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Resolution of 1-*n*-Butyl-3-Methyl-3-Phospholene 1-Oxide with TADDOL Derivatives and Calcium Salts of *O,O*'-Dibenzoyl-(2*R*,3*R*)- or *O,O*'-di-*p*-Toluoyl-(2*R*,3*R*)-tartaric Acid

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ABSTRACT The resolution methods applying (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane ("TADDOL"), (−)-(2*R*,3*R*)-α,α,α',α'-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol ("spiro-TADDOL"), as well as the acidic and neutral Ca^{2+} salts of (−)-*O,O*'-dibenzoyl- and (−)-*O,O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid were extended for the preparation of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide in optically active form. In one case, the intermediate diastereomeric complex could be identified by single crystal X-ray analysis. The absolute P-configuration of the enantiomers of the phospholene

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oxide was also determined by comparing the experimentally obtained and calculated CD spectra.

KEY WORDS: Alkyl-3-Phospholene 1-oxide; P-chirality; resolution methods; optical isomers; X-ray crystallography; CD-spectroscopy; absolute P-configuration

INTRODUCTION

The preparation of chiral phosphines in enantiopure form is of great interest in organic chemistry, as the transition metal complexes of these compounds may be applied as enantioselective catalysts in various homogenous catalytic reactions.[1,2]

Since the first enantiomeric separation of compounds having a non-symmetrically substituted phosophorus atom by Meisenheimer and Lichtenstadt,[3] the preparation of optically active P-stereogenic substances has been the subject of continuing interest. The separation of optical isomers may be based on the formation of covalent diastereomers, diastereomeric salts, diastereomeric transition metal complexes and molecular complexes.[4–6]

There are several methods reported in the literature for the resolution of phosphine oxides, but none of these methods are of general use. The separation of enantiomers of several secondary and tertiary phosphine oxides with a stereogenic center either on the phosophorus atom, or on the backbone was accomplished via molecular complex formation with *O,O*'-dibenzoyl-(2*R*,3*R*)-tartaric acid.[7–15] In some special instances, the bromocamphorsulfonic acid,[3,16,17] camphorsulfonic acid,[17] mandelic acid,[18,19] 2,2'-dihydroxy-1,1'-binaphthalene,[18,20] as well as the α-methylbenzylamine[21] were also used successfully to prepare optically active phosphine oxides.

Five-membered P-heterocycles, such as 1-substituted-3-methyl-3-phospholene 1-oxides are important starting materials for several five-, six-, seven- and eight-membered derivatives.[22–25] *Pietrusiewicz* and his co-workers have reported several methods for the preparation of the enantiomers of phospholene oxides and their derivatives, but these methods are rather special.[26–29] Recently, our research group has developed efficient resolution methods for the separation of the enantiomers of 1-substituted-3-methyl-3-phospholene 1-oxides. The resolution of the 3-phospholene oxides was accomplished via molecular complex formation using TADDOL derivatives (**2** and **3**).[30–32] The acidic Ca^{2+} salts of *O,O*'-dibenzoyl- and *O,O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (**4** and **5**) were also found suitable resolving agents via diastereomeric coordinative complex formation.[33,34] These resolution methods were also extended to several phenyl-substituted 6-membered P-heterocycles.[35]

In this paper, we studied the possibilities of the resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) considering the methods developed in our research group (Fig. 1). The absolute P-configuration of the resulting enantiomers of *n*-butyl-3-phospholene oxide (**1**) was identified by independent methods.

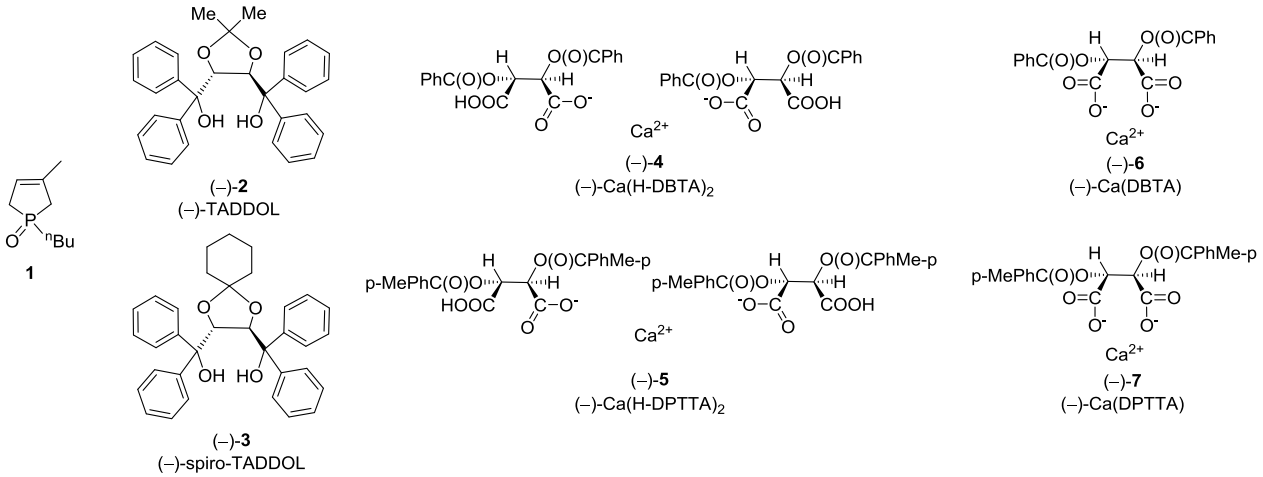


Fig. 1. The *n*-butyl-3-phospholene oxide (**1**) and resolving agents [(−)-**2**-(−)-**7**] used in this study

MATERIALS AND METHODS

General

The ^{31}P and ^{1}H 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 DEX^{TM} 120 column (30 m × 0.25 mm, 0.25 μm film, FID detector, nitrogen as carrier gas, injector 240°C, detector 300°C, head pressure: 10 psi, at 1:100 split ratio). Retention times of **1** by chiral GC (program: 2 min at 140°C, 20°C/min to 175°C, followed by 1°C/min to 190°C, then kept at 190°C): 20.50 min for (*R*)-**1** and 20.86 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°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-*n*-Butyl-3-methyl-3-phospholene 1-oxide (**1**),[36] (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane [(−)-**2**], (–)-(2*R*,3*R*)-α,α,α’,α’-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol [(−)-**3**][37] and calcium hydrogen (−)-

O,O'-dibezoyl-(2*R*,3*R*)-tartarate [(−)-**4**][33] were synthesized as described earlier. (−)-*O,O*'-Dibezoyl- and (–)-*O,O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid were purchased from Aldrich Chemical Co.

