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A Case-Study on the Resolution of the 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide via Diastereomeric Complex Formation Using TADDOL Derivatives and via Diastereomeric Coordination Complexes Formed from the Calcium Salts of *O,O'*-Diaroyl-(2*R*,3*R*)-tartaric Acids

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ABSTRACT

The resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide was studied applying TADDOL [(−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane], spiro-TADDOL [(−)-(2*R*,3*R*)- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol], or the acidic and neutral Ca²⁺ salts of (−)-*O,O'*-dibenzoyl- and (−)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid as the resolving agent. The absolute configuration of the P-asymmetric center was determined by CD spectroscopy and related quantum chemical calculations. In one instance, the single crystal of the diastereomeric complex incorporating *i*-butyl-3-phospholene oxide and spiro-TADDOL was subjected to X-ray analysis which suggested a feasible hypothesis for the

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efficiency of the resolution process under discussion that may be an example for the “solvent inhibited” resolution.

Keywords: *i*-Butyl-3-phospholene 1-oxide; TADDOL derivatives; Tartaric acid derivatives; Resolution of optical isomers; X-ray crystallography; CD-spectroscopy; Theoretical calculations.

INTRODUCTION

The optically active P(III)-compounds bearing an asymmetric center on the phosphorous atom are of great importance, as they may be potential ligands in transition metal catalysts used in asymmetric syntheses (*e.g.* hydrogenation and hydroformylation) [1,2].

Among the P-ligands, the P-heterocyclic phosphines form a representative class [3]. The methods for the preparation of optically active P-chiral compounds, including P-heterocycles were summarized in the review of *Pietrusiewicz* and *Zablocka* [4], as well as in the book of *Grabulosa* [5]. *Tang et al.* elaborated the resolution of the key intermediate of bisdihydrobenzooxaphosphole and phosphino-dihydrobenzooxaphosphole ligands (BIBOP and POP) by forming covalent diastereomers from the *t*-butyl-hydroxy-benzodihydrooxaphosphole oxide with menthyl chloroformate. The diastereomers were separated and then hydrolyzed to afford enantiopure *t*-butyl-hydroxy-benzodihydrooxaphosphole oxide [6,7]. *Pietrusiewicz* and his co-workers separated the enantiomers of phenyl-hexahydrocyclopenta[*b*]phosphole by reacting it with menthyl bromoacetate. The covalent diastereomeric salts were separated, and then the optically active phenyl-hexahydrocyclopenta[*b*]phosphole was obtained in two steps [8].

The enantiomers of several 4-, 5- and 6-membered P-chiral heterocyclic phosphonium salts were separated via the formation of diastereomeric salts using the silver salts of dibenzoyl-tartaric acid, champhorsulfonic acid or menthoxy-acetic acid [9-14].

Some heterocyclic mono- and bisphosphine oxides were resolved via the formation of diastereomeric molecular complexes using the dibenzoyl tartaric acid [4,15,16]. The palladium(II)-complexes of phenylethylamine or naphthylethylamine found widespread application for the synthesis of enantiopure mono- and bidentate heterocyclic P(III)-compounds including BIPNOR via the formation of the corresponding diastereomeric coordination complexes [17-22].

In the recent years, our research group elaborated resolution methods for the preparation of 3-phospholene oxides, as well as a few 6-membered P-heterocycles in optically active form. The enantiomers of the heterocyclic phosphine oxides were separated via diastereomeric molecular complex formation using TADDOL derivatives [23] or via diastereomeric coordination complexes applying the Ca^{2+} -salts of dibenzoyl- or di-*p*-toluoyl-tartaric acid [24-30].

In a previous paper, we reported a method for the preparation of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) in enantiopure form using spiro-TADDOL [(-)-**3**] as the resolving agent [31]. However, the efficiency of this approach remained low. So in this paper, the results of our detailed study on the resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) are reported applying a series of resolving agents, such as the TADDOL-derivatives [(-)-**2** and (-)-**3**] and the Ca^{2+} -salts of dibenzoyl- or di-*p*-toluoyl-tartaric acid [(-)-**4** - (-)-**7**]. The absolute P-configuration of the enantiomerically pure 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) is evaluated by theoretical methods.

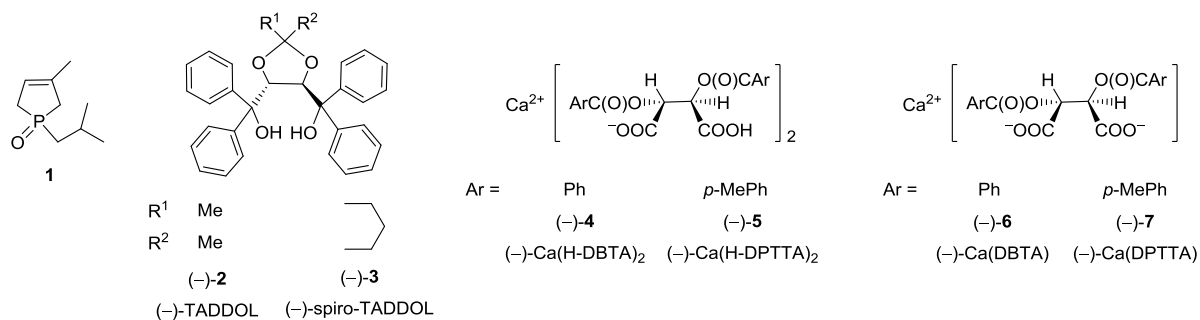


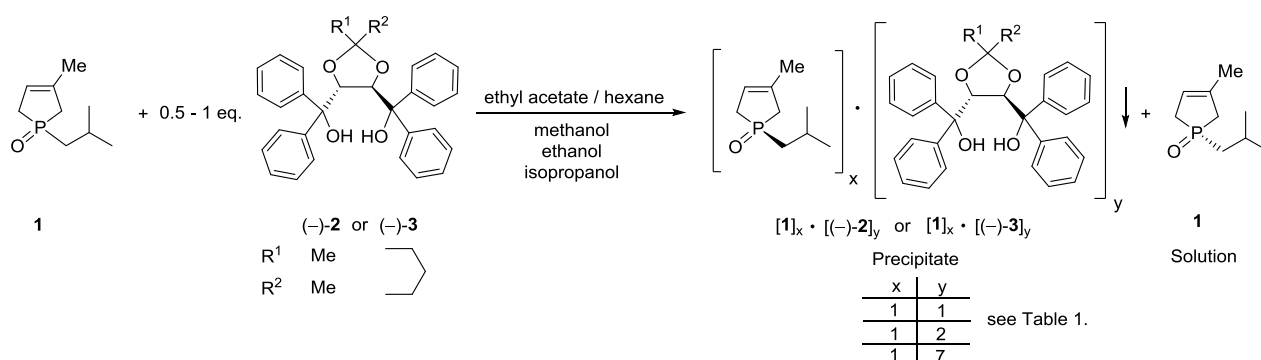
FIGURE 1 The 1-*i*-butyl-3-methyl-3-phospholene oxide (**1**) and resolving agents [(-)-**2**-(-)-**7**] used in this study.

