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# Constrained cycloalkyl analogues of glutamic acid: stereocontrolled synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) and its 6-phosphonic acid analogue

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

ABSTRACT

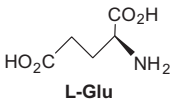
A new stereocontrolled synthesis of (+)-2-aminobicyclo[3.1.0]hexane-2.6-dicarboxylic acid (LY354740) **1**, a potent and selective 2mGluR agonist, has been accomplished in four steps with an overall yield of 27% starting from the enantiopure (+)-(*R*)-2-(*p*-tolylsulfinyl)cyclopent-2-enone **3**. The key steps include asymmetric cyclopropanation of **3** with (dimethylsulfuranylidene)acetate (EDSA) and removal of the chiral *p*-tolylsulfinyl auxiliary from the cycloadduct *ent*-**4c** upon treatment with *iso*-propylmagnesium chloride. The stereoselective hydantoin formation from the bicyclic ketone **6** formed (Bucherer–Bergs reaction) and subsequent hydrolysis completed the synthesis of **1**. The same reaction sequence has been applied in the first synthesis of enantiopure (+)-2-amino-6-phosphonobicyclo[3.0.1]hexane-2-carboxylic acid **2**, a structural 6-phosphono analogue of **1**. The starting bicyclic ketophosphonates **9–11** have been obtained by asymmetric cyclopropanation of (−)-(*S*)-**3** with phosphoryl sulfonium ylides, producing only two *endo*-isomers. The major *endo*-isomer (+)-**11a** containing the 6-diisopropoxyphosphoryl group has been converted in three steps into (+)-*endo*-**2** in 46% overall yield.



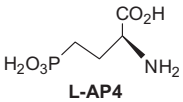
## 1. Introduction

It is now generally agreed that ionotropic (iGluRs) as well as metabotropic (mGluRs) glutamate receptors play an important role in the healthy as well as diseased central nervous system (CNS), and that all subtypes of these receptors are potential targets for therapeutic intervention in a number of diseases. These achievements form the basis of the almost explosive increase of research activities in the excitatory amino acids (EAA) receptor field. A major goal of these molecular biological, physiological, structure/function and medicinal chemistry approaches is to identify subtype-selective EAA receptor ligands. Such compounds capable of activating, blocking or modulating iGluRs or mGluRs are essential pharmacological tools, which may be further developed into therapeutically useful drugs.

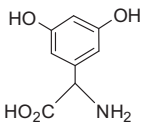
L-Glutamic acid is the principal EAA neurotransmitter in the mammalian CNS,[1] activating two types of EAA receptors: the ion channel-coupled or ionotropic glutamate receptors (iGluRs) and the G-protein coupled or metabotropic glutamate receptors (mGluRs). The mGluRs have been subdivided into three groups on the basis of protein sequence homology, agonist pharmacology and signal transduction mechanisms. Group 1 mGluRs are coupled to phospholipase C and are selectively activated by 3,5-dihydroxyphenylglycine (3,5-DHPG). Group 2 and group 3 mGluRs are negatively coupled to adenylate cyclase. Group 2 mGluRs are selectively activated by (2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate (2*R*,4*R*-APDC), while group 3 mGluRs are selectively activated by L-2-amino-4-phosphonobutanoic acid (L-AP4).



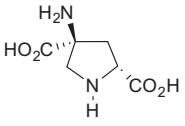
L-Glu



L-AP4



3,5-DHPG



(2*R*,4*R*)-APDC

It has been found that constrained aminoacids can be highly potent and specific agonists since they closely mimic the bioactive conformation of natural neurotransmitters. Thus, 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid **1** (LY354740) is an exceptionally potent agonist for group 2 mGluRs,[2] possessing no activity at other glutamate receptors.[3] Phosphonocyclopropyl aminoacids

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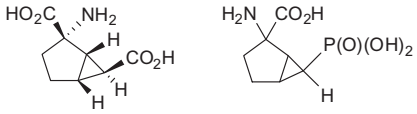
characterized by an appropriate intermediate chain and by the D-configuration at the amino acidic moiety have been found to be competitive antagonists for the NMDA receptor,[4] whereas phosphonocyclopropyl glycine, a conformationally constrained analogue of L-2-amino-4-phosphonobutanoic acid (AP4), has been shown to be a group 3 mGluRs agonist with micromolar activity.[5]