*Resolution of 1-n-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with TADDOL [(−)-**2**] (Representative Procedure A)*

0.15 g (0.90 mmol) of racemic 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) and 0.42 g (0.90 mmol) of TADDOL [(−)-**2**] was dissolved in 0.84 ml of hot ethyl acetate, and then 4.2 ml of hexane was added. Colourless crystalline diastereomeric complex (*S*)-**1**·$(TADDOL)_2$ appeared immediately. After standing at 26°C for 3 h, the crystals were separated by filtration to give 0.32 g (65%) of (*S*)-**1**·$(TADDOL)_2$ with a de of 26%. The diastereomeric complex (*S*)-**1**·$(TADDOL)_2$ was purified further by two recrystallizations from a mixture of 0.84 ml of ethyl acetate and 4.2 ml of hexane to afford 0.14 g (28%) of the complex (*S*)-**1**·$(TADDOL)_2$ with a de of 74%. The (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] was recovered from the diastereomer by column chromatography (silica gel, dichloromethane:methanol 97:3) to give 0.018 g (23%) of phospholene oxide (*S*)-**1** with an ee of 74%. $[\alpha]_D^{25} = -12.1$ (c 2.4, $CHCl_3$). (Table 1, Entry 1). Resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL [(−)-**2**] was also performed in isopropyl alcohol. In this case, the racemic 3-phospholene oxide **1** and the TADDOL [(−)-**2**] were dissolved in hot isopropyl alcohol, and the corresponding diastereomeric complexes precipitated by cooling down the mixture to 26°C (Table 1, Entry 2).

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

1-*n*-butyl-3-phospholene oxide (**1**) was resolved with spiro-TADDOL [(−)-**3]** according to the *Representative Procedure A*. The conditions and the results are shown in Table 1, Entries 3–6.

*Resolution of 1-n-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with Calcium Hydrogen O,O'-Dibenzoyl-(2R,3R)-tartarate [(−)-**4**] (Representative Procedure B)*

To 0.17 g (0.22 mmol) of $Ca(H\text{-}DBTA)_2 \cdot (H_2O)_2$ [(−)-**4**·$(H_2O)_2$] in 0.51 ml of hot ethanol was added 0.15 g (0.88 mmol) of racemic 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) in 0.51 ml of acetonitrile. After the addition, the solution was allowed to cool down to 26°C, whereupon colourless crystals appeared. After standing at 26°C for 24 h, the crystals were

filtered off to give 0.17 g (72%) of Ca[((*S*)-**1**)$_2$(H-DBTA)$_2$] with a de of 31%. The diastereomeric complex was purified further by two digestions, by stirring the suspension of the diastereomeric complex at 26°C in a mixture of 0.51 ml of ethanol, 0.51 ml of acetonitrile for 24 h to afford 0.067 g (28%) of Ca[((*S*)-**1**)$_2$(H-DBTA)$_2$] with a de of 76%. The phospholene oxide (*S*)-**1** was recovered from the diastereomeric complex by treatment of the 2 ml dichloromethane solution of Ca[((*S*)-**1**)$_2$(H-DBTA)$_2$] with 2 ml of a 10% aqueous ammonia. The organic layer was washed with 0.5 ml of water, dried (Na_2SO_4), and concentrated to give 0.016 g (21%) of (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**)] with an ee of 76%. Resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with Ca(H-DBTA)$_2$ [(−)-**4**] was also performed in a mixture of ethanol and ethyl-acetate. The conditions and the results are shown in Table 3, Entries 1 and 2.

*Resolution of 1-n-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with Calcium Hydrogen O,O'-di-p-Toluoyl-(2R,3R)-tartarate [(−)-**5**] (Representative Procedure C)*

To 0.18 g (0.45 mmol) of DPTTA·H_2O in a mixture of 0.56 ml of ethanol and 0.06 ml of water was added 0.013 g (0.23 mmol) of CaO, and the mixture was heated at the boiling point until it became clear. 0.16 g (0.91 mmol) of racemic 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) in 0.56 ml of ethyl acetate was then added to the solution of the *in situ* formed resolving agent Ca(H-DPTTA)$_2$ [(−)-**5**]. After the addition, the solution was allowed to cool down to 26°C, whereupon colourless crystals appeared. After standing at 26°C for 24 h, the crystals were filtered off to give 0.18 g (68%) of Ca[((*S*)-**1**)$_2$(H-DPTTA)$_2$] with a de of 38%. The diastereomeric complex was purified further by two digestions, by stirring the suspension of the diastereomeric complex at 26°C for 24 h in a mixture of 0.56 ml of ethanol, 0.56 ml of ethyl acetate and 0.06 ml of water to afford 0.13 g (49%) Ca[((*S*)-**1**)$_2$(H-DPTTA)$_2$] with a de of 45%. The phospholene oxide (*S*)-**1** was recovered by treatment of the 2 ml dichloromethane solution of the complex with 2 ml of 10% aqueous ammonia. The organic phase was washed with 0.5 ml of water, dried (Na_2SO_4), and concentrated to give 0.034 g (44%) of (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] with an ee of 45%. The resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with Ca(H-DPTTA)$_2$ [(−)-**5**] was accomplished in a mixture of ethanol and water, or in a mixture of ethanol, acetonitrile and water. The conditions and the results are shown in Table 2, Entries 3–5.

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

1-*n*-Butyl-3-phospholene oxide (**1**) was resolved with Ca(DBTA) and Ca(DPTTA) [(−)-**6** and (−)-**7**] according to *Representative Procedure C*. Ca(DBTA) and Ca(DPTTA) [(−)-**6** and (−)-**7**] were formed by the reaction of a 1:1 mixture of CaO and DBTA or DPTTA. The conditions and the results are shown in Table 3.

