperature below 30 °C (CAUTION exothermic reaction). An important precipitate formed during the addition, and the resulting suspension was stirred at room temperature for 2 h. The reaction mixture was filtered, rinsed with tetrahydrofuran (2 × 100 mL), and the combined filtrate was



Scheme 9.

concentrated under reduced pressure. The residue was taken up in diethyl ether (200 mL) and the precipitated triethylamine hydrochloride salt was filtered off and rinsed. The filtrate was concentrated under reduced pressure to give a yellow liquid which was distilled under water-pump vacuum to yield a colorless liquid (50.8 g; 91% yield). Bp = 130 °C (16 mm Hg). ^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C) δ 4.3–4.15 (m, 4H), 3.5 (d, J = 10.5 Hz, 2H), 1.35 (t, J = 7.0 Hz, 6H). ^{31}P NMR ($CDCl_3$, 81 MHz, 24 °C) δ 19.

4.3. General procedure for the synthesis of α-chloro β-keto phosphonates 3

Procedure described with ethyl *iso*-butyrate: to a −78 °C solution of *n*-butyl lithium (1.3 M solution in hexane; 42.3 mL, 55 mmol) in THF (45 mL) was added dropwise a solution of diethyl 1-chloromethylphosphonate (9.33 g, 50 mmol) in THF (15 mL). The reaction mixture was stirred at this temperature for 30 min, then a solution of ethyl *iso*-butyrate (6.4 g, 55 mmol) in THF (15 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 1 h. The reaction mixture was poured onto a mixture of 12 N HCl (15 mL), ice (15 g), and dichloromethane (50 mL). The layers were separated and the aqueous phase was further extracted with dichloromethane (2 × 50 mL). The combined organic phases were washed with water (2 × 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

4.3.1. Diethyl 1-chloro-2-oxopropylphosphonate 3a

Prepared according to the general procedure, using *n*-butyl lithium (1.48 M solution in hexane, 37.2 mL, 55 mmol) in THF (35 mL), a solution of diethyl 1-chloromethylphosphonate (9.33 g, 50 mmol) in THF (15 mL), and a solution of ethyl acetate (5.3 g, 60 mmol) in THF (20 mL). After attempted purification by distillation failed, the recovered product was purified by chromatography on silica gel (eluent cyclohexane/ethyl acetate 5:5) to give a yellow syrup (4.6 g; 40% non optimized yield). Bp = 134 °C (1 mm Hg). ^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C) δ 4.5 (d, J = 17.5 Hz, 1H), 4.3–4.15 (m, 4H), 2.45 (s, 3H), 1.4–1.35 (m, 6H). ^{31}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 197.4, 64.4 (m, J = 7 Hz), 57.3 (d, J = 138.5 Hz), 27.6, 16.2 (m, J = 5.9 Hz). ^{31}P NMR ($CDCl_3$, 81 MHz, 24 °C) δ 14.

4.3.2. Diethyl 1-chloro-2-oxobutylphosphonate 3b

Prepared according to the general procedure, using *n*-butyl lithium (1.47 M solution in hexane, 37.4 mL, 55 mmol) in THF (45 mL), a solution of diethyl 1-chloromethylphosphonate (9.33 g, 50 mmol) in THF (15 mL), and a solution of ethyl propanoate (6.12 g, 60 mmol) in THF (15 mL). After attempted purification by distillation failed, the recovered product was purified by chromatography on silica gel (eluent cyclohexane/ethyl acetate 5:5) to give a yellow syrup (5.0 g; 41% non optimized yield). ^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C) δ 4.5 (d, J = 17.5 Hz, 1H), 4.3–4.1 (m, 4H), 2.9 (dq, J = 18.8, 7.2 Hz, 1H), 2.65 (dq, J = 18.8, 7.1 Hz, 1H), 1.4–1.25 (m, 6H), 1.1 (t, J = 7.2 Hz, 3H). ^{31}P NMR ($CDCl_3$, 81 MHz, 24 °C) δ 15. ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 200.4, 64.5 (d, J = 6.9 Hz), 64.3 (d, J = 6.9 Hz), 56.7 (d, J = 138.6 Hz), 33.7, 16.2, 16.1, 7.6.