In the course of our studies on biologically active cyclopropane derivatives[6] and aminophosphonic acids,[7] we embarked on a chemical program aimed at the synthesis of conformationally restricted analogues of glutamic acid: (+)-**1** (LY354740) and the structurally related phosphonic acid analogue **2**. We hoped to develop a new asymmetric approach to the first target[8] and to apply it for the first preparation of **2** in enantiomerically pure state.[9] Pursuing our interest in asymmetric cyclopropanation mediated by the chiral sulfinyl group[10–15] we turned our attention to 2-(*p*-tolylsulfinyl)cyclopent-2-enone **3** as a convenient starting material in the synthesis of both target structures. This chiral sulfoxide has been introduced to asymmetric synthesis by Posner[16] and both its enantiomeric forms (−)-(*S*) and (+)-(*R*) can easily be prepared from commercially available (−)-($S_S$)- and (+)-($R_S$)-menthyl *p*-toluenesulfinates. Part of this work has been previously communicated.[17]

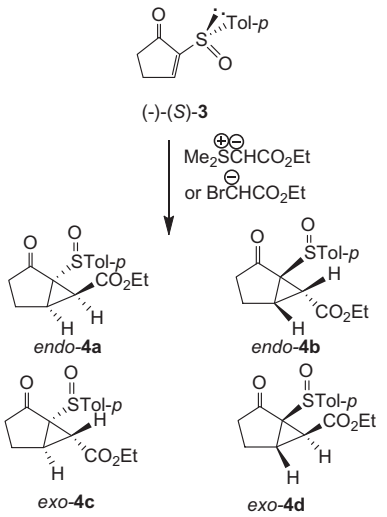



(+)-**1**(LY354740) **2**

## 2. Results and discussion

### 2.1. Asymmetric cyclopropanation of (−)-(*S*)-3 with sulfur ylides and α-bromoacetate carbanion

Previously,[17] it has been found that the reaction of (−)-(*S*)-**3** with ethyl (dimethylsulfuranylidene)acetate (EDSA) occurs effectively and leads to the formation of four diastereomeric cyclopropanation products **4a–d** (Scheme 1). They were separated by column chromatography and fully characterized.




**Scheme 1.** Cyclopropanation of (−)-(*S*)-**3** with EDSA and α-bromoacetate carbanion.

The *endo*/*exo* configuration was assigned to each one of them based on the diagnostic coupling constants between protons at C(5) and C(6) in $^1$H NMR spectra. Moreover, X-ray crystal-structure analysis of *endo*-**4a** revealed that it has the (1*S*,5*R*,6*R*,$S_S$) absolute configuration. This allowed us to attribute absolute configurations to other three diastereomers of **4**. The stereochemical outcome of the cyclopropanation reaction under discussion was rationalized in terms of a nucleophilic attack of EDSA on the non-chelated *s-cis* form of the cyclopentenone sulfoxide (*S*)-**3** from the less-hindered π-face occupied by the sulfur lone electron pair leading to the major diastereomers **4a** and **4c**.

Further investigations showed that the facial and *endo*/*exo* selectivity depends on the nature of the ylide or carbanion component, the base used for ylide generation and to some extent on solvent and reaction temperature. The most interesting observation from this part of our work was that, in contrast to our expectations, the cyclopropanation reaction of (+)-(*S*)-**3** carried out in the presence of $ZnBr_2$ occurred also in a non-chelated mode (Table 1, entries 7 and 8).

An inspection of the above results from the viewpoint of the synthesis of (+)-**1** (LY354740) indicates that the diastereomer *exo*-**4d** having the same absolute configuration for all the three stereogenic carbon atoms should be used for further conversion to (+)-**1**. However, it is formed as the minor isomer in the cyclopropanation reaction of (−) (*S*)-**3**. Therefore, in order to accomplish the efficient synthesis of (+)-**1** the cyclopropanation reaction was performed with the (+)-(*R*)-enantiomer of **3** since the desired diastereomer of **4** is produced here as the major one.

### 2.2. Synthesis of (+)-1 (LY354740)

The details of our synthesis of (+)-**1** are outlined in Scheme 2 and briefly discussed below.