*Complete Resolution Process for 1-n-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with spiro-TADDOL [(−)-**3**]*

The (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] was obtained by the resolution of 0.75 g (4.3 mmol) of racemic **1** with 2.2 g (4.3 mmol) of spiro-TADDOL [(−)-**3**] in a mixture of 4.4 ml of ethyl acetate and 22 ml of hexane according to *Representative Procedure A*. The diastereomereic complex [(*S*)-**1**·(spiro-TADDOL)$_2$] was purified by three recrystallizations in a mixture of 4.4 ml of ethyl acetate and 22 ml of hexane. The (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] was recovered by column chromatography (silica gel, dichloromethane:methanol 97:3) to afford 0.19 g (52%) of (*S*)-**1** in an ee of 95%. The mother liquors of the crystallization and recrystallizations were combined, and the solvent was evaporated to afford 1.3 g (61%) of a white powder as a 3:2 mixture of (*R*)-**1** with an ee of 32% and spiro-TADDOL [(−)-**3**]. 0.86 g (1.7 mmol) of spiro-TADDOL [(−)-**3**] was added to this mixture and the resolution was performed in 10 ml of ethanol according to *Representative Procedure A*. The [(*R*)-**1**·(spiro-TADDOL)$_2$] complex was purified by three recrystallizations in 10 ml of ethanol and it was decomposed by column chromatography (silica gel, dichloromethane:methanol 97:3) to afford 0.04 g (11%) of (*R*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] in an ee of 98%.

X-Ray Measurements

X-ray quality crystals of the diastereomeric complex **1**:spiro-TADDOL 1:1 were grown from the saturated ethyl acetate solution of 252 mg (1.46 mmol) of (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] and 7.4 mg (0.015 mmol) of spiro-TADDOL [(−)-**3**].

A selected single colourless, prism crystal (0.15 × 0.2 × 0.4 mm) of 1 : spiro-TADDOL 1:1 was mounted on a Rigaku R-AXIS RAPID diffractometer (graphite monochromator Mo-*K*α radiation, λ = 0.71075 Å). Data collection was performed at room temperatures (T = 295(2) K). Crystal data for **1** : spiro-TADDOL 1:1 = $C_{43}H_{51}O_5P$, triclinic, space group *P1*, *a* = 9.4378(7) Å, *b* = 10.0316(9) Å, *c* = 20.3550(17) Å, *a* = 83.320(2), *b* = 82.798(2), *g* = 89.034(2), *V* = 1899.0(3) Å3, *T* = 295(2) K, *Z* = 2, *Dx* = 1.187 Mg/m^3, μ = 0.116 mm^{-1}. Initial structure model was obtained by SHELXS-97,[38] completed by successive difference Fourier

syntheses and refined to convergence by SHELXL-97,[38] $R1$ = 0.0669 and wR^2 = 0.1567 for 5644 [$I>2\sigma(I)$] and $R1$ = 0.1064 and wR^2 = 0.1816 for all (8968) intensity data. Refined absolute structure parameter x = 0.08(19).[39] Relevant X-ray diffraction and model information have been deposited at the Cambridge Crystallographic Data centre under deposition number CCDC XXXXXX. 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).

CD Measurements

The UV absorption and CD spectra were measured in acetonitrile solution. The UV spectra were recorded on an Agilent 8453 diode array spectrometer, the CD spectra were obtained with a Jasco J-810 spectropolarimeter.

Theoretical Calculations

Quantum chemical calculations at the density functional theory (DFT) level choosing the PBE0 functional[40,41] and the 6-311++G** basis set were performed. Vertical excitation energies, as well as oscillator and rotator strengths (in the velocity gauge) were calculated using the time-dependent DFT method[42] with the same functional and basis set. Since the absorption and CD spectra were measured in acetonitrile, all the DFT calculations were performed invoking the polarized continuum model[43] with acetonitrile as the solvent. All calculations were carried out by the Gaussian 09 package.[44]

RESULTS AND DISCUSSION

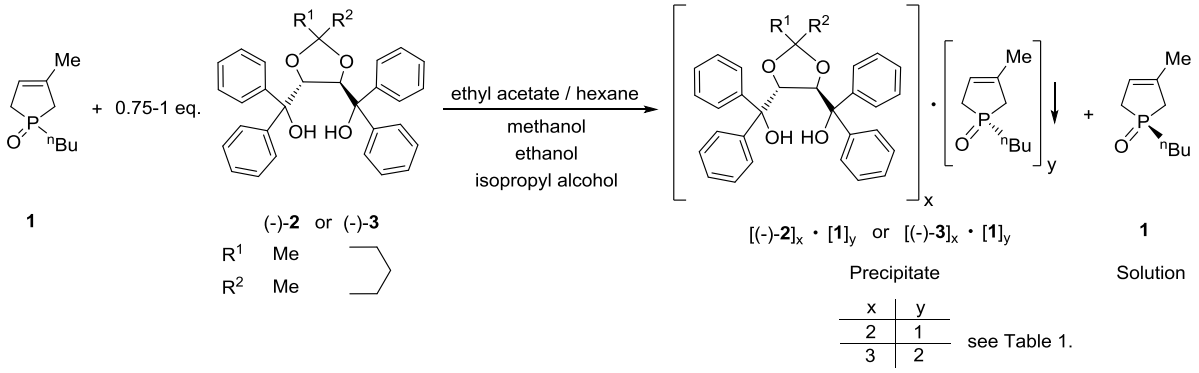
*Resolution of 1-n-Butyl-3-methyl-3-phospholene 1-Oxide (**1**) with TADDOL Derivatives [(−)-**2** and (−)-**3**]*

The resolution of 3-phospholene oxide **1** was attempted with TADDOL and spiro-TADDOL [(−)-**2** and (−)-**3**] in different solvents. Results of the successful resolutions leading to crystalline diastereomers are summarized in Table 1.

Following the resolution method developed in our research group,[30,31] the resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) was attempted first with TADDOL derivatives [(−)-**2** and (−)-**3**] in a mixture of ethyl-acetate and hexane. According to this procedure, the mixture of racemic 3-phospholene 1-oxide (**1**) and TADDOL or spiro-TADDOL [(−)-**2** or (−)-**3**, respectively] was dissolved in hot ethyl acetate. The corresponding diastereomeric complex precipitated after the addition of hexane to the mixture.