4.3.3. Diethyl 1-chloro-3-methyl-2-oxobutylphosphonate 3c

Prepared according to the general procedure, using *n*-butyl lithium (1.3 M solution in hexane; 42.3 mL, 55 mmol) in THF (45 mL), a solution of diethyl 1-chloromethylphosphonate (9.33 g, 50 mmol) in THF (15 mL), and a solution of ethyl *iso*-butyrate (6.4 g, 55 mmol) in THF (15 mL). The residue was purified by chromatography on silica gel (eluent cyclohexane/ethyl acetate 3:7) to give a yellow syrup (7.5 g; 59% yield). Bp = 110–120 °C (1 mm Hg). ^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C) δ 4.65 (d, J = 17.5 Hz, 1H), 4.35–4.15 (m, 4H), 3.2 (sept, J = 6.8 Hz, 1H), 1.65–1.3 (m, 6H), 1.15 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 203.6, 64.4, 55.3 (d, J = 139 Hz), 38.8, 18.9, 18.3, 16.2 (d, J = 6 Hz). ^{31}P NMR ($CDCl_3$, 81 MHz, 24 °C) δ 13.0.

4.3.4. Diethyl 1-chloro-3,3-dimethyl-2-oxobutylphosphonate 3d

^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.87 (d, J = 12.6, 1H), 4.26 (m, 4H), 1.37 (dt, J = 3.9, 7.1 Hz, 3H), 1.36 (dt, J = 4.0, 7.0 Hz, 3H), 1.24 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 205.4, 64.5 (d, J = 6.5 Hz), 64.2 (d, J = 7.0 Hz), 46.9 (d, J = 146.9 Hz), 45.8 (d, J = 3.3 Hz), 26.1, 16.4, 16.3.

4.3.5. Diethyl 1-chloro-2-phenyl-ethyl-phosphonate 3e

^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.01 (m, 2H), 7.62 (m, 1H), 7.49 (m, 2H), 5.47 (d, J = 16.3, 1H), 4.23 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 189.5, 134.7, 134.0, 129.2, 128.5, 64.5 (d, J = 7.4 Hz), 64.4 (d, J = 7.4 Hz), 52.6 (d, J = 143.7 Hz), 16.1 (d, J = 6.5 Hz), 16.1 (d, J = 6.7 Hz).

4.3.6. Diethyl 1-chloro-2-(4-chloro-phenyl)-2-oxo-ethyl-phosphonate 3f

^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.00 (m, 2H), 7.46 (m, 2H), 5.37 (d, J = 16.6, 1H), 4.22 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 188.5, 140.8, 133.0, 130.8, 129.0, 64.7 (d, J = 6.9 Hz), 52.9 (d, J = 143.2 Hz), 16.3 (d, J = 4.6 Hz), 16.2 (d, J = 5.1 Hz).

4.4. General procedure for the dynamic kinetic resolution of α-chloro β-keto phosphonates 3

Compound **3** (1 mmol) and MeOH (2 mL) were introduced in a 10-mL round-bottomed flask equipped with a magnetic stirrer. The system was connected to a supply of vacuum/argon and the solution was carefully degassed by three vacuum/argon cycles. Solid catalyst [(RuCl{(*R*)-SYNPHOS})$_2$(μ-Cl)$_3$][NH_2Me_2] was added in one portion. The orange solution was degassed by another vacuum/argon cycle. Under a flow of argon, the solution was introduced via cannula in a 25 mL stainless steel autoclave which was connected to a 1590,000 TOP INDUSTRIE25 parallel hydrogenation system equipped with a central mechanical stirrer and a gas consumption control and display system (TOP VIEW software). The atmosphere of the autoclave was purged three times with argon (8 bar) and twice with H_2 (5 bar). The autoclave was adjusted to the required temperature and H_2 pressure (stirring 200 rpm). The autoclave was then filled with H_2 (required pressure, stirring 200 rpm). The stirring rate was adjusted to 1200 rpm and the H_2 uptake was monitored. After total conversion of the substrate (end of H_2 uptake), the autoclave was adjusted to rt and atmospheric pressure and finally purged three times with argon (8 bar, stirring 200 rpm). The contents were drained off and the autoclave was rinsed with MeOH (20 mL). The MeOH was distilled off in vacuo to give the crude α-chloro β-hydroxyphosphonate.