The synthesis commenced with the reaction of the cyclopentenone sulfoxide (+)-(*R*)-**3** with ethyl (dimethylsulfuranylidene)acetate (EDSA). As expected, the cyclopropanation product **4** was obtained as a mixture of four diastereomers from which the major diastereomer *ent-exo*-**4c** was isolated by column chromatography in 56% yield and used for further transformations. The next step involved removal of the chiral *p*-tolylsulfinyl auxiliary. Initially, desulfurization was performed with Raney nickel. However, under the reaction conditions reduction of the carbonyl group also took place affording the corresponding alcohol **5** in 87% yield as a mixture of two diastereomers in a 3:1 ratio. Although alcohol **5** was easily and efficiently oxidized to cyclopentanone **6**, the latter was obtained directly from *ent-exo*-**4c** in the reaction with *iso*-propylmagnesium chloride. Then, introduction of the aminoacid moiety was achieved by Bucherer–Bergs methodology[18] giving rise to a single spirohydantoin **7** in 73% yield. Finally, alkaline hydrolysis of **7** followed by ion exchange chromatography yielded the desired (+)-**1** in 85% yield. Its specific rotation and other spectroscopic data were in excellent agreement with those reported in the literature.[3,18,19] In this way the synthesis of (+)-**1** has been accomplished in four steps with an overall yield of 27% starting from the cyclopentenone sulfoxide (+)-(*R*)-**3**.

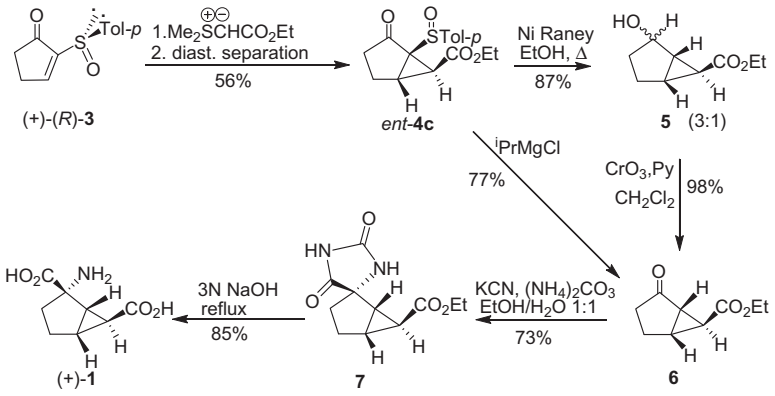
### 2.3. Asymmetric cyclopropanation of (−)-(*S*)-3 with phosphoryl stabilized sulfur ylides

A successful synthesis of (+)-**1** (LY354740) encouraged us to apply the same strategy for the preparation of our second target, that is, optically active bicyclic aminophosphonic acid **2**. According to our strategy, the introduction of the phosphonic acid moiety at C(6) of the bicyclic structure should be accomplished in the cyclopropanation reaction between the cyclopentenone sulfoxide (−)-(*S*)-**3** and sulfur ylides bearing the dialkoxyphosphoryl group. Hence, the phosphoryl containing sulfonium salts **8a–c**, required for generation of the corresponding ylides, were obtained according to Kondo[20] by alkylation of the appropriate α-phosphorylmethyl sulfides in the presence of silver perchlorate. Generally,

**Table 1**
Cyclopropanation of (*S*)-2-(*p*-tolylsulfinyl)cyclopent-2-enone **3** with sulfur ylides and α-bromoacetate carbanion

| Entry | Reagent[a]/conditions | Yield (%) of **4** | Diastereomer ratio | | | | Selectivity | |
|---|---|---|---|---|---|---|---|---|
| | | | *endo*-**4a** | *endo*-**4b** | *exo*-**4c** | *exo*-**4d** | π-Facial | *endo*/*exo* |
| 1 | $Me_2S^{\oplus}$–$C^{\ominus}HCO_2Et/CH_2Cl_2$ | 72 | 31 | 7 | 50 | 12 | 81/19 | 38/62 |
| 2 | $(Me_2S^{\oplus}$–$CH_2CO_2Et)Br^{\ominus}$/DBU/$CH_2Cl_2$ | 83 | 29 | 5 | 56 | 10 | 85/15 | 34/66 |
| 3 | $(Me_2S^{\oplus}$–$CH_2CO_2Et)Br^{\ominus}$/DBU/$CH_2Cl_2$/$ZnBr_2$[b] | 70 | 26 | 8 | 53 | 13 | 79/21 | 34/66 |
| 4 | $(Me_2S^{\oplus}$–$CH_2CO_2Et)Br^{\ominus}$/DBU/THF/$ZnBr_2$[b] | 80 | 26.5 | 7 | 52.5 | 14 | 79/21 | 33.5/66.5 |
| 5 | $(Ph_2S^{\oplus}$–$CH_2CO_2Et)BF_4^{\ominus}$/DBU/$CH_2Cl_2$ | 73 | 46 | 42 | 9 | 3 | 55/45 | 88/12 |
| 6 | $BrCH_2CO_2Et$/LDA/THF[c] | 66 | 85.5 | 5 | 7.5 | 2 | 93/7 | 90.5/9.5 |
| 7 | $BrCH_2CO_2Et$/LDA/THF/$ZnBr_2$[b,c] | 78 | 85 | 4 | 8 | 3 | 93/7 | 89/11 |
| 8 | $BrCH_2CO_2Et$/LDA/THF/$ZnBr_2$[c,d] | 75 | 85.5 | 4 | 7.5 | 3 | 93/7 | 89.5/10.5 |