Previously, it was established in our research group that the replacement of ethyl acetate by other solvents may influence the efficiency of the resolutions of the aryl-, alkyl- and alkoxy-substituted-3-phosphole oxides with TADDOL derivatives [(−)-**2** and (−)-**3**].[45] Hence, the resolution of the 3-phospholene oxide (**1**) with TADDOL derivatives [(−)-**2** or (−)-**3**] was also attempted using methanol, ethanol and isopropyl alcohol as the solvent. In these cases, the mixtures of the racemic 3-phospholene oxide (**1**) and TADDOL derivatives [(−)-**2** or (−)-**3**] were dissolved in hot alcohol, the mixtures were cooled down to 26°C, whereupon crystalline diastereomeric complex appeared (Scheme 1).

In all cases, the diastereomers formed were filtered off from the mother liquors after 3 hours of crystallization. The diastereomeric complexes were purified further by two recrystallizations from the corresponding solvents. The 3-phospholene oxide (**1**) was recovered from the corresponding diastereomers by column chromatography using silica gel and 3% of methanol in dichloromethane as the eluent.



Scheme 1. General resolution procedure for racemic 3-phospholene oxide (**1**) using TADDOL derivatives [(−)-**2** and (−)-**3**]

The composition of the diastereomers was determined by ^{1}H NMR. It depended on the resolving agent [(−)-**2** or (−)-**3**] and the solvent used. In all but one instance, diastereomers obtained contained the *n*-butyl-3-phospholene oxide (**1**) and the TADDOL derivatives [(−)-**2** or (−)-**3**] in a ratio of 1:2 (Table 1, Entries 1 and 3–6). The resolution of *n*-butyl-phospholene oxide **1** with TADDOL [(−)-**2**] in isopropyl alcohol afforded a diastereomer of $(\mathbf{1})_2 \cdot [(-)\text{-}\mathbf{2}]_3$ (Table 1, Entry 2). In case of all resolution experiments, the half equivalent methodology[46] was followed, hence, considering the composition of the diastereomeric complexes, 0.75-1 equivalents of the resolving agents [(−)-**2** or (−)-**3**] were used (Table 1).

The diastereomeric complexes obtained were analysed by chiral GC after regenerating the 3-phospholene oxide (**1**) from the sample of the corresponding diastereomer by preparative

TLC using silica gel and 3% of methanol in dichloromethane as eluent. The enantiomeric excess values were in the range of 26–62% after crystallization. The enantiomeric purity increased significantly to 70–84% after two recrystallizations (Table 1).

It was found that the resolving agent [(−)-**2** or (−)-**3**] and the solvent used influenced the efficiency of the resolution, as well as the enantiomer of the 3-phospholene oxide (**1**) incorporated in the diastereomeric complex. The highest resolving capability (S = 0.52) was achieved with spiro-TADDOL [(−)-**3**] in ethyl acetate and hexane (Table 1, Entry 3). Generally, a decrease in resolving capability (S) was observed, when different alcohols were used as the solvent instead of a mixture of ethyl acetate and hexane. However, it is noteworthy that in a few instances, the use of different solvents with the same resolving agent [(−)-**2** or (−)-**3**] led to complex formation with different enantiomers of the 3-phospholene oxide (**1**). Resolution with spiro-TADDOL [(−)-**3**] in isopropyl alcohol or in a mixture of ethyl acetate and hexane afforded (*S*)-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**], while the resolution in methanol or in ethanol led to the other antipode [(*R*)-**1**] (Table 1, Entries 3 and 6 or 4 and 5).

TABLE 1. Resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL derivatives [(−)-**2** and (−)-**3**]

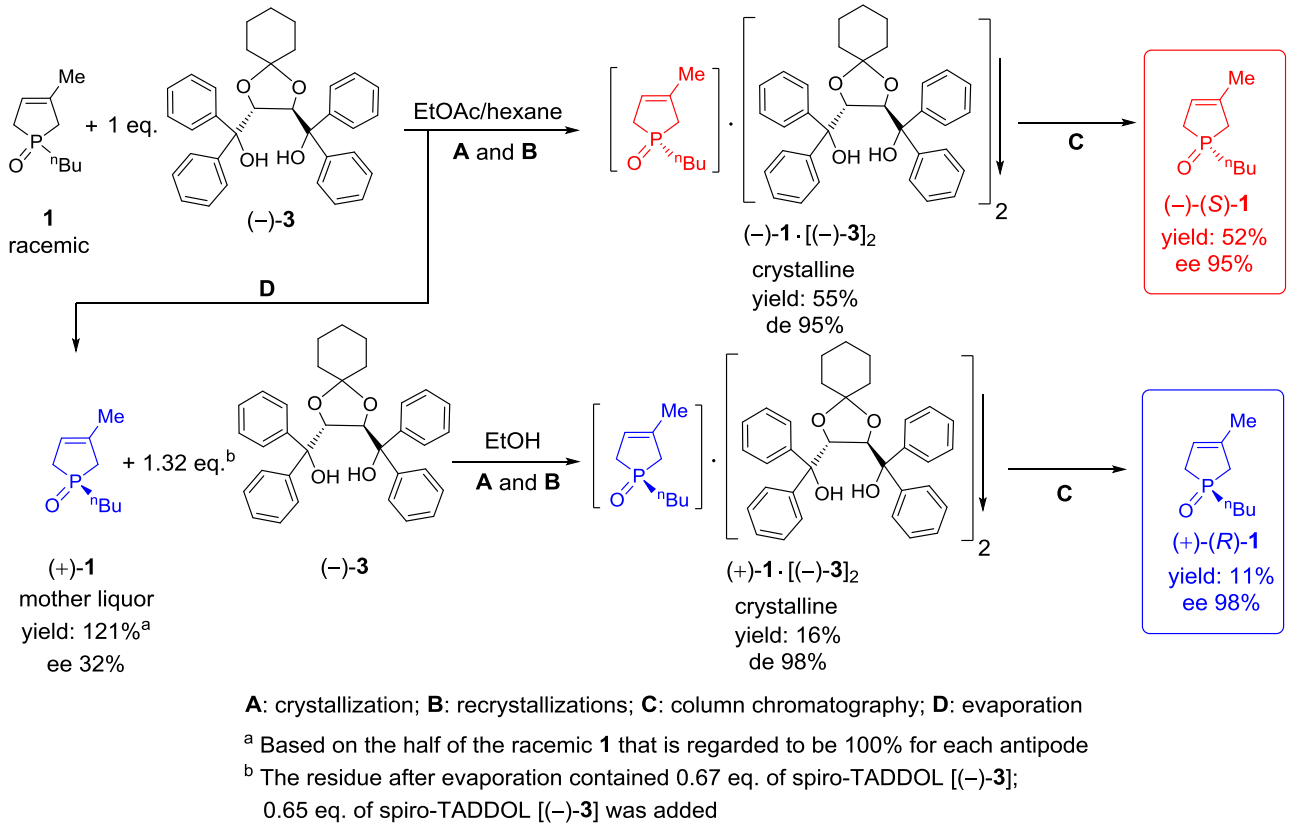
Entry	Resolving agent	Eq.	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	ee[d,f] (%)	S[e,f] (-)	Abs. Config.[g]
1	TADDOL	1	2×EtOAc/10×Hexane	(**1**)(TADDOL)$_2$	(65) **23**	(26) **74**	(0.17) **0.17**	(*S*)
2	TADDOL	0.75	6×iPrOH	(**1**)$_2$(TADDOL)$_3$	(44) **5**	(41) **78**	(0.18) **0.04**	(*S*)
3	spiro-TADDOL	1	2×EtOAc/10×Hexane	(**1**)(spiro-TADDOL)$_2$	(83) **62**	(54) **84**	(0.45) **0.52**	(*S*)
4	spiro-TADDOL	1	6×MeOH	(**1**)(spiro-TADDOL)$_2$	(75) **33**	(51) **77**	(0.38) **0.26**	(*R*)
5	spiro-TADDOL	1	6×EtOH	(**1**)(spiro-TADDOL)$_2$	(80) **17**	(28) **70**	(0.22) **0.12**	(*R*)
6	spiro-TADDOL	1	6×iPrOH	(**1**)(spiro-TADDOL)$_2$	(86) **43**	(62) **78**	(0.53) **0.33**	(*S*)