4.4.1. Diethyl 1-chloro-2-hydroxypropylphosphonate (1*R*,2*S*)-4a and (1*S*,2*S*)-4a

Syn diastereomer ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C) δ 4.4–4.15 (m, 5H), 3.85 (dd, J = 12.4, 2.3 Hz, 1H), 3.3 (br s, 1H), 1.4–1.3 (m, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 66.0, 64.5 (d, J = 6.9 Hz), 63.2 (d, J = 7 Hz), 57.2 (d, J = 156 Hz), 20.1 (d, J = 11 Hz), 16.3. ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 20.3. *Anti* diastereomer ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C) δ idem except 3.89–3.81 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 67.5, 64.2 (d, J = 7.1 Hz), 63.4 (d, J = 6.8 Hz), 56.2 (d, J = 152 Hz), 19.8 (d, J = 7.2 Hz), 16.3. ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 20.0.

4.4.2. Diethyl 1-chloro-2-hydroxybutylphosphonate (1*R*,2*S*)-4b and (1*S*,2*S*)-4b

Syn diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C) δ 4.3–4.15 (m, 4H), 4.1–4.0 (m, 1H), 3.95 (dd, J = 13.2, 1.9 Hz, 1H), 1.65–1.6 (m, 2H), 1.35 (t, J = 7.1 Hz, 6H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 71.1, 64.4 (d, J = 6.8 Hz), 63.1 (d, J = 7.1 Hz), 55.3 (d, J = 157 Hz), 26.8 (d, J = 11 Hz), 16.2, 9.8. ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 20.9. *Anti* diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C) δ idem except 3.95–3.9 (m, 1H), 3.84 (dd, J = 9.9, 7.2 Hz, 1H), 1.77–1.72 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 72.4, 64.3 (d, J = 6.8 Hz), 63.2 (d, J = 7.1 Hz), 54.1 (d, J = 152 Hz), 26.3 (d, J = 8 Hz,), 16.2, 9.0. ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 20.9.

4.4.3. Diethyl 1-chloro-3-methyl-2-hydroxybutylphosphonate (1*R*,2*S*)-4c and (1*S*,2*S*)-4c

Syn diastereomer ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C) δ 4.3–4.1 (m, 4H), 4.05 (dd, J = 14.0, 1.7 Hz, 1H), 3.65 (ddd, J = 8.7, 4.4, 1.6 Hz, 1H), 3.2 (br d, J = 4.4 Hz, 1H), 1.95–1.85 (m, 1H), 1.3 (t, J = 7.1 Hz, 6H), 1.01 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 74.9, 64.5 (d, J = 6.7 Hz), 63.1 (d, J = 7 Hz), 54.2 (d, J = 158 Hz), 31.0 (d, J = 11 Hz), 18.8, 18.5, 16.2. ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 21.4. MS (CI, NH_3) m/z 276 (100%, $[M+NH_4]^+$), 259 (60%, $[M+H]^+$). MS (EI, 70 eV) m/z 259 (25%, $[M+H]^+$), 215 (65%), 186 (90%), 159 (100%), 130 (40%), 81 (50%). *Anti* diastereisomer ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C) δ 4.35–4.15 (m, 4H), 3.85–3.75 (m, 2H), 2.25–2.15 (m, 1H), 1.4–1.35 (m, 6H), 1.03 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C) δ 75.0, 64.4 (d, J = 6.9 Hz), 63.5 (d, J = 6.7 Hz), 51.6 (d, J = 152 Hz), 29.3 (d, J = 10 Hz), 19.6, 16.4, 14.1. ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 22.1. MS (CI, NH_3) m/z 276 (100%, $[M+NH_4]^+$), 259 (90%, $[M+H]^+$). MS (EI, 70 eV) m/z 259 (5%, $[M+H]^+$), 215 (50%), 186 (55%), 159 (100%), 130 (30%), 81 (50%).