RESULTS AND DISCUSSION

Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with TADDOL Derivatives [(-)-**2** and (-)-**3**]

The resolution of the 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) was first attempted with TADDOL derivatives [(-)-**2** and (-)-**3**]. According to the procedure reported first by our research group [24,25], 3-phospholene oxide (**1**) and TADDOL or spiro-TADDOL [(-)-**2** or (-)-**3**] were dissolved in hot ethyl acetate. The addition of hexane to this reaction mixture resulted in the precipitation of the diastereomeric complex (*R*)-**1**·TADDOL or (*S*)-**1**·spiro-TADDOL. Alcohols were also found to be suitable solvents for the resolution of 3-phospholene oxides with TADDOL derivatives [(-)-**2** or (-)-**3**] [29,30], so the resolution of 1-*i*-butyl-3-phospholene oxide (**1**) was also attempted with TADDOL derivatives (-)-**2** and (-)-**3** in methanol, ethanol or isopropanol. In these instances, the racemic 3-phospholene oxide (**1**) and the resolving agent [(-)-**2** or (-)-**3**] were dissolved in the hot alcohol. The diastereomer (*R*)-**1**·(spiro-TADDOL)₂ or (*R*)-**1**·(spiro-TADDOL)₇ then precipitated on cooling down the reaction mixture to 26 °C (Scheme 1). In all experiments, a 3 hours time was allowed for the crystallization. The first generation of the solid product was purified further by two recrystallizations from the corresponding solvent. The composition of the diastereomers was

determined by ^1H NMR. The enantiomeric excess was established by chiral GC after recovering the enantiomeric mixture of the 3-phospholene oxide (**1**) from a small sample of the diastereomeric mixture by preparative TLC (silica gel, 3% methanol in dichloromethane). The enantiomeric mixtures of the *i*-butyl-3-phospholene oxide (**1**) could be obtained from the diastereomeric mixture by column chromatography (using silica gel and a 97:3 mixture of dichloromethane and methanol). The results are summarized in Table 1.



SCHEME 1 General procedure for the resolution of racemic 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) using TADDOL derivatives [(-)-**2** and (-)-**3**].

The resolution of the 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL derivatives [(-)-**2** or (-)-**3**] could be accomplished in a mixture of ethyl acetate and hexane with limited success, as the maximum ee and resolving capability were, after two recrystallizations, 35% and 0.10, respectively, (Table 1, Entries 1 and 2). However, applying spiro-TADDOL [(-)-**3**] in alcohols led to enantiomeric mixtures of *i*-butyl-3-phospholene oxide (**1**) exhibiting ee values of 67-96% and resolving capabilities of 0.05-0.41 after two recrystallizations (Table 1, Entries 3-5). The highest resolving capability value ($S=0.41$) was achieved using spiro-TADDOL [(-)-**3**] in ethanol after two recrystallizations. The enantiomeric excess of 87% was improved further by a third recrystallization of the diastereomeric complex to afford the (*R*)-1-*i*-butyl-3-phospholene oxide [(*R*)-**1**] with an ee of 96% and in a yield of 26% (Table 1, Entry 4). No crystalline diastereomers were formed,

when the resolution of *i*-butyl-3-phospholene oxide (**1**) was attempted with TADDOL [(-)-**2**] applying alcohols as the solvent.

The ratio of the *i*-butyl-3-phospholene oxide (**1**) and the resolving agent [(-)-**2** or (-)-**3**] in the diastereomers was 1:1, 1:2 or 1:7 which was influenced by the solvent (Table 1). The (*R*)-**1**·(spiro-TADDOL)₇ composition of the diastereomeric complex is rather unusual (Table 1, Entry 3). In this case, the formation of an inclusion diastereomeric complex was assumed contrary to the other instances, when the corresponding diastereomers comprised the *i*-butyl-3-phospholene oxide (**1**) and the resolving agent [(-)-**2** or (-)-**3**] in a stoichiometric ratio of 1:1 or 1:2 (Table 1, Entries 1-2 and 4-5).

The solvent also influenced which enantiomer of the *i*-butyl-3-phospholene oxide [(*R*)-**1** or (*S*)-**1**] was incorporated in the diastereomer using spiro-TADDOL [(-)-**3**] as the resolving agent. Applying spiro-TADDOL [(-)-**3**], the (*S*)-*i*-butyl-3-phospholene oxide [(*S*)-**1**] could be obtained in a mixture of ethyl acetate and hexane (Table 1, Entry 2), while using methanol, ethanol or isopropanol as the solvent, the other enantiomer [(*R*)-**1**] could be separated (Table 1, Entries 3-5).

TABLE 1 Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) using TADDOL Derivatives [(*-*)-**2** and (*-*)-**3**]

Entry	Resolving agent	Eq.	Solvents ^a	Diastereomeric complex ^b	Yield (%) ^{c,f}	ee (%) ^{d,f}	S (<i>-</i>) ^{e,f}	Abs. Config. ^g
1	TADDOL	0.5	2×EtOAc/10×hexane	(1)·(2)	(73)	(7)	(0.05)	(<i>R</i>)
					14	35	0.05	
2	spiro-TADDOL	0.5	2×EtOAc/10×hexane	(1)·(3)	(90)	(7)	(0.06)	(<i>S</i>)
					39	25	0.10	
3 ^[31]	spiro-TADDOL	0.5	6×MeOH	(1)·(3) ₇	(14)	(71)	(0.10)	(<i>R</i>)
					5	96	0.05	
4	spiro-TADDOL	1	6×EtOH	(1)·(3) ₂	(88)	(51)	(0.45)	(<i>R</i>)
					47	87	0.41	
5	spiro-TADDOL	1	6×iPrOH	(1)·(3) ₂	[26] ^h	[96] ^h	[0.25] ^h	
					(74)	(11)	(0.08)	(<i>R</i>)
					19	67	0.13	

^a Mixture of solvents for the crystallization and recrystallizations [mL of solvent/g of resolving agent].