[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 ^{1}H 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 = Y x ee).[47]
[f]Results obtained after the first crystallization are shown in "( )", 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.

The phenomena that TADDOL-derivatives [(−)-**2** or (−)-**3**] may form diastereomeric complexes with both antipodes of the 3-phospholene oxide (**1**) in different solvents allowed us

to develop resolution procedures to obtain both enantiomers from racemic 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**).

Both enantiomers of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) could be prepared by resolution with spiro-TADDOL [(−)-**3**] using either a mixture of ethyl acetate and hexane, or ethanol. So the racemic *n*-butyl-3-phospholene 1-oxide (**1**) was resolved with 1 equivalent of spiro-TADDOL [(−)-**3**] in a mixture of ethyl acetate and hexane to afford (−)-(*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] with an ee of 95% and in a yield of 52% after the purification of the diastereomeric complex [(−)-**1**]·[(−)-**3**]$_2$ by three recrystallizations and decomplexation by column chromatography. To obtain the other antipode, the mother liquors of the crystallization and recrystallizations were combined, the solvent was evaporated to obtain a 2:3 mixture of spiro-TADDOL [(−)-**3**] and (*R*)-*n*-butyl-3-phospholene 1-oxide [(*R*)-**1**] with an ee of 32% and in a yield of 121% (based on the half of the racemic **1** that is regarded to be 100% for each antipode). To this mixture 0.65 equivalent of spiro-TADDOL [(−)-**3**] was added to have 1.32 equivalent of spiro-TADDOL [(−)-**3**] in total, and the resolution was accomplished in ethanol to afford (+)-(*R*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] with an ee of 98% and in a yield of 11% after the purification of the diastereomeric complex [(+)-**1**]·[(−)-**3**]$_2$ by three recrystallizations and the decomplexation by column chromatography (Scheme 2).



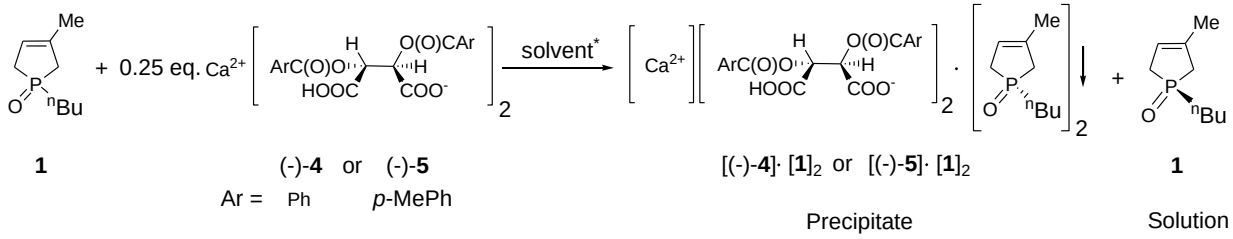
Scheme 2. The complete resolution process of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with spiro-TADDOL (−)-**3**.

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

The resolution of the 3-phospholene oxide (**1**) was also attempted with the acidic Ca^{2+}-salts of (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**4** or (−)-**5**]. The results are summarized in Table 2.

$Ca(H\text{-}DBTA)_2$ [(−)-**4**] was prepared in advance as described in our earlier studies,[33,34] while $Ca(H\text{-}DPTTA)_2$ [(−)-**5**] was always prepared *in situ* by the reaction of (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid and CaO in a 10:1 mixture of ethanol and water. The racemic 3-phospholene oxide (**1**) in ethanol, ethyl acetate or acetonitrile was added to the hot ethanolic solution of 0.25 equivalents of $Ca(H\text{-}DBTA)_2$ or $Ca(H\text{-}DPTTA)_2$ [(−)-**4** or (−)-**5**]. The crystalline diastereomers were filtrated off after 24 hours. ^{1}H NMR studies proved, that the composition of the diastereomeric complexes were $Ca(\mathbf{1})_2(H\text{-}DBTA)_2$ or $Ca(\mathbf{1})_2(H\text{-}DPTTA)_2$. These diastereomers [$Ca(\mathbf{1})_2(H\text{-}DBTA)_2$ or $Ca(\mathbf{1})_2(H\text{-}DPTTA)_2$] were purified further by two digestions (i.e., stirring the crystals in the corresponding solvent at 26°C for 24 hours). The 3-phospholene oxide (**1**) was recovered by treating the dichloromethane solution of the

corresponding complex Ca(**1**)$_2$(H-DBTA)$_2$ or Ca(**1**)$_2$(H-DPTTA)$_2$ with 10% aqueous ammonia. The enantiomeric excess of the 3-phospholene enantiomers (**1**) was determined by chiral GC.