4.4.4. Diethyl 1-chloro-2-hydroxy-2-phenyl-ethyl-phosphonate (1*R*,2*S*)-4e and (1*S*,2*S*)-4e

Syn diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.38 (m, 5H), 5.37 (dd, J = 2.5, 5.3, 1H), 4.17 (m, 5H), 1.36 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 139.4 (d, J = 11.8 Hz), 128.1, 128.0, 126.3, 71.4, 64.6 (d, J = 6.8 Hz), 63.1 (d, J = 7.1 Hz), 57.6 (d, J = 153.6 Hz), 16.3 (d, J = 5.4 Hz), 16.2 (d, J = 5.6 Hz). *Anti* diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.38 (m, 5H), 5.00 (dd, J = 8.4, 12.0, 1H), 4.17 (m, 5H), 1.39 (dt, J = 0.5, 7.1 Hz, 3H), 1.35 (t, J = 0.6, 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 139.4 (d, J = 11.8 Hz), 128.5, 128.2, 127.2, 74.3, 64.6 (d, J = 7.1 Hz), 63.6 (d, J = 6.7 Hz), 54.3 (d, J = 150.1 Hz), 16.3 (d, J = 4.5 Hz), 16.2 (d, J = 6.1 Hz). HPLC: Chiralcel AS-H, 98.5:0.5 hexane/*iso*-propanol, 0.5 mL/min, λ = 215 nm, t_R 89.2 min for (1*R*,2*S*), 162.2 min for (1*S*,2*R*), 98.1 min and 138.3 min for (1*R*,2*R*) and (1*S*,2*S*).

4.4.5. Diethyl 1-chloro-2-(4-chloro-phenyl)-2-hydroxy-ethyl-phosphonate (1*R*,2*S*)-4f and (1*S*,2*S*)-4f

Syn diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.32 (m, 4H), 5.31 (m, 1H), 4.20 (m, 5H), 4.01 (dd, J = 2.6, 12.8 Hz, 1H), 1.31 (t, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 137.9 (d, J = 12.3 Hz), 133.8, 128.3, 127.8, 70.9, 65.0 (d, J = 6.8 Hz), 63.3 (d, J = 7.1 Hz), 57.3 (d, J = 153.7 Hz), 16.4 (d, J = 5.1 Hz), 16.3 (d, J = 5.2 Hz). *Anti* diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.32 (m, 4H), 4.96 (m, 1H), 4.80 (d, J = 3.1 Hz, 1H). 4.20 (m, 4H), 3.95 (d, J = 9.4 Hz, 1H), 1.29 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 138.0 (d, J = 11.0 Hz), 134.2, 128.6, 128.3, 73.9, 64.7 (d, J = 7.1 Hz), 63.8 (d, J = 7.0 Hz), 54.0 (d, J = 150.0 Hz), 16.4 (d, J = 4.5 Hz), 16.3 (d, J = 5.9 Hz). HPLC: Chiralcel AS-H, 98.5:0.5 hexane/*iso*-propanol, 0.5 mL/min, λ = 215 nm, t_R 77.9 min for (1*R*,2*S*) and 146.2 min for (1*S*,2*R*), 91.3 min and 122.6 min for (1*R*,2*R*) and (1*S*,2*S*).

4.5. General procedure for the benzoylation of compounds 4

A mixture of **4a** (0.22 mmol, 51 mg), 0.5 mL of anhydrous pyridine, and benzoyl chloride (0.22 mmol, 1 equiv, 27 μL) was stirred at room temperature. After 3 h, brine was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with a 1 M solution of hydrochloric acid, saturated aqueous bicarbonate and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (6:4) as eluent to give the product (67 mg, 94% yield) as a colorless oil.

4.5.1. Benzoyl ester 4a′

Syn diastereomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.10 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.70 (dqd, J = 3.6, 6.4, 7.4 Hz, 1H), 4.19 (m, 4H), 4.09 (dd, J = 3.6, 13.6 Hz, 1H), 1.55 (dd, J = 1.1, 6.4 Hz, 3H), 1.29 (dt, J = 0.5, 7.1 Hz, 3H), 1.25 (dt, J = 0.6, 7.1 Hz,

3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 165.2, 133.1, 129.8, 129.7, 128.3, 68.8, 63.8, 63.7, 55.4 (d, J = 159.5 Hz), 18.1 (d, J = 8.5 Hz), 16.3 (d, J = 5.5 Hz), 16.3 (d, J = 5.9 Hz). *Anti* diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.07 (m, 2H), 7.58 (m, 1H), 7.45 (m, 2H), 5.63 (ddq, J = 3.2, 4.3, 6.4 Hz, 1H), 4.39 (dd, J = 3.1, 15.0 Hz, 1H), 4.27 (m, 4H), 1.58 (d, J = 6.4 Hz, 3H), 1.39 (dt, J = 0.5, 7.1 Hz, 3H), 1.37 (dt, J = 0.6, 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 165.5, 133.3, 130.0, 129.8, 128.4, 69.5, 64.2, 64.1, 55.1 (d, J = 154.8 Hz), 18.1 (d, J = 8.5 Hz), 16.3 (d, J = 5.5 Hz), 16.3 (d, J = 5.9 Hz). HPLC: Chiralcel AS-H, 99.5:00.5 hexane/*iso*-propanol, 0.5 mL/min, λ = 215 nm, t_R 58.2 min for (1*S*,2*R*), 72.6 min for (1*R*,2*S*), 127.7 min and 144.1 min for (1*R*,2*S*) and (1*S*,2*R*).