^b The ratio of **1** and (*-*)-**2** or (*-*)-**3** was determined by ¹H NMR.

^c Based on the half of the racemate **1** that is regarded to be 100% for each antipode.

^d Determined by chiral GC.

^e Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)] [32].

^f Results obtained after the first crystallization are shown in parantheses, while results obtained after two recrystallizations are shown in boldface.

^g The absolute configuration of **1** was determined by X-Ray analysis and CD spectroscopy.

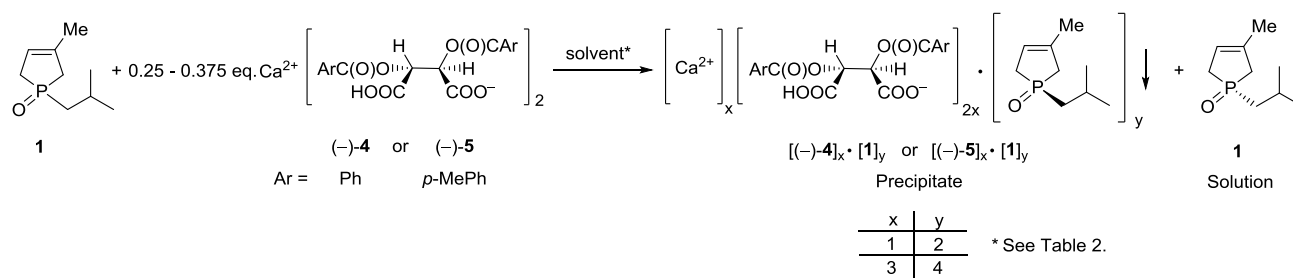
^h After three recrystallizations.

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with Calcium Hydrogen (*-*)-*O,O'*-Dibenzoyl- or (*-*)-*O,O'*-di-*p*-Toluoyl-(2*R*,3*R*)-tartrate [(*-*)-**4** or (*-*)-**5**]*

The acidic calcium salts of the (*-*)-*O,O'*-dibenzoyl- or (*-*)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(*-*)-**4** or (*-*)-**5**] were also suitable resolving agents to separate the enantiomers of the *i*-butyl-3-phospholene oxide (**1**). Resolving agents (*-*)-**4** and (*-*)-**5** were synthesized by the reaction of CaO with (*-*)-*O,O'*-dibenzoyl- or (*-*)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid. The Ca(H-DBTA)₂ [(*-*)-**4**] was prepared in advance as described earlier [26], while the Ca(H-DPTTA)₂ [(*-*)-**5**] was always formed *in situ*.

In the resolution experiments, the *i*-butyl-3-phospholene oxide (**1**) dissolved in ethanol, ethyl acetate or acetonitrile was added to the hot ethanolic solution of Ca(H-DBTA)₂ or Ca(H-DPTTA)₂ [(*-*)-**4** or (*-*)-**5**]. On cooling the mixture to 26 °C, the crystalline diastereomer precipitated that was filtered after a 24 h of crystallization. The diastereomer separated was purified by two digestions (*i.e.* by stirring the crystals in the corresponding solvent at 26 °C).

To recover the enantiomeric mixture of the *i*-butyl-3-phospholene oxide (**1**), the dichloromethane solution of the diastereomer was treated with 10% aqueous ammonia (Scheme 2). The ee of the 3-phospholene oxide (**1**) was determined by chiral GC. The results are shown in Table 2.



SCHEME 2 General procedure for the resolution of racemic 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) using $\text{Ca}(\text{H-DBTA})_2$ or $\text{Ca}(\text{H-DPTTA})_2$ [(-)-4 or (-)-5].

The successful resolutions of the *i*-butyl-3-phospholene oxide (**1**) with $\text{Ca}(\text{H-DBTA})_2$ [(-)-4] or $\text{Ca}(\text{H-DPTTA})_2$ [(-)-5] afforded the (*R*)-1-*i*-butyl-3-phospholene oxide [(*R*)-**1**] in excess, in which cases the ee was 22-73%, and the resolving capability value fell in the range of 0.02-0.17 after two recrystallizations (Table 2). The application of $\text{Ca}(\text{H-DBTA})_2$ [(-)-4] as the resolving agent in a mixture of ethanol and acetonitrile did not lead to the successful resolution of *i*-butyl-3-phospholene oxide (**1**) (Table 2, Entry 3). The application of the acidic Ca^{2+} -salt of the (-)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(-)-5] seemed to be more favorable, than that of the dibenzoyl-derivative [(-)-4], as higher ee values (60-73% vs. 0-29%) and resolving capability values (0.04-0.17 vs. 0.00-0.05) could be obtained with the former resolving agent [(-)-5] (Compare Entries 1-3 and 4-6 of Table 2). The ^1H NMR study of the diastereomeric complexes revealed that in all but one case, the resolving agents $\text{Ca}(\text{H-DBTA})_2$ [(-)-4] and $\text{Ca}(\text{H-DPTTA})_2$ [(-)-5] incorporated two molecules of the (*R*)-*i*-butyl-3-phospholene oxide [(*R*)-**1**].

TABLE 2 Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) using Ca(H-DBTA)₂ [(**-**)-**4**] or Ca(H-DPTTA)₂ [(**-**)-**5**]