[a] A 1.1 equimolar excess of ylide or α-bromo carbanion in respect to (*S*)-**3** was used.
[b] Equimolar amounts of zinc bromide were used.
[c] The carbanion of α-bromoacetate was generated at −78 °C with LDA and then added to (*S*)-**3** at this temperature.
[d] Two equimolar amounts of zinc bromide were used.




**Scheme 2.** Synthesis of (+)-**1** (LY354740).

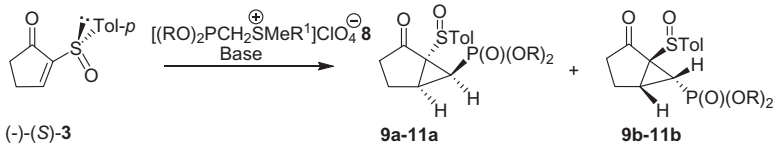
the cyclopropanation reaction was carried out by mixing (−)-(*S*)-**3**, the appropriate sulfonium salts **8a–c** and the base (DBU, $K_2CO_3$) in a methylene chloride solution and stirring at room temperature for ca. 12 h. Under these conditions the slowly generated ylides reacted in situ with the sulfoxide **3** to give the corresponding bicyclic products **9**–**11** (Scheme 3).

When (−)-(*S*)-**3** was reacted with (dimethoxyphosphorylmethyl)dimethyl sulfonium perchlorate **8a** in the presence of DBU, the cyclopropanation product **9** was obtained as a mixture of only two diastereomers **9a** and **9b** (4:1 ratio) inseparable by column chromatography. However, they were separated by HPLC and fully characterized. Based on the coupling constants between protons at C(5) and C(6) ($^3J$ = 9.4 Hz) in $^1$H NMR spectra and Overhauser effect (5.1% and 3.5% for major and minor isomer, respectively), the *endo* configuration was assigned to both diastereomers of **9**. By making a reasonable assumption that the cyclopropanation reaction occurs here in a non-chelated mode, the (1*R*,5*R*,6*S*,$S_S$) absolute configuration can tentatively be ascribed to the major diastereomer **9a**.

Due to some problems with separation of diastereomeric **9** and low diastereoselectivity, the cyclopropanation was performed using the salt **8b** with the more bulky 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanyl moiety. In this case, the reaction was highly stereoselective affording also two *endo* diastereomers **10a** and **10b** (10:1 ratio) which were separated by simple column chromatography though with a rather low yield. The crystals of the minor isomer **10b** were suitable for X-ray structure determination and its absolute stereochemistry was established as (1*S*,5*S*,6*R*,$S_S$) (Fig. 1).

With the sulfonium salt **8c** as a source of the corresponding ylide, the cyclopropanation of (−)-(*S*)-**3** resulted in the formation of the diastereomeric cyclopropanes **11a** and **11b**, however, with a lower diastereoselectivity (3:1). Their $^1$H NMR spectra and X-ray crystal-structure analysis of the major isomer **11a** (Fig. 2) confirmed the *endo* configuration of both isomers and the (1*S*,5*S*,6*R*,$S_S$) absolute configuration of the latter.