4.5.2. Benzoyl ester 4b′

Syn diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.00 (m, 2H), 7.50 (m, 1H), 7.39 (m, 2H), 5.52 (ddd, J = 3.0, 6.8, 13.9 Hz, 4.14 (m, 5H), 1.91 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 165.4, 133.1, 130.0, 129.9, 128.3, 72.7 (d, J = 1.7 Hz), 63.9 (d, J = 6.8 Hz), 63.7 (d, J = 7.0 Hz), 53.5 (d, J = 160.5 Hz), 25.0 (d, J = 8.8 Hz), 16.3 (d, J = 5.4 Hz), 16.3 (d, J = 5.5 Hz), 9.6. *Anti* diastereisomer ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.00 (m, 2H), 7.50 (m, 1H), 7.39 (m, 2H), 5.39 (ddd, J = 3.7, 6.0, 12.5 Hz, 4.31 (dd, J = 3.6, 14.8 Hz, 1H), 4.14 (m, 4H), 1.91 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.4 Hz, 3H).). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 165.9, 133.2, 129.8, 129.7, 128.4, 74.2 (d, J = 6.1 Hz), 64.2 (d, J = 6.9 Hz), 63.7 (d, J = 7.0 Hz), 54.0 (d, J = 154.5 Hz), 23.3, 16.3 (d, J = 5.5 Hz), 16.2 (d, J = 6.3 Hz), 9.9. HPLC: Chiralcel AS-H, 99:01 hexane/*iso*-propanol, 0.5 mL/min, λ = 215 nm, t_R 95.6 min for (1*S*,2*R*), 106.9 min for (1*R*,2*S*), 124.3 min and 138.8 min for (1*R*,2*S*) and (1*S*,2*R*).

4.6. Ester 4c″

A solution of the diethyl α-chloro β-keto phosphonate (0.1 mmol; 1 equiv) in anhydrous ether (1 mL) was cooled at 0 °C with an ice-bath. Pyridine (0.2 mL), then (*S*)-2-acetoxypropionyl chloride (0.125 mL; 1 mmol; 10 equiv) were added dropwise and the resulting suspension was stirred at 0 °C, then at room temperature for 1–2 h. After addition of ethyl acetate (3 mL) and saturated sodium carbonate (3 mL) to the reaction mixture, the organic phase was decanted, washed with brine (3 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure. The derivatized product was generally obtained as an oil with quantitative conversion. Direct analysis of this product was performed by 1H and/or 31P NMR, or by GC on chiral column (after filtration of a sample on silica gel using ethyl acetate or dichloromethane as eluent). ^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C) δ 5.3–5.0 (m, 2H), 4.35–4.15 (m, 5H), 2.5–2.0 (m, 1H), 2.14 (s, 1H), 1.65–1.5 (m, 3H), 1.5–1.2 (m, 6H), 1.1–0.85 (m, 6H). Major diastereomers ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 18.1 and 17.9. Minor diastereomers ^{31}P NMR ($CDCl_3$, 162 MHz, 24 °C) δ 18.3 and 18.1.

4.7. Methyl 3-oxo-3-phenyl-propanoate 8

Into a three-necked flask equipped with an argon inlet and a condenser were placed sodium hydride (60% in mineral oil, 8.15 g, 210 mmol), dimethylcarbonate (17.6 mL, 210 mmol), and 30 mL of toluene. The mixture was stirred at reflux and a solution of acetophenone (10.0 g, 83 mmol) in toluene (30 mL) was added dropwise. After 30 min at reflux, the reaction was cooled down and a solution of acetic acid (5 mL) in water (20 mL) was added. After decantation, the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with saturated aqueous potassium carbonate, dried over magnesium sulfate, and concentrated under reduced pressure to give a yellow oil. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give the β-keto ester **8** (13.3 g, 90% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.94 (m, 2H), 7.78 (m, 1H), 7.58 (m, 1H), 7.45 (m, 2H), 5.68 (s, 1H), 4.01 (s, 2H), 3.80 (s, 3H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 192.3, 173.4, 171.6, 167.9, 135.9, 133.8, 133.0, 128.9, 128.5, 128.3, 126.2, 87.0, 52.4, 51.4, 45.4. MS (DCI, NH_3): m/z 196 (100%, $[M+NH_4]^+$), 179 (68%, $[M+H]^+$).