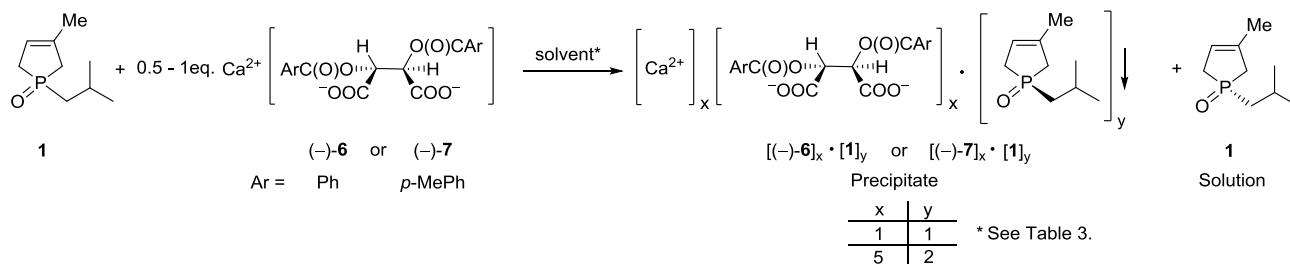
Entry	Resolving agent	Eq.	Solvents ^a	Diastereomeric complex ^b	Yield (%) ^{c,f}	ee (%) ^{d,f}	S (-) ^{e,f}	Abs. Config. ^g
1	Ca(H-DBTA) ₂	0.375	6×EtOH	Ca ₃ (1) ₄ (H-DBTA) ₆	(74) 22	(18) 22	(0.13) 0.05	(<i>R</i>)
2	Ca(H-DBTA) ₂	0.25	3×EtOH/3×EtOAc	Ca(1) ₂ (H-DBTA) ₂	(65) 7	(12) 29	(0.08) 0.02	(<i>R</i>)
3	Ca(H-DBTA) ₂	0.25	3×EtOH/3×MeCN	Ca(1) ₂ (H-DBTA) ₂	(80)	(racemic)	(0.00)	-
4	Ca(H-DPTTA) ₂	0.25	6×EtOH/10%H ₂ O	Ca(1) ₂ (H-DPTTA) ₂	(48) 16	(42) 60	(0.20) 0.10	(<i>R</i>)
5	Ca(H-DPTTA) ₂	0.25	3×EtOAc/3×EtOH/10%H ₂ O	Ca(1) ₂ (H-DPTTA) ₂	(56) 23	(39) 73	(0.22) 0.17	(<i>R</i>)
6	Ca(H-DPTTA) ₂	0.25	3×MeCN/3×EtOH/10%H ₂ O	Ca(1) ₂ (H-DPTTA) ₂	(48) 5	(38) 71	(0.18) 0.04	(<i>R</i>)

See Table 1 for footnotes.

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with Calcium (-)-*O,O'*-Dibenzoyl- and (-)-*O,O'*-di-*p*-Toluoyl-(2*R*,3*R*)-tartrate [(**-**)-**6** and (**-**)-**7**]*

The resolution of the *i*-butyl-3-phospholene oxide (**1**) was also attempted with CaDBTA or CaDPTTA [(**-**)-**6** or (**-**)-**7**] (Scheme 3). The results of the successful resolutions leading to crystalline diastereomers are summarized in Table 3.

The resolving agents CaDBTA or CaDPTTA [(**-**)-**6** or (**-**)-**7**] were always prepared *in situ* by reacting CaO with DBTA or DPTTA in a 1:1 molar ratio, similarly to the preparation of Ca(H-DBTA)₂ [(**-**)-**4**] and Ca(H-DPTTA)₂ [(**-**)-**5**]. The resolution of racemic phospholene oxide **1** and the separation of the diastereomers were carried out according to the procedure described for the acidic (-)-*O,O'*-dibenzoyl- or (-)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(**-**)-**4** or (**-**)-**5**] (Scheme 3). However, in two experiments, the diastereomers were purified by only one recrystallization (Table 3, Entries 1 and 4).



Scheme 3 General procedure for the resolution of racemic 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) using CaDBTA or CaDPTTA [(-)-**6** or (-)-**7**].

Applying the CaDBTA [(-)-**6**] or CaDPTTA [(-)-**7**] as the resolving agent, the resolving capability values fell in the range of 0.01-0.14, and the enantiomeric mixtures containing the (*R*)-*i*-butyl-3-phospholene oxide [(*R*)-**1**] were obtained in an ee of 17-81% (Table 3, Entries 1 and 3-4). However, in one instance the resolution attempt with CaDBTA [(-)-**6**] afforded racemic 3-phospholene oxide (**1**) (Table 3, Entry 2). Comparing the two resolving agents, CaDBTA [(-)-**6**] and CaDPTTA [(-)-**7**], the use of CaDPTTA [(-)-**7**] afforded the (*R*)-*i*-butyl-3-phospholene oxide [(*R*)-**1**] in a higher ee and resolving capability (Compare Entries 1-2 and 3-4 of Table 3).

Comparing the results of the resolutions with the neutral Ca^{2+} -salts of (-)-*O,O'*-dibenzoyl- and (-)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(-)-**6** and (-)-**7**] with those performed with the corresponding acidic Ca^{2+} -salts [(-)-**4** and (-)-**5**], it can be concluded that the application of $\text{Ca}(\text{H-DBTA})_2$ [(-)-**4**] and $\text{Ca}(\text{H-DPTTA})_2$ [(-)-**5**] is more advantageous, as higher resolving capability could be obtained with these agents (Compare Table 2, Entries 1-3 with Table 3, Entries 1 and 2; or Table 2, Entries 4-6 with Table 3, Entries 3 and 4).

TABLE 3. Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with Ca(DBTA) [(-)-**6**] or Ca(DPTTA) [(-)-**7**]

Entry	Resolving agent	Eq.	Solvents ^a	Diastereomeric complex ^b	Yield (%) ^{c,f}	ee (%) ^{d,f}	S (-) ^{e,f}	Abs. Config. ^g
1	CaDBTA	0.5	3×EtOAc/3×EtOH/10%H ₂ O	Ca(1)(DBTA)	(73) 7*	(3) 17*	(0.02) 0.01*	(R)
2	CaDBTA	0.5	3×MeCN/3×EtOH/10%H ₂ O	Ca(1)(DBTA)	(57)	(racemic)	(0.00)	–
3	CaDPTTA	1.25	6×EtOH/10%H ₂ O	Ca ₅ (1) ₂ (DPTTA) ₅	(74) 29	(2) 50	(0.01) 0.14	(R)
4	CaDPTTA	0.5	3×EtOAc/3×EtOH/10%H ₂ O	Ca(1)(DPTTA)	(58) 3*	(53) 81*	(0.30) 0.02*	(R)

See Table 1 for footnotes.

* The diastereomeric complex was purified with one recrystallization.

Single Crystal X-Ray Analysis of the Diastereomeric Complex Incorporating (R)-i-Butyl-3-phospholene Oxide, spiro-TADDOL and Isopropanol in a Ratio of 1:2:1 (1)

The structure in the crystallographic asymmetric unit (Fig. 2) of the 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) : spiro-TADDOL [(-)-**3**] : isopropanol 1 : 2 : 1 inclusion complex, apart from confirming an overall “(R)” absolute configuration for all chiral centres, reveals a wealth of information. Among others, such are the rather well defined H-bonding pattern and the identity of the components of a multiple supra-molecular aggregate. Five O – H ...O type H-bridges fuse these four independent molecules into a tight associated bundle of molecules. The so formed associate has many of the polar (hydrophilic) groups turned inward and towards each other, while the outer surface of the associate remains largely hydrophobic.