With regard to the stereochemical course of cyclopropanation of (−)-(*S*)-**3** with phosphoryl stabilized sulfonium ylides, it should




| | | | |
|---|---|---|---|
| **8a:** | $R^1$=Me R= Me | 4 / 1 | 96% (a+b) |
| **8b:** | $R^1$=Tol-*p* R= $Me_2C(CH_2)_2$ | 10 / 1 | 95% (a+b) |
| **8c:** | $R^1$=Me R=$^i$Pr | 3 / 1 | 96% (a+b) |

**Scheme 3.** Cyclopropanation of (−)-(*S*)-**3** with phosphoryl sulfonium ylides.

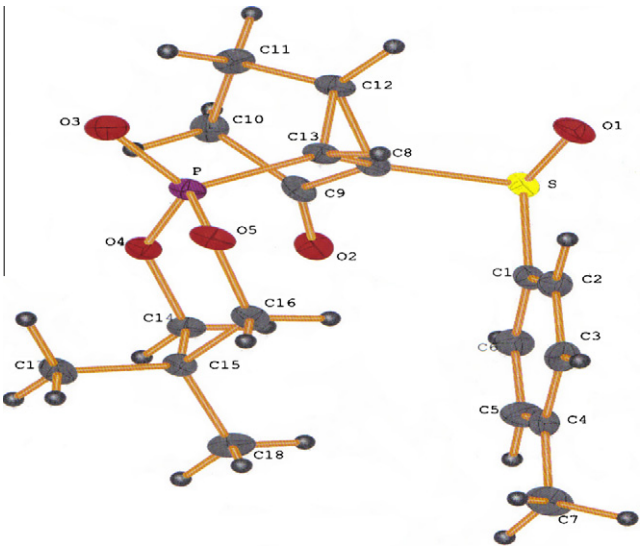



**Figure 1.** X-ray structure of **10b** (minor isomer). Thermal ellipsoids are shown at the 50% probability level.

be pointed out that there is an analogy with that of EDSA. With ylides **8** the reaction occurs via the non-chelated s-*cis* form of the cyclopentenone sulfoxide (*S*)-**3** and the nucleophilic ylide is preferentially approaching from the less hindered π-face occupied by the lone electron pair at sulfur. The most probable structure of the transition state (see below, **a**) of this initial addition step may be

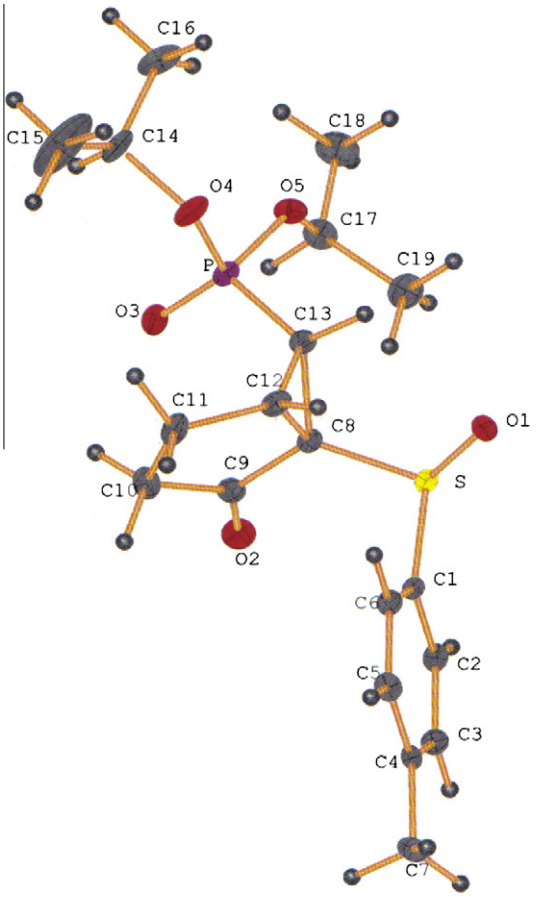
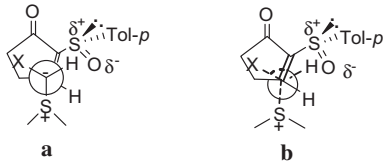



**Figure 2.** X-ray structure of **11a** (major isomer). Thermal elipsoids are shown at the 50% probability level.

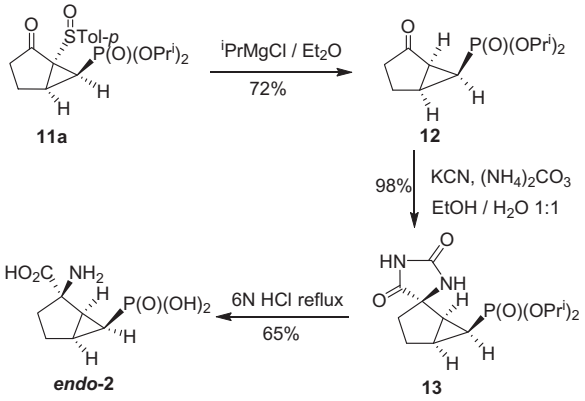
stabilized by a dipole–dipole interaction involving the S=O and ylidic C–S bonds.