* See Tables 2

Scheme 3. General resolution procedure for racemic 3-phospholene oxide (**1**) using Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**4** or (−)-**5**]

In case of the resolutions with Ca(H-DBTA)$_2$ [(−)-**4**], the enantiomer of the 3-phosphospholene oxide (**1**) incorporated in the diastereomeric complex Ca(**1**)$_2$(H-DBTA)$_2$ was dependent on the solvent used. The (*R*)- or the (*S*)-*n*-butyl-3-phospholene 1-oxide [(*R*)-**1** or (*S*)-**1**] could be obtained with Ca(H-DBTA)$_2$ using either a mixture of ethyl acetate and ethanol, or a mixture of acetonitrile and ethanol, respectively (Table 2, Entries 1 and 2).

The highest ee and resolving capability (S) values obtained with Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**4** or (−)-**5**] were 77% and 0.21 after purification by two digestions (Table 2, Entry 4). Considering the resolving capability (S), the application of Ca(H-DPTTA)$_2$ [(−)-**5**] seems to be more advantageous than that of Ca(H-DBTA)$_2$ [(−)-**4**] (Compare Table 2, Entries 1–2 and 3–5).

Compared to the results achieved with the TADDOL-derivatives [(−)-**2** and (−)-**3**], lower ee and resolving capability (S) values could be obtained by using Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**4** or (−)-**5**]. However, the use of the Ca(H-DBTA)$_2$ and Ca(H-DPTTA)$_2$ [(−)-**4** and (−)-**5**] may seem more favourable when the price difference between (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid and the TADDOL-derivatives [(−)-**2** and (−)-**3**] is considered. Moreover, the decomposition of the diastereomeric complexes of the Ca(H-DBTA)$_2$ and Ca(H-DPTTA)$_2$ [(−)-**4** and (−)-**5**] is simpler, than that of the TADDOL-derivatives [(−)-**2** and (−)-**3**] (extraction versus column chromatography).

TABLE 2. Resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with 0.25 equivalent of $Ca(H\text{-}DBTA)_2$ or $Ca(H\text{-}DPTTA)_2$ [(−)-**4** or (−)-**5**]

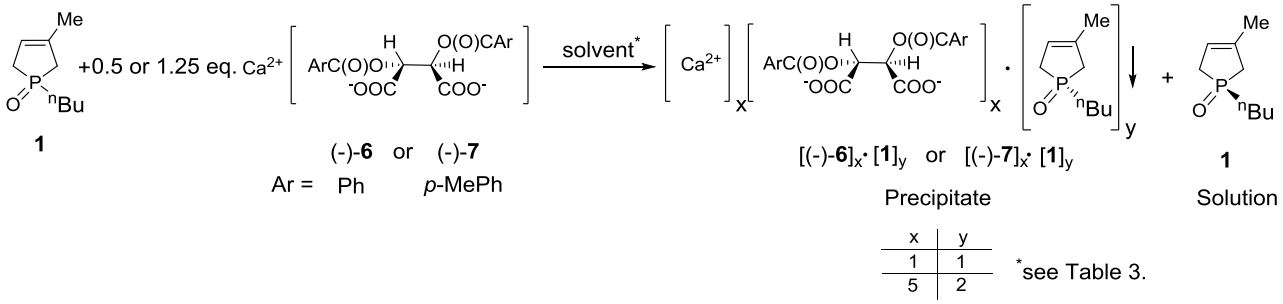
Entry	Resolving agent	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	ee[d,f] (%)	S[e,f] (-)	Abs. Config.[g]
1	$Ca(H\text{-}DBTA)_2$	3×EtOAc/3×EtOH	$Ca(\mathbf{1})_2(H\text{-}DBTA)_2$	(67) **14**	(6) **13**	(0.04) **0.02**	(*R*)
2	$Ca(H\text{-}DBTA)_2$	3×MeCN/3×EtOH	$Ca(\mathbf{1})_2(H\text{-}DBTA)_2$	(72) **21**	(31) **76**	(0.22) **0.16**	(*S*)
3	$Ca(H\text{-}DPTTA)_2$	3×EtOAc/3×EtOH/10%H_2O	$Ca(\mathbf{1})_2(H\text{-}DPTTA)_2$	(68) **44**	(38) **45**	(0.26) **0.20**	(*S*)
4	$Ca(H\text{-}DPTTA)_2$	6×EtOH/10%H_2O	$Ca(\mathbf{1})_2(H\text{-}DPTTA)_2$	(65) **27**	(61) **77**	0.40 **0.21**	(*S*)
5	$Ca(H\text{-}DPTTA)_2$	3×MeCN/3×EtOH/10%H_2O	$Ca(\mathbf{1})_2(H\text{-}DPTTA)_2$	(55) **21**	(38) **62**	(0.21) **0.13**	(*S*)

See Table 1 for footnotes.

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

Based on our earlier study,[34] the resolution of *n*-butyl--3-phospholene oxide (**1**) was also attempted 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**], as these resolving agents have also been found suitable for the resolution of some 3-phosholene oxides. Results of the successful resolutions leading to crystalline diastereomers are summarized in Table 3.

In all instances, the Ca(DBTA) and Ca(DPTTA) [(−)-**6** and (−)-**7**] were prepared *in situ* by the reaction of a 1:1 ratio of CaO and (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid in a mixture of ethanol and water. To this solution was added the racemic 3-phospholene oxide (**1**) in ethanol, ethyl acetate or acetonitrile. The crystalline diastereomeric complexes formed were removed from the mother liquor by filtration after 24 hours. The diastereomers were purified by digestions. In one case, only one purification step was applied, as the corresponding diastereomeric complex may have dissolved completely during the second digestion (Table 3, Entry 1).