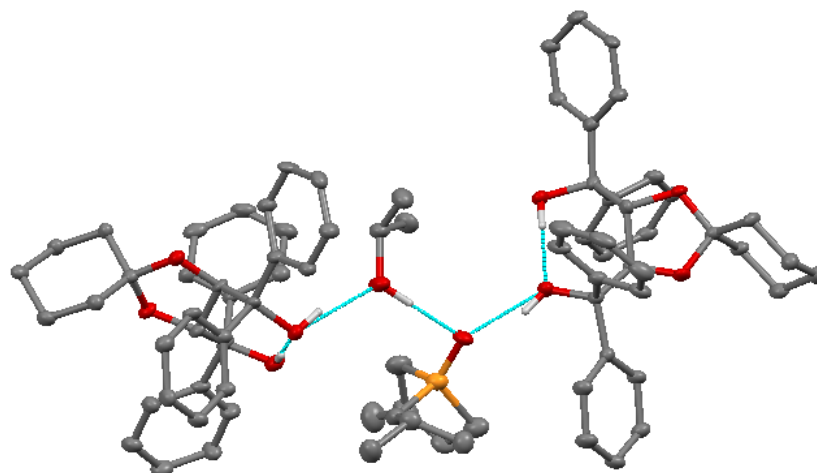


FIGURE 2 Atomic displacement representation of the asymmetric unit of the (1) - spiro-TADDOL [(-)-**3**] - isopropanol 1 : 2 : 1 inclusion complex with the principal H-bridges shown in dotted lines (H atoms less of the –OH ones are omitted for clarity).

H-bonding dimensions (*c.f.* Table 4, deposited) are all well-defined and comply with expectations. The H-bonding pattern retains the well-known internal H-bridge structure of the resolving tool, providing thus a single-donor function only for H-bridging from each spiro-TADDOL [(-)-**3**] host molecules. Also the appearance of two independent hosts is a frequently observed stoichiometry feature in this line of experiments. However, a conspicuous feature is the inclusion of the solvent media used both in the resolution (*c.f.* Table 1) and in the crystallization of this associate product. The space filling representation of the two spiro-TADDOL [(-)-**3**] hosts shows that not only the H-bridging capacity of the included solvent is fully exploited, but it also fits well with its apolar tail into the aromatic surroundings from the delimiting benzene groups of the two hosts (Fig. 3).

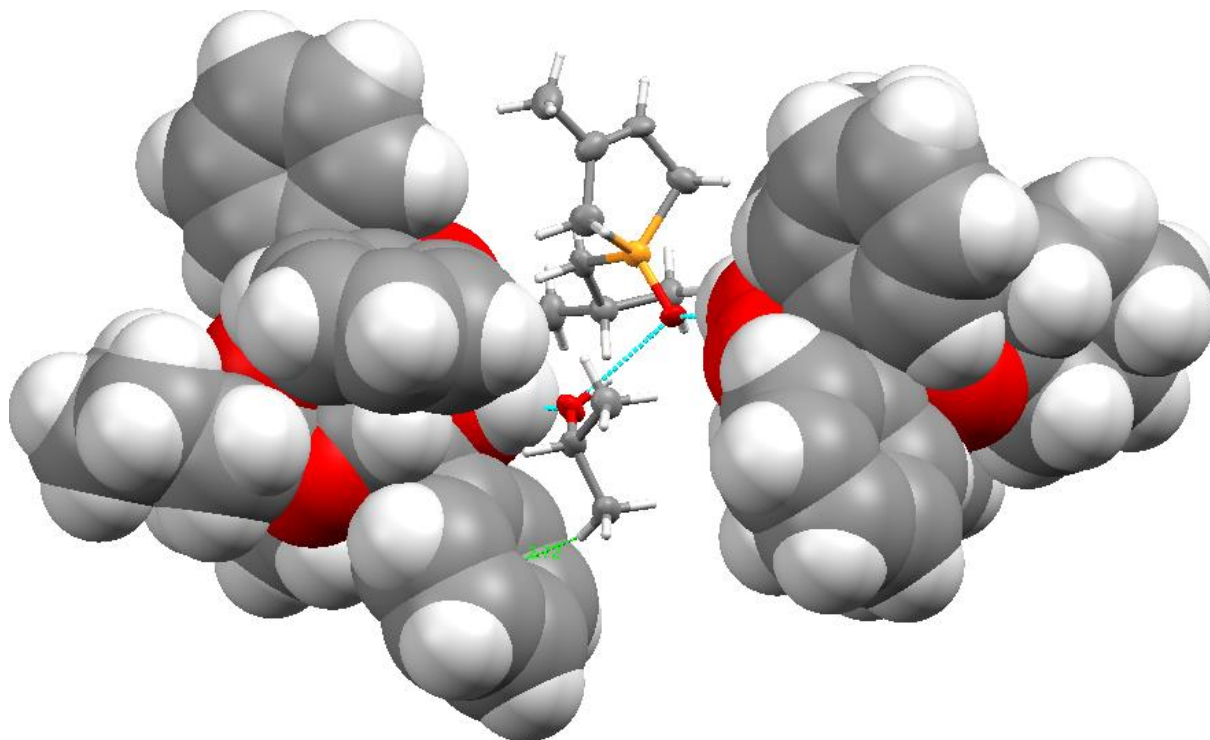


FIGURE 3 Space filling representation of the two spiro-TADDOL [(–)-**3**] hosts with the other two components (**1** and *i*-PrOH molecules) in atomic displacements for the non-H atoms and visible H-bridges (broken lines). A short C—H··· π contact from the *i*-PrOH to a close phenyl ring is shown in green broken line.

A possible C—H··· π interaction may also help in the construction of this intricate complex. Such attractive interaction is best illustrated by the methyl C-H ... ring center short distance and its geometry (see C2S-H2S ... Cg¹², last entry in Table 4 deposited). The visibly important role of the included *i*-PrOH solvent in sustaining the H-bridging system and its fit for the apolar regions qualify this guest molecule to compete for the binding sites of the spiro-TADDOL [(–)-**3**] resolving agent. In our case, the quaternary system shown in Fig. 3 was formed as in the crucial step of the resolution that is the crystallization of the less soluble associate. This directs attention to the altered stoichiometry from the frequently observed 2 : 2 host : guest ratio. Two examples from our recent studies with 2 : 2 resolving host - target guest ratio are the 1-*n*-butyl-3-methyl-3-phospholene oxide [28] and the 1-*n*-propoxy-3-