4.8. Methyl 2-chloro-3-oxo-3-phenyl-propanoate 9

A mixture of methyl 3-oxo-3-phenyl-propanoate (73 mmol, 13.0 g) and sulfuryl chloride (73 mmol, 6.0 mL) in dichloromethane (150 mL) was stirred for 15 min at room temperature, then heated at reflux until the gas evolution ceased. The reaction was then cooled down and the solvent evaporated under reduced pressure. The residual oil was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to give the α-chloro-β-keto ester **9** (13.9 g, 90% yield) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz, 24 °C): δ 7.99 (m, 2H), 7.62 (m, 1H), 7.51 (m, 2H), 5.64 (s, 1H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 188.1, 165.7, 134.4, 133.3, 129.3, 129.0, 57.7, 53.8. IR (cm^{-1}): ν 2954, 1764, 1687, 1269, 1169. MS (DCI, NH_3): m/z 230 (100%, $[M+NH_4]^+$).

4.9. Methyl (2*R*,3*R*)-2-chloro-3-hydroxy-3-phenyl-propanoate (2*R*,3*R*)-10

In a 100-mL flask were placed Ru(cod)[η^3-$(CH_2)_2CHCH_3]_2$ (0.1 mmol, 32 mg, 0.5 mol %), (*R*)-DIFLUORPHOS® (0.14 mmol, 94 mg, 0.55 mol %), and methyl 2-chloro-3-oxo-3-phenyl-propanoate **9** (20 mmol, 4.25 g) and the vessel was purged by a vacuum-argon cycle. Anhydrous dichloromethane (40 mL) previously degassed by three vacuum-argon cycles was added at room temperature. The flask was then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 100 bar. The autoclave was heated at 50 °C and stirring was maintained for 45 h. After cooling, the reaction mixture was concentrated under reduced pressure. ^{1}H NMR analysis revealed a conversion of 58%. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (9:1) as eluent to afford the *anti* (2*R*,3*R*)-α-chloro-β-hydroxy ester **10** as a pale yellow oil (2.35 g, 55% yield, 96% de, 93% ee). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.39 (m, 5H), 5.04 (dd, J = 4.9, 7.9 Hz, 1H), 4.39 (d, J = 7.9 Hz, 1H), 3.80 (s, 3H), 2.98 (d, J = 4.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz, 24 °C): δ 169.1, 138.7, 128.5, 126.9, 126.5, 75.3, 59.0, 53.0. MS (DCI, NH_3): m/z 232 (100%, $[M+NH_4]^+$). $[\alpha]_D^{21} = -43$ (c 1.1, $CHCl_3$). HPLC: Chiralcel OJ, 80:20 hexane/*iso*-propanol, 1.0 mL/min, λ = 215 nm, t_R 11.4 min and 15.3 min for (2*R*,3*R*) and (2*S*,3*S*) respectively and 17.7 min and 20.6 min for (2*R*,3*S*) and (2*S*,3*R*), respectively.

4.10. *trans*-Methyl (2*S*,3*R*)-3-phenyl-glycidate (2*S*,3*R*)-11

To a solution of methyl (2*R*,3*R*)-2-chloro-3-hydroxy-3-phenyl-propanoate **10** (10.66 mmol, 2.28 g) in dichloromethane (20 mL) was added DBU (1.77 mL, 11.63 mmol). After 4 hours at room temperature, the reaction was quenched with a buffer solution (pH 7). The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give the crude glycidate. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (85:15) as eluent (1.86 g, 98% yield, 93% ee) to afford the *trans*-(2*S*,3*R*)-epoxy ester **11** as pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 7.35 (m, 3H), 7.29 (m, 2H), 4.10 (d, J = 1.7 Hz, 1H), 3.83 (s, 3H), 3.52 (d, J = 1.7 Hz, 1H). ^{13}C

NMR ($CDCl_3$, 50 MHz, 24 °C): δ 168.6, 143.9, 129.0, 128.7, 125.8, 58.0, 56.6, 52.6. MS (DCI, NH_3): *m*/*z* 196 (100%, $[M+NH_4]^+$). $[\alpha]_D^{26} = +162$ (*c* 1.5, $CHCl_3$). HPLC: Chiralcel OD-H, 98:02 hexane/*iso*-propanol, 1.0 mL/min, *l* = 215 nm, t_R 16.0 min and 23.1 min for (2*R*,3*S*) and (2*S*,3*R*), respectively (t_R 9.6 min and 13.2 min for *cis* glycidate (2*R*,3*R*) and (2*S*,3*S*)).