Scheme 4. General resolution procedure for racemic 3-phospholene oxide (**1**) using CaDBTA or CaDPTTA [(−)-**6** or (−)-**7**]

The composition of the diastereomeric complexes was determined by ^{1}H NMR. The ratio of the 3-phospholene oxide (**1**) and the CaDBTA or CaDPTTA [(−)-**6** or (−)-**7**] was 1:1 (Table 3, Entries 1 and 2), but diastereomers with a ratio of 2:5 were also formed (Table 3, Entries 3–4). In all instances, the (*S*)-*n*-butyl-3-phospholene oxide [(*S*)-**1**] was obtained by resolution with CaDBTA or CaDPTTA [(−)-**6** and (−)-**7**] (Table 3).

In all but one instances, using CaDBTA and CaDPTTA [(−)-**6** and (−)-**7**], the resolving capability (S) was in the range of 0.02-0.08 after purification (Tables 3), what is lower than the results obtained with the corresponding acidic Ca^{2+} salts [(−)-**4** and (−)-**5**] (Table 2). The difference in the resolving capability (S) may be explained by the lower yields (3–12%) obtained with CaDBTA and CaDPTTA [(−)-**6** and (−)-**7**]. However, among the acidic and the neutral Ca^{2+}-salts of the (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**4** - (−)-**7**], the highest resolving capability (S = 0.36) was obtained during the resolution of *n*-butyl-3-phospholene oxide (**1**) with CaDPTTA in a mixture of ethanol and water (Table 3, Entry 3).

TABLE 3. Resolution of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) with Ca(DBTA) or Ca(DPTTA) [(−)-**6** or (−)-**7**]

Entry	Resolving agent	Eq.	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	ee[d,f] (%)	S[e,f] (-)	Abs. Config.[g]
1	CaDBTA	0.5	3×MeCN/3×EtOH/10%H_2O	Ca(**1**)(DBTA)	(25) **11***	(58) **75***	(0.14) **0.08***	(*S*)
2	CaDPTTA	0.5	3×EtOAc/3×EtOH/10%H_2O	Ca(**1**)(DPTTA)	(41) **12**	(51) **55**	(0.21) **0.07**	(*S*)
3	CaDPTTA	1.25	6×EtOH/10%H_2O	Ca_5(**1**)$_2$(DPTTA)$_5$	(79) **48**	(44) **75**	(0.34) **0.36**	(*S*)
4	CaDPTTA	1.25	3×MeCN/3×EtOH/10%H_2O	Ca_5(**1**)$_2$(DPTTA)$_5$	(80) **3**	(56) **56**	(0.44) **0.02**	(*S*)

See Table 1 for footnotes.
* Diastereomeric complex was purified with one recrystallization.

*Single Crystal X-Ray Analysis of Diastereomeric Complex [(S)-**1**](spiro-TADDOL)*

X-ray quality crystals could only be grown by mixing spiro-TADDOL [(−)-**3**] with a large excess of (*S*)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] in ethyl acetate. The slow evaporation of solvent afforded a single crystal incorporating (*S*)-1-*n*-butyl-3-phospholene 1-oxide [(*S*)-**1**] and spiro-TADDOL [(−)-**3**] in a ratio of 1:1, contrary to the diastereomeric complex [(*S*)-**1**](spiro-TADDOL)$_2$ obtained during the resolution experiments by reacting the 1-*n*-butyl-3-phospholene 1-oxide (**1**) with an equimolar amount of spiro-TADDOL [(−)-**3**] (Table 1, Entry 3).

Results from the crystal structure determination of the **1** : spiro-TADDOL 1:1 molecular associate (Fig. 2) apart from revealing the respective molecular structures as well as absolute configurations of its components also give an insight into the mode of binding and the underlying physical phenomena of molecular recognition. The disordered alkyl tail on the P-heterocycle underlines the possibility of alternating conformations of this moiety. This, apart from an obvious entropic gain for these crystals also indicates that the phospholene rings do have some intrinsic pseudo-rotatory ability. This kind of inherent disorder gives an indication as to the origin of the relative low scattering power of the crystals. The recognition of **1** is apparently facilitated by the H-bridges. These, apart from the expected internal O—H ... O bridge lending some additional stiffness to the spiro-TADDOL backbone bind the phospholene oxide O-acceptor to the remaining OH of the master molecule, another classic recognition motif of the TADDOL - type host molecules.

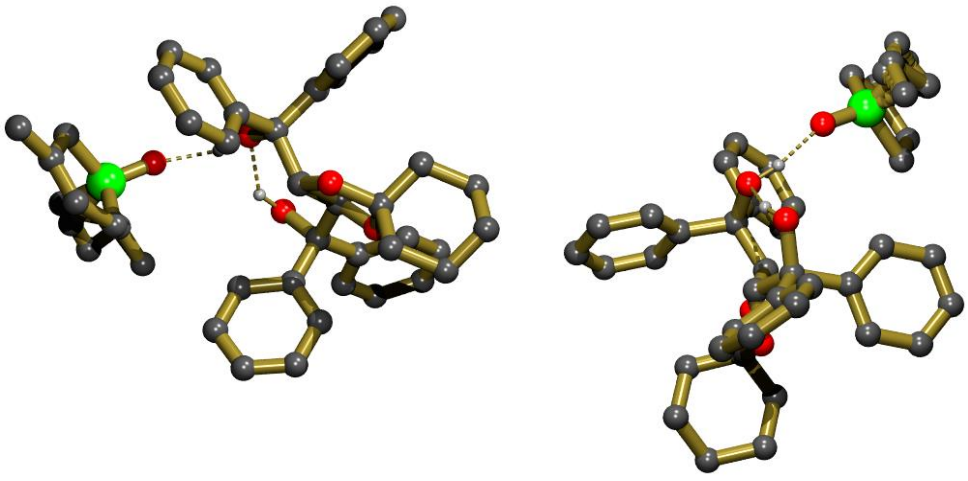


Fig. 2. Perspective view of the crystallographic asymmetric unit of the **1** : spiro-TADDOL 1:1 molecular associate with all H atoms but those involved in O—H ... O hydrogen bridges (shown in broken lines) omitted for the sake of visibility. Disordered atomic positions of *n*-butyl tails are clearly visible at both independent molecules

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

The UV absorption and CD spectra of the 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) were recorded (Table 4) and analyzed. To determine the absolute configuration of the 3-phospholene 1-oxide (**1**), quantum chemical calculations at the density functional theory (DFT) level choosing the PBE0 functional and the 6-311++G** basis set were performed.