methyl-3-phospholene oxide [29] guest containing crystal structures. This ratio is violated here by the inclusion of the solvent *i*-PrOH instead of a second phospholene. Thus, one may reasonably suppose that the stoichiometry of this crystal structure is the reason for the overall weaker yield of the resolution (Table 1, Entry 5). To analyse this hypothesis further, a quick study of the INTERMOLECULAR INTERACTION ENERGIES in the (**1**) - spiro-TADDOL [(–)-**3**] - isopropanol 1 : 2 : 1 inclusion crystal complex was done by using program RPLUTO [33]. The results seem to support the competitive nature of the *i*-PrOH solvent molecule included. Calculation of the empirical potential energy [34,35] shows the following. Amongst the top 8 strongest of the total 178 intermolecular contacts are those to the *i*-PrOH solvent with -10.3 kcal/mol and to the 3-phospholene oxide (**1**) guest target with -8.7 kcal/mol interaction energies, respectively (see Fig. 5, deposited). The 1.6 kcal/mol more negative potential energy of the *i*-PrOH solvent as compared to that of the 3-phospholene oxide (**1**) indicate somewhat preferential binding of the solvent. Those top 8 interactions, including the two above mentioned ones account over 40% of the total interaction energy calculated for the crystal. Even considering that these potentials are empirical and somewhat approximate in nature, these figures make it highly probable that the included *i*-PrOH solvent is indeed an effective competitor in the crystallization process. Thus, the idea of the competitive inhibition at the crucial resolution step appears to be reasonable.

*CD Spectra of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (**1**)*

Though the title compound (**1**) is relatively small, considering its flexible structure, the occurrence of numerous stable conformers could be expected at room temperature, whose CD spectra may be rather different. To accurately determine the proportion of the various conformers of **1** and to compute their spectral properties, molecular mechanics (MM), density

functional theory (DFT), and direct random phase approximation (dRPA) calculations have been carried out.

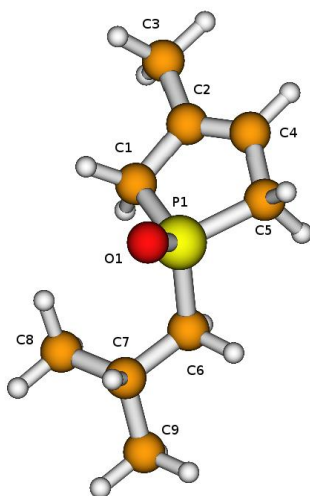


FIGURE 4 DFT-optimized geometry for the most stable conformer of (*R*)-1-*i*-butyl-3-methyl-3-phospholene 1-oxide [(*R*)-1]. Characteristic bond lengths (in Å), angles and torsion angles (in degree) are as follows: P1-O1 1.512, P1-C1 1.837, C1-C2 1.508, C2-C3 1.492, C2-C4 1.338, C4-C5 1.500, C5-P1 1.836, P1-C6 1.822, C6-C7 1.532, C7-C8 1.525, C7-C9 1.526, C1-P1-C5 95, O1-P1-C6 113 and O1-P1-C6-C7 45, O1-P1-C1-C2 107.

First, a systematic MM conformation analysis was performed, and 57 stable conformers were found. The conformers which lie at most at 13 kJ/mol above the lowest energy one were selected, and their geometries were optimized at the DFT level. Since the accurate knowledge of the relative energies of the conformers is the prerequisite of the calculation of reliable CD spectra, single point energy calculations were performed at the DFT-optimized geometries with the dRPA method, which is known to provide accurate conformational energies. Relying on these calculations, 8 conformers were identified which lie within 8 kJ/mol relative to the most stable one. Finally, excitation energies, as well as oscillator and rotator strengths were computed for the selected conformers with the time-dependent DFT (TD-DFT) level, and the simulated absorption and CD spectra of the individual conformers were Boltzmann-weighted

to enable a direct comparison with the corresponding experimental spectra. The optimized geometry of the most stable conformer is displayed in Fig. 4, while the theoretical and experimental spectra are presented in Fig. 5.

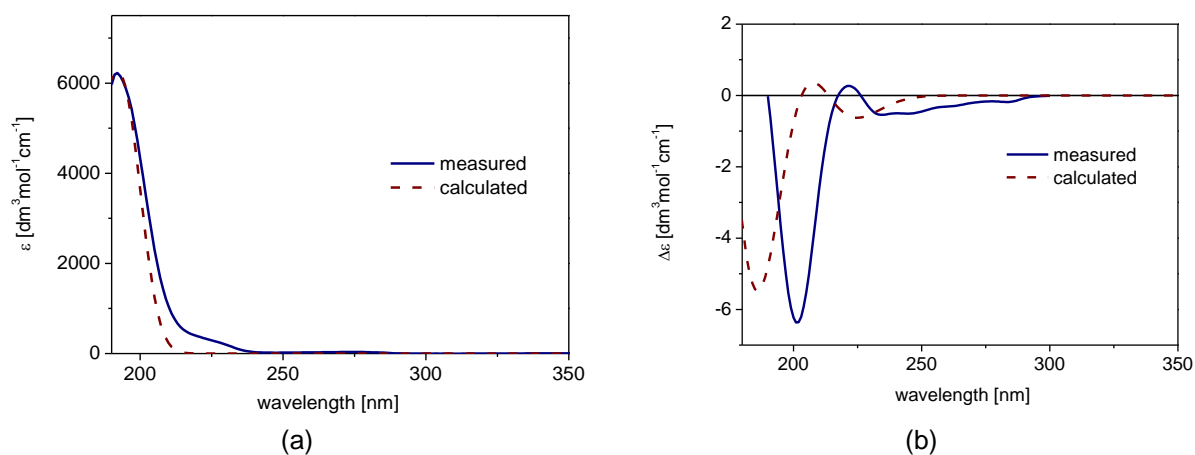


FIGURE 5 Measured and calculated UV (a) and CD (b) spectra of (*R*)-1-*i*-butyl-3-phospholene oxide [(*R*)-1].

The agreement of the measured and computed absorption spectra of the compound is good and justifies the selection of the theoretical model. The structure of the experimental and theoretical CD spectra are very similar, though the spectra are somewhat shifted relative to one another. The sign of the dominant peaks in the two spectra are identical, consequently the absolute configuration of the enantiomer obtained by resolution is identical to that of the enantiomer considered in the calculations.