4.11. Methyl (2*S*,3*S*)-3-azido-2-hydroxy-3-phenyl-propanoate 12

To a solution of methyl (2*S*,3*R*)-3-phenyl-glycidate **11** (1.80 g, 10.13 mmol) in an acetone/water mixture (4:1, 25 mL) was added sodium azide (1.70 g, 26.01 mmol) followed by ammonium chloride (242 mg, 3.80 mmol). After 5 h at reflux, the reaction mixture was concentrated under reduced pressure, diluted with dichloromethane, then washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to afford the desired product **11** (1.79 g, 80% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.32–7.39 (m, 5H), 4.88 (d, *J* = 4.0 Hz, 1H), 4.54 (dd, *J* = 4.0, 6.6 Hz, 1H), 3.72 (s, 3H), 2.94 (d, *J* = 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 171.8, 134.4, 128.9, 128.7, 127.7, 73.8, 67.3, 52.7. MS (DCI, NH_3): *m*/*z* 239 (100%, $[M+NH_4]^+$). $[\alpha]_D^{26} = +42$ (*c* 0.3, $CHCl_3$).

4.12. Methyl (2*S*,3*S*)-2-hydroxy-3-(*N*-*tert*-butoxycarbonylamino)-3-phenyl-propanoate 13

To a solution of methyl (2*S*,3*S*)-3-azido-2-hydroxy-3-phenylpropanoate **12** (3.75 mmol, 830 mg) and di-*tert*-butyl dicarbonate (4.87 mmol, 1.06 g) in ethyl acetate (10 mL) was added Pd/C (0.78 mmol, 83 mg). The argon atmosphere was then replaced with hydrogen and stirring was maintained at room temperature for 16 h. The suspension was then filtered on a Celite pad and washed with ethyl acetate (60 mL) and water (20 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane/ethyl acetate (8:2) as eluent to afford **13** as a white solid (950 mg, 83% yield). Mp 135 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 7.21–7.33 (m, 5H), 5.59 (br d, *J* = 7.1 Hz, 1H), 5.11 (br d, *J* = 1.7, 6.7 Hz, 1H), 4.60 (dd, *J* = 3.4, 7.0 Hz, 1H), 3.71 (s, 3H), 2.87 (d, *J* = 7.0 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 172.3, 155.0, 136.8, 128.4, 128.1, 127.3, 80.0, 73.3, 56.7, 52.6, 28.3. MS (DCI, NH_3): *m*/*z* 313 (35%, $[M+NH_4]^+$), 296 (56%, $[M+H]^+$), 257 (100%, $[M-C_4H_8+NH_4]^+$), 240 (22%, $[M-C_4H_8+H]^+$). $[\alpha]_D^{26} = +33$ (*c* 0.5, $CHCl_3$).

4.13. Methyl (4*S*,5*S*)-3-(*tert*-butoxycarbonyl)-2-(*p*-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-methanoate 14

A solution of methyl (2*S*,3*S*)-2-hydroxy-3-(*N*-*tert*-butoxycarbonylamino)-3-phenylpropanoate **13** (1.36 mmol, 400 mg) and pyridinium *p*-toluenesulfonate (0.135 mmol, 34.6 mg) in toluene (15 mL) was heated at reflux and a solution of (*para*-methoxyphenyl) dimethoxymethane in toluene was added dropwise. The heating was maintained until completion of the reaction (monitored by TLC). After cooling down, the reaction mixture was concentrated under reduced pressure and the residue purified by silica gel column chromatography using cyclohexane/ethyl acetate (98:2–9:1) as eluent to afford the oxazolidine **14** as a white solid (390 mg, 70% yield, 7:3 mixture of C2-isomers). Mp 105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ (major isomer) 7.48 (d, *J* = 8.7 Hz, 2H), 7.42 (m, 2H), 7.29 (m, 3H), 6.91 (m, 2H), 6.05 (br s, 1H), 5.27 (br d, *J* = 7.0 Hz, 1H), 5.01 (d, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 3.37 (s, 3H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ (major isomer) 167.3, 160.2, 153.3, 138.2, 129.6, 129.0, 128.2, 128.1, 127.7, 113.6, 90.9, 81.1, 79.9, 62.6, 55.3, 51.8, 28.1. MS (DCI, NH_3): *m*/*z* 431 (40%, $[M+NH_4]^+$), 414 (100%, $[M+H]^+$), 375 (19%, $[M-C_4H_8+NH_4]^+$), 358 (14%, $[M-C_4H_8+H]^+$).