Due to repulsive interactions between the *trans*-oriented very bulky tetrahedral dialkoxyphosphoryl group and the sulfinyl moiety at C(2), the addition reaction and the subsequent fast ring closure results in an exclusive formation of the *endo*-isomers **9a**–**11a**. Similarly, the minor *endo*-isomers **9b**–**11b** are formed by addition of the sulfonium ylide from the less favoured diastereotopic π-face of (*S*)-**3** (via transition state **b**) followed by cyclization. In this way the chiral sulfinyl group at C(2) not only controls facial selectivity but is also responsible for a full *endo* selectivity.

### 2.4. Synthesis of (+)-2-amino-2-carboxybicyclo[3.1.0]hexane-2-phosphonic acid 2

Having in hand diastereomerically pure bicyclic phosphonates **9**–**11,** we could execute the synthesis of optically active bicyclic aminophosphonic acid **2** in a similar reaction sequence as that designed for the synthesis of (+)-**1**. It involved three steps: removal of the chiral sulfinyl moiety (desulfurization), spirohydantoin formation and hydrolysis. Initially, the desulfurization was carried out with the phosphonate *endo*-**10a** which is preferentially formed in the reaction between (−)-(*S*)-**3** and the sulfonium ylide generated from the salt **8b**. However, the reaction was accompanied by the formation of many side products and the yield of the sulfur-free product was very low. Therefore, the phosphonate *endo*-**11a** was used as a substrate for the conversion into **2** (Scheme 4).




**Scheme 4.** Synthesis of bicyclic aminophosphonic acid (+)-*endo*-**2**.

The sulfinyl group was efficiently removed from *endo*-**11a** by treatment with iso-propylmagnesium chloride and the bicyclic phosphonate **12** formed was subjected to Bucherer–Bergs reaction. It afforded a single spirohydantoin **13** in almost quantitative yield. The (*R*) configuration of the newly created stereogenic centre at C(2) in **13** is a result of an approach of the cyanide anion to the carbonyl group from the less sterically hindered face that is not occupied by the bulky tetrahedral diisopropoxyphosphoryl moiety (steric approach control). Acidic hydrolysis of **13** afforded fully deprotected enantiopure bicyclic aminophosphonic acid (+)-*endo*-**2**. In this context, it is interesting to point out that the literature records only the synthesis of racemic *exo*-**2**. Hence, we report herein the first approach to enantiomeric bicyclic aminophosphonic acids **2**.

## 3. Summary

A new, four step stereocontrolled synthesis of (+)-2-aminobicyclo[3.0.1]hexane-2,6-dicarboxylic acid **1**(LY354740) has been developed. The key step included asymmetric cyclopropanation of the easily available (+)-(*R*)-2-(*p*-tolylsulfinyl)cyclopent-2-enone with (dimethylsulfuranylidene)acetate (EDSA). The appropriate diastereomer formed in this reaction was converted into (+)-**1** in three steps involving desulfurization, stereoselective hydantoin formation and hydrolysis. By the same strategy (+)-(2-amino-2-carboxy)bicyclo[3.1.0]hexane-6-phosphonic acid **2**, a structural phosphonic analogue of **1**, has been prepared. The starting 6-phosphoryl containing bicyclic substrates *endo*-**9**–**11** were obtained in the cyclopropanation reaction between cyclopentenone sulfoxide (−)-(*S*)-**3** and α-phosphoryl stabilized sulfonium ylides. The described stereocontrolled synthesis of enantiomeric **1** and **2** has a general character and may be applied in the synthesis of other structurally related cyclopropanes.