CONCLUSIONS

The resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) was accomplished applying TADDOL derivatives (–)-**2** and (–)-**3** along with the acidic and neutral Ca²⁺-salts of (–)-*O,O'*-dibenzoyl- or (–)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acids [(–)-**4** - (–)-**7**] as the resolving agents. Efficient resolution method was elaborated for the preparation of optically

active *i*-butyl-3-phospholene oxide (**1**) using spiro-TADDOL as the resolving agent and ethanol as the solvent. The absolute configuration of the enantiopure *i*-butyl-3-phospholene oxide (**1**) was determined by X-Ray crystallography and CD spectroscopy combined by theoretical calculations. Both the yield of the resolution and the Fogassy parameter are linked with the appearance and role of the applied *i*-PrOH solvent in the (**1**) - spiro-TADDOL [(-)-**3**] - isopropanol 1 : 2 : 1 inclusion complex crystal. The idea that the included solvent has a negative influence on the outcome of the resolution is also supported by the inspection of the interaction energies in the crystal.

EXPERIMENTAL

The ^{31}P and ^1H NMR spectra were taken on a Bruker AV-300 or DRX-500 spectrometer operating at 121.5 and 300 or 202.4 and 500 MHz, respectively.

The enantiomeric excess (ee) values of the phospholene oxide **1** were determined by chiral GC on Agilent 4890D instrument equipped with a Supelco BETA DEXTM 120 column (30 m \times 0.25 mm, 0.25 μm film, FID detector, nitrogen as carrier gas, injector 240 $^\circ\text{C}$, detector 300 $^\circ\text{C}$, head pressure: 15 psi, at 1:100 split ratio). Retention times of **1** by chiral GC (program: 2 min at 140 $^\circ\text{C}$, 1 $^\circ\text{C}/\text{min}$ to 190 $^\circ\text{C}$, then kept at 190 $^\circ\text{C}$): 25.3 min for (*R*)-**1** and 25.8 min for (*S*)-**1**.

Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

The UV and CD spectra were measured in acetonitrile solution at 25 $^\circ\text{C}$. The UV spectra were recorded on an Agilent 8453 diode array spectrometer, the CD spectra were taken on a Jasco J-810 spectropolarimeter.

1-*i*-Butyl-3-methyl-3-phospholene 1-oxide (**1**), [31] (-)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane [(-)-**2**], (-)-(2*R*,3*R*)- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol [(-)-**3**] [36] and calcium hydrogen (-)-

O,O'-dibenzoyl-(2*R*,3*R*)-tartrate [(-)-**4**] [26] were synthesized as described earlier. (-)-*O,O'*-Dibenzoyl- and (-)-*O,O'*-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid were purchased from Aldrich Chemical Co.

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with TADDOL [(-)-2] (Representative Procedure I.)*

To the solution of 0.11 g (0.63 mmol) of racemic 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) and 0.15 g (0.32 mmol) TADDOL [(-)-**2**] in 0.30 mL of hot ethyl acetate was added 1.5 mL of hexane, whereupon the crystalline diastereomer (*R*)-**1**·(TADDOL) appeared immediately. After standing at 26 °C for 3 hours, the crystals were filtrated to afford 0.15 g (73%) of (*R*)-**1**·(TADDOL) in a de of 7%. The diastereomer (*R*)-**1**·(TADDOL) was purified further by two recrystallizations in a mixture of 0.30 mL of ethyl acetate and 1.5 mL of hexane to afford 0.034 g (18%) of (*R*)-**1**·(TADDOL) in a de of 35%. 0.0078 g (14%) of (*R*)-1-*i*-butyl-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] was recovered in an ee of 35% from (*R*)-**1**·(TADDOL) by column chromatography (silica gel, 3% methanol in dichloromethane) (Table 1, Entry 1).

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with spiro-TADDOL [(-)-3]*

The resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) was also accomplished with spiro-TADDOL [(-)-**3**] in ethyl acetate – hexane, methanol, ethanol or isopropanol according to Representative Procedure I. When alcohols were used, the racemic 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) and the spiro-TADDOL [(-)-**3**] were dissolved in hot methanol, ethanol or isopropanol, respectively, and the corresponding diastereomer precipitated by cooling down the reaction mixture to 26 °C. The conditions and the results are summarized in

Table 1. The specific optical rotation of the (*R*)-1-*i*-butyl-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] having an ee of 96% was measured (Table 1, Entry 4). $[\alpha]_{\text{D}}^{25} = +7.7$ (c 1.3, CHCl₃).

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with Calcium Hydrogen *O,O'*-Dibenzoyl-(2*R*,3*R*)-tartrate [(*-*)-**4**] (Representative Procedure II.)*

0.16 g (0.94 mmol) of 1-*i*-Butyl-3-methyl-3-phospholene 1-oxide (**1**) in 0.83 mL of ethanol was added to 0.28 g (0.35 mmol) of Ca(H-DBTA)₂·(H₂O)₂ [(*-*)-**4**·(H₂O)₂] dissolved in 0.83 mL of hot ethanol. The diastereomeric complex Ca₃[(*R*)-**1**]₄(H-DBTA)₆ precipitated on cooling down the reaction mixture gradually to 26 °C was separated from the mother liquor after 24h to provide 0.26 g (74%) of Ca₃[(*R*)-**1**]₄(H-DBTA)₆ in a de of 18%. The diastereomer Ca₃[(*R*)-**1**]₄(H-DBTA)₆ was purified further by two digestions (*i.e.* by stirring the diastereomer in 1.66 mL of ethanol) to afford 0.086 g (25%) of Ca₃[(*R*)-**1**]₄(H-DBTA)₆ in a de of 22%. To recover the (*R*)-1-*i*-butyl-3-methyl-3-phospholene 1-oxide [(*R*)-**1**], the 2 mL dichloromethane solution of Ca₃[(*R*)-**1**]₄(H-DBTA)₆ was extracted with 2 mL of 10% aqueous ammonia. The organic layer was separated and dried (Na₂SO₄), and concentrated to furnish 0.017 g (22%) of (*R*)-**1** in an ee of 22% (Table 2, Entry 1).

The resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with Ca(H-DBTA)₂·(H₂O)₂ [(*-*)-**4**·(H₂O)₂] was also performed in a mixture of ethanol and ethyl acetate or ethanol and acetonitrile. The conditions and the results are summarized in Table 2 (Entries 2 and 3).