4.14. (4*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-2-(*p*-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylic acid 15

To a solution of **14** (0.62 mmol, 257 mg) in a mixture of methanol (20 mL) and water (4 mL) was added potassium carbonate (2.32 mmol, 321 mg). The reaction mixture was stirred for 20 h at room temperature and concentrated under reduced pressure. The residue was diluted in water (50 mL), washed with diethyl ether, and then cooled down to 0 °C. Under vigorous stirring, dichloromethane (50 mL) was added and the resulting mixture was acidified until pH 1 with 1 M aqueous hydrochloric acid. After decantation and extraction with dichloromethane, the combined organic layers were washed with water, saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated under reduced pressure to give the desired acid **15** (220 mg, 89% yield) as a 7:3 mixture of C2-isomers. Mp 132 °C. ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ (major isomer) 7.28–7.52 (m, 7H), 6.92 (m, 2H), 6.05 (br s, 1H), 5.28 (br d, *J* = 7.2 Hz, 1H), 4.99 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ (major isomer) 170.4, 160.1, 153.4, 137.6, 129.1, 128.9, 128.1, 127.5, 113.5, 90.7, 81.3, 79.2, 62.1, 55.3, 28.0. MS (DCI, NH_3): *m*/*z* 417 (33%, $[M+NH_4]^+$), 400 (35%, $[M+H]^+$).

4.15. Compound 17

To a solution of **15** (53 mg, 130 μmol) in toluene was added DCC (28 mg, 130 μmol) at room temperature. After stirring for 5 min, DMAP (5 mg, 45 μmol) was added followed by baccatin III derivative **16** (40 mg, 45 μmol). The reaction mixture was heated at 72 °C overnight, then diluted with AcOEt, washed with water, saturated $NaHCO_3$, then brine. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography using cyclohexane/ethyl acetate (85:15) as eluent afforded **17** (34 mg, 60% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 8.04 (d, *J* = 7.1 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.43 (m, 9H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.50 (s, 1H), 6.36 (t, *J* = 9.0 Hz, 1H), 6.27 (s, 1H), 5.69 (d, *J* = 7.1 Hz, 1H), 5.58 (dd, *J* = 7.1, 10.6 Hz, 1H), 5.32 (d, *J* = 3.9 Hz, 1H), 4.91 (d, *J* = 11.8 Hz, 2H), 4.86 (t, *J* = 3.6 Hz, 1H), 4.79 (s, 2H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.28 (d, *J* = 8.5 Hz, 1H), 4.13 (d, *J* = 8.2 Hz, 1H), 3.92 (d, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 2.62 (ddd, *J* = 7.2, 9.4, 14.5 Hz, 1H), 2.30 (m, 2H), 2.11 (s, 2H), 2.01 (s, 1H), 1.90 (s, 2H), 1.84 (s, 3H), 1.42 (s, 9H), 1.34 (s, 3H), 1.31 (s, 6H). MS (ESI): *m*/*z* 1291.6 $[M+NH_4]^+$. HRMS (ESI) *m*/*z* calcd for $C_{57}H_{61}O_{19}NCl_6Na$: 1296.18612, found: 1296.18619.

4.16. Bis-*O*-(2,2,2-trichloroethoxycarbonyl)docetaxel 18

To a solution of **17** (27 mg, 21 μmol) in MeOH (400 μL) was added APTS (4.4 mg, 23 μmol) and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted in EtOAc and washed with water. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography using cyclohexane/ethyl acetate (7:3) as eluent afforded **18** (6 mg, 25%) together with recovered **17** (15 mg, 55%) as white solids. The spectroscopic data matched published ones.[21] HRMS (ESI) *m*/*z* calcd for $C_{49}H_{55}O_{18}Cl_6NNa$: 1178.14425, found: 1178.14528.

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