TABLE 4. Observed UV and CD spectral bands of 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**)

	UV spectra		CD spectra	
	λ [nm]	ε [$dm^3mol^{-1}cm^{-1}$]	λ [nm]	Δε [$dm^3mol^{-1}cm^{-1}$]
1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**)	191	3200	Negative Cotton effect	
	216 (sh)	1300	215	9.6
			238	–8.3

In our calculations simplified model compounds were considered. We modelled 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) by 1-ethyl-3-methyl-3-phospholene 1-oxide (Fig. 3.). This simplification significantly reduces the computation time, but it is not expected to affect the assignment of absolute configuration because the spectral properties of the compounds in the UV-visible region are almost independent of the substituent. This is well justified by the fact that the measured spectrum was in good agreement with that of the *n*-propyl-substituted derivative available from our previous studies.[31]

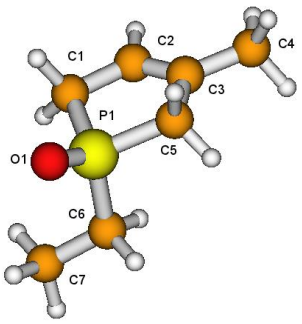
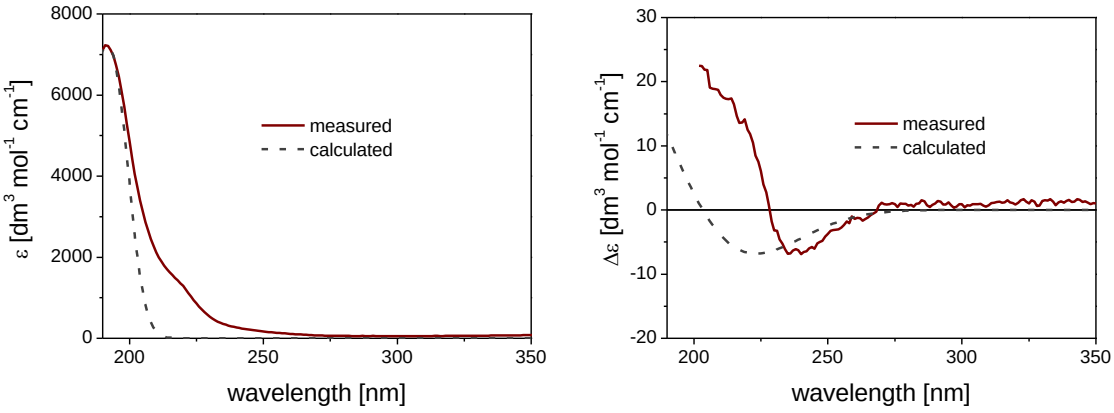


Fig. 3. Optimized geometry for the lowest-energy conformer of 1-ethyl-3-methyl-3-phospholene 1-oxide. Selected bond lengths (Å) and angles (°) are as follows: P1-O1 1.510, P1-C1 1.836, C1-C2 1.501, C2-C3 1.339, C3-C4 1.492, C3-C5 1.508, C5-P1 1.833, P1-C6 1.819; C1-P1-C5 95, O1-P1-C6 114; O1-P1-C6-C7 56, O1-P1-C1-C2 140.

First, a systematic conformation analysis was carried out for the simplified molecule. Three low energy conformers were found for the model compound, which lie at ca. 5 kJ/mol above the most stable one. These conformers were considered in the subsequent calculations. The geometries for all of them were optimized, and excitation energies and the transition moments were calculated. The theoretical UV absorption and CD curves were obtained as superpositions of individual Gaussian functions centered at the wavelengths of the theoretically calculated transitions and having heights proportional to the corresponding calculated oscillator and rotator strengths, respectively. The spectra of the individual conformers were Boltzmann-weighted. The simulated spectra were normalized so that the height of the dominating peak is identical to that of the experimental spectra, beside this, the spectra were shifted to the red so that the position of the most intense band of the absorption spectra be identical.

The optimized geometry and selected geometrical parameters for the most stable conformer are presented in Fig. 3, while the calculated and measured spectra are compared in Fig. 4. The agreement of the experimental and theoretical absorption spectra of the compounds is satisfactory and justifies the selection of the applied theoretical model. The sign of the dominant features in the measured and computed CD spectra are identical, thus the absolute configuration of the synthesized compounds corresponds to that for the isomers considered in the calculations.



(a) (b)

Fig. 4. Calculated (dashed line) UV absorption (a) and CD (b) spectra of (*S*)-1-ethyl-3-methyl-3-phospholene 1-oxide together with the respective measured (solid line) spectra of (−)-1-*n*-butyl-3-methyl-3-phospholene 1-oxide [(−)-**1**] in acetonitrile

The dominant features of the spectra could be assigned on the basis of the theoretical calculations. The intense negative band at 238 nm in the CD spectrum belongs to two close lying transitions, which can be described as excitations from the $\pi_{C=C}$ and n_{oxygen} orbitals to low lying diffuse virtual orbitals. These transitions have low oscillator strengths, but high rotator strengths, leading only to a weak absorption in the UV spectrum at the position of their intense signal in the CD spectrum.

CONCLUSIONS

Resolution procedures were elaborated for 1-*n*-butyl-3-methyl-3-phospholene 1-oxide (**1**) using TADDOL-derivatives [(−)-**2** and (−)-**3**], as well as acidic and neutral Ca^{2+}-salts of the (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**4** - (−)-**7**]. It was investigated how the solvents influence the efficiency of the resolutions. Both antipodes of 1-*n*-butyl-3-phospholene 1-oxide (**1**) were prepared with an ee > 95% by exploiting the different antipode preference of the TADDOL-derivatives [(−)-**2** and (−)-**3**] in different solvents.

The absolute configuration of 3-phospholene oxide enantiomer **1** was determined by X-ray crystallography and CD spectroscopy using quantum chemical calculations for the analysis of the spectra. The X-ray crystallographic measurement allowed us to investigate the interactions between the resolving agent and the 3-phospholene oxides **1,** thus revealing apart from the expected H-bonding scheme, the inherent mobility of these P-heterocycles.

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