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with Calcium Hydrogen *O,O'*-*p*-Toluoyl-(2*R*,3*R*)-tartrate [(*-*)-**5**] (Representative Procedure III.)*

The mixture of 0.20 g (0.48 mmol) of DPTTA·H₂O and 0.014 g (0.24 mmol) of CaO was dissolved in a hot mixture of 0.64 mL of ethanol and 0.06 mL of water. To this hot solution of

the *in situ* formed $\text{Ca}(\text{H-DPTTA})_2$ [(-)-**5**] was added 0.17 g (0.97 mmol) of racemic 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) in 0.64 mL of ethyl acetate. Cooling down the reaction mixture gradually to 26 °C, the crystalline diastereomer $\text{Ca}[(R)\text{-1}]_2(\text{H-DPTTA})_2$ appeared that was separated from the mother liquor after 24h to give 0.16 g (56%) of $\text{Ca}[(R)\text{-1}]_2(\text{H-DPTTA})_2$ in a de of 39%. The diastereomer $\text{Ca}[(R)\text{-1}]_2(\text{H-DPTTA})_2$ was purified further by two digestions in a mixture of 0.64 mL of ethanol, 0.64 mL of ethyl acetate and 0.06 mL of water. This led to 0.076 g (27%) of $\text{Ca}[(R)\text{-1}]_2(\text{H-DPTTA})_2$ with a de of 73%. Then, the 2 mL dichloromethane solution of $\text{Ca}[(R)\text{-1}]_2(\text{H-DPTTA})_2$ was treated with 2 mL of 10% aqueous ammonia. The organic layer was separated, dried (Na_2SO_4) and concentrated to furnish 0.019 g (23%) of (*R*)-1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) in an ee of 73% (Table 2, Entry 5).

The resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) was also accomplished using $\text{Ca}(\text{H-DPTTA})_2$ [(-)-**5**] as the resolving agent in a mixture of ethanol and water or acetonitrile, ethanol and water. The conditions and the results are summarized in Table 2 (Entries 4 and 6).

*Resolution of 1-*i*-Butyl-3-methyl-3-phospholene 1-Oxide (1) with Calcium *O,O'*-di-Benzoyl-(2*R*,3*R*)-tartrate and Calcium *O,O'*-di-*p*-Toluoyl-(2*R*,3*R*)-tartrate [(-)-**6** and (-)-**7**]*

The resolution of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) was also accomplished using CaDBTA or CaDPTTA [(-)-**6** or (-)-**7**] as the resolving agent according to Representative Procedure III. The resolving agents [(-)-**6** or (-)-**7**] were prepared *in situ* by reacting CaO with DBTA or DPTTA in a molar ratio of 1:1. The conditions and the results are summarized in Table 3.

X-Ray Measurements

X-ray quality crystals of the 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) : spiro-TADDOL [(-)-**3**] : isopropanol 1 : 2 : 1 inclusion complex were grown from a saturated isopropanol solution of 2.3 mg (0.013 mmol) of (*R*)-**1** and 13.5 mg (0.027 mmol) spiro-TADDOL [(-)-**3**].

Crystal data: C₈₀H₉₃O₁₀P, Fwt.: 1245.51, colorless, prism, size: 0.35 x 0.30 x 0.25 mm, monoclinic, space group *P*21, $a = 9.4730(2)\text{\AA}$, $b = 34.6740(6)\text{\AA}$, $c = 10.2450(2)\text{\AA}$, $\alpha = 90^\circ$, $\beta = 95.1190(7)^\circ$, $\gamma = 90^\circ$, $V = 3351.72(11)\text{\AA}^3$, $T = 93(2)\text{ K}$, $Z = 2$, $F(000) = 1336$, $D_x = 1.234\text{ Mg/m}^3$, $\mu = 0.846\text{ mm}^{-1}$. A crystal of 1-*i*-butyl-3-methyl-3-phospholene 1-oxide (**1**) : spiro-TADDOL [(-)-**3**] : isopropanol 1:2:1 inclusion complex was mounted on a loop. Cell parameters were determined by least-squares of the setting angles of 26125 ($6.61 \leq \theta \leq 71.92^\circ$) reflections. Intensity data were collected on an R-Axis RAPID diffractometer (graphite monochromator; Cu- $K\alpha$ radiation, $\lambda = 1.54178\text{\AA}$) at 93(2) K in the range $6.61 \leq \theta \leq 66.59^\circ$ using ω scans. A total of 33600 reflections were collected of which 10593 were unique [$R(\text{int}) = 0.0630$, $R(\sigma) = 0.0909$]; intensities of 7258 reflections were greater than $2\sigma(I)$. Completeness to $\theta = 0.936$. A numerical absorption correction was applied to the data (the minimum and maximum transmission factors were 0.76 and 0.82 [37]). The structure was solved by direct methods and subsequent difference syntheses [38]. Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0664$ and $wR^2 = 0.1474$ for 7258 [$I > 2\sigma(I)$] and $R_1 = 0.1056$ and $wR^2 = 0.1928$ for all (10593) intensity data, (number of parameters = 827, goodness-of-fit = 1.093, absolute structure parameter $x = -0.01(4)$ [39], the maximum and mean shift/esd is 0.003 and 0.000) [40]. Hydrogen atomic positions were calculated from assumed geometries except the -OH ones that were located in constrained difference maps and kept riding. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters

of the hydrogen atoms were approximated from the $U(eq)$ value of the atom they were bonded to. All pertinent calculations including structure validation and plotting were performed by using program PLATON [41] and Mercury [42]. A final structure model is deposited with the Cambridge Crystallographic Data centre under CCDC 1006292. Copies of these data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 00 44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk) or via www.ccdc.cam.ac.uk/data_request/cif.

Theoretical Calculations

In the MM conformational analysis the MMFF94 [43] force field was used. The DFT and TD-DFT [44,45] calculations were carried out using the PBE0 [46] functional and the 6-311++G** basis set. Rotator strengths were calculated in the velocity gauge. All the DFT calculations were performed using the polarized continuum model [47] with acetonitrile as the solvent since the experimental spectra were recorded in the latter. The dRPA energies were computed with the aug-cc-pVTZ basis set and PBE0 orbitals. To calculate the 298 K Gibbs energies of the conformers in the solvent the gas-phase dRPA energies were adjusted by temperature corrections, entropy contributions, and Gibbs energies of solvation evaluated at the DFT level at the corresponding DFT-optimized geometries. The MM, DFT, and dRPA calculations were performed by the Marvin [48], Gaussian 09 [49], and MRCC [50] packages, respectively.

The theoretical absorption (CD) curves for each conformer were obtained as superpositions of Gaussian functions placed at the wavelengths of the computed transitions with heights proportional to the corresponding calculated oscillator (rotator) strengths. The spectra of the conformers were Boltzmann-weighted using the Gibbs energies obtained as described above. The averaged spectra were normalized so that the height of the biggest peak

be identical to that of the experimental spectra, in addition, the spectra were shifted by 3 nm to longer wavelengths so that the position of the most intense band of the calculated and measured absorption spectra be identical.

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