## 4. Experimental

### 4.1. General

$^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded on a Bruker MSL 300 and Bruker AC 200 Spectrometer using deuterochloroform as a solvent. Mass spectra were recorded on Finnigan MAT95. IR spectra were recorded on a Ati Mattson FTIR Spectrometer. The optical rotations were measured on a Perkin–Elmer 241 MC photopolarimeter at 20 °C. The microanalyses were performed on an Elemental Analyzer EA 1108. TLC was carried out on silica gel plates (Merck F254) and Silica Gel 60 (70–230 ASTM) was used for chromatography. THF was freshly distilled over potassium/benzophenone.

### 4.2. Cyclopropanation of (−)-(*S*)-2-(*p*-tolylsulfinyl)cyclopent-2-enone 3

Cyclopropanation was performed using 440 mg (2 mmol) of (−)-(*S*)-**3**, $[\alpha]_D = -142$ (*c* 2.5, acetone) and the appropriate reagent. Purification and diastereomer separation were done by column chromatography.

**A**. 2.2 mmol of ethyl (dimethylsulfuranylidene)acetate was generated prior to the reaction which was performed in $CH_2Cl_2$ (10 mL) at 0 °C for 1 h. After solvent evaporation the crude product **4** was purified by chromatography (diethyl ether/petroleum ether, 4:1); yield 72%.

**B**. 2.2 mmol of (ethoxycarbonylmethyl)dimethyl sulfonium bromide and 2.2 mmol of DBU in $CH_2Cl_2$ (10 mL) were stirred overnight; yield 83%.

**C**. 2.2 mmol of (ethoxycarbonylmethyl)dimethyl sulfonium bromide and 2.2 mmol of DBU were added to a solution of (−)-(*S*)-**3** containing 2.1 mmol of $ZnBr_2$; the reaction was performed in $CH_2Cl_2$ (20 mL) for 12 h; yield 70%.

**D**. 2.2 mmol of (ethoxycarbonylmethyl)dimethyl sulfonium bromide and 2.2 mmol of DBU were added to the solution of (*S*)-(*p*-tolylsulfinyl)-2-cyclopentenone **1** containing 2.1 mmol of $ZnBr_2$; the reaction was performed in THF (20 mL) for 12 h; yield 80%.

**E**. 2.2 mmol of diphenyl(ethoxycarbonylmethyl)sulfonium tetrafluoroborate and 2.2 mmol of DBU in $CH_2Cl_2$ (10 mL) were stirred with (−)-(*S*)-**3** overnight. Solvent evaporation afforded the crude product **4**; yield 73%.

**F**. The carbanion of ethyl bromoacetate generated by the addition of LDA (2.3 mmol) was added to (−)-(*S*)-**3** in THF (20 mL) at −78 °C. After 3 h of stirring at −78 °C, the reaction mixture was allowed to warm up to 0 °C and quenched with aq $NH_4Cl$. Extraction with $CHCl_3$ (2 × 20 mL) afforded the crude product **4**; yield 66%.

**G**. The carbanion generated as above was added to a solution of (−)-(*S*)-**3** containing 2.1 mmol of $ZnBr_2$ in THF (20 mL); yield of **4** was 78%.

#### 4.2.1. (1*S*,5*R*,6*R*,$S_S$)-1-(*p*-Tolylsulfinyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate *endo*-4a

*endo*-**4a**: (1.5 g, 29%) $[\alpha]_D^{20} = +31.3$ (*c* 4.7, acetone). IR (KBr): 2982, 1731, 1192, 1049. $^1$H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.1 Hz), 1.88–2.05 (m, 3H), 2.40 (s, 3H, $C_6H_4CH_3$), 2.36–2.51 (m, 1H), 2.77 (dd, 1H, *J* = 3.5, 9.3 Hz), 2.99 (d, 1H, *J* = 9.3 Hz), 4.19 (2q, 2H, $OCH_2CH_3$, *J* = 7.2 Hz), 7.28 and 7.48 (AA′BB′, 4H, $C_6H_4CH_3$); (200 MHz, $C_6D_6$): δ 0.89 (t, 3H, *J* = 7.1 Hz), 1.22–1.35 (m, 1H), 1.53–1.68 (m, 2H), 1.91 (s, 3H, $C_6H_4CH_3$), 2.48 (ddd, 1H, *J* = 0.7, 6.8, 9.3 Hz), 3.15 (d, 1H, *J* = 9.2 Hz), 3.72 (q, 1H, *J* = 7.1 Hz), 3.74 (q, 1H, $OCH_2CH_3$, *J* = 7.1 Hz), 7.00 and 7.55 (AA′BB′, 4H, $C_6H_4CH_3$).

#### 4.2.2. (1*S*,5*R*,6*S*,$S_S$)-1-(*p*-Tolylsulfinyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate *exo*-4c

*exo*-**4c**: (2.84 g, 56%) $[\alpha]_D^{20} = +22.9$ (*c* 2.1, acetone); IR (film): 2955, 1737, 1197, 1052. $^1$H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.1 Hz), 2.05–2.33 (m, 4H), 2.39 (s, 3H, $C_6H_4CH_3$), 2.46 (d, 1H, *J* = 4.8 Hz), 3.32 (m, 1H), 4.22 (q, 2H, $OCH_2CH_3$, *J* = 7.2 Hz), 7.28 and 7.58 (AA′BB′, 4H, $C_6H_4CH_3$); (200 MHz, $C_6D_6$): δ 1.02 (t, 3H, *J* = 7.2 Hz), 1.03–1.56 (m, 4H), 1.77 (d, 1H, *J* = 4.9 Hz), 1.93 (s, 3H, $C_6H_4CH_3$), 3.00 (t, 1H, *J* = 4.9 Hz), 4.01, 4.05 (2xq, 2H, $OCH_2CH_3$, *J* = 7.2 Hz), 6.93 and 7.85 (AA′BB′, 4H, $C_6H_4CH_3$); Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92. Found: C, 62.59; H, 6.01.

#### 4.2.3. (1*R*,5*S*,6*R*,$S_S$)-1-(*p*-Tolylsulfinyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate *exo*-4d

*exo*-**4d**: Mp 165–167 °C, $[\alpha]_D^{20} = +106.2$ (*c* 1.5, acetone). $^1$H NMR (200 MHz, $CDCl_3$): δ 1.26 (t, 3H, $OCH_2CH_3$, *J* = 7.1 Hz), 2.02–2.10 (br s, $4H_\Delta$), 2.39 (s, 3H, $C_6H_4CH_3$), 2.46 (d, 1H, *J* = 4.8 Hz), 3.20 (br s, 1H, C*H*), 4.02–4.20 (m, 2H, $OCH_2CH_3$), 7.29 and 7.57 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): δ 13.9, 20.8, 21.3, 31.4, 33.2, 33.5, 56.9, 62.1, 124.4, 129.6, 138.6, 141.0, 166.3, 204.7. HRMS: calcd for $C_{16}H_{18}O_4S$: 306.0924. Found 306.0926.

### 4.3. Cyclopropanation of (+)-(*R*)-(*p*-tolylsulfinyl)cyclopent-2-enone 3

To a mixture of (ethoxycarbonylmethyl)dimethyl sulfonium bromide (2.5 g, 11 mmol) and DBU (1.7 mL, 11 mmol) in $CH_2Cl_2$ (50 mL) (+)-(*R*)-**3** (2.2 g, 10 mmol) was slowly added. The reaction mixture was stirred for 12 h and solvent evaporated. The crude product as a mixture of four diastereomers was purified by column chromatography (diethyl ether/petroleum ether 4:1) and the *exo* isomers were separated.

#### 4.3.1. (1*R*,5*S*,6*R*,$R_S$)-1-(*p*-Tolylsulfinyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate *ent*-4c

*ent*-**4c**: 2.84 g (56%), white needles (recrystallization from $Et_2O$), mp 83–84 °C, $[\alpha]_D^{20} = -24.0$ (*c* 3.0, acetone). IR (KBr): 3029, 2927, 1735, 1726, 1196. $^1$H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.1 Hz), 1.99–2.36 (m, $5H_D$), 2.39 (s, 3H, $C_6H_4CH_3$), 3.32 (br s, 1H, C*H*), 4.22 (q, 2H, $OCH_2CH_3$, *J* = 7.1 Hz), 7.28 and 7.60 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): δ 14.0, 20.5, 21.4, 32.3, 33.2, 33.7, 55.4, 62.1, 125.3, 129.4, 138.4, 141.5, 166.5, 203.6. HRMS: calcd for $C_{16}H_{18}O_4S$ 306.0924. Found 306.0926.

#### 4.3.2. (1*S*,5*R*,6*S*,$R_S$)-1-(*p*-Tolylsulfinyl)-2-oxobicyclo[3.1.0]hexane-6-carboxylate *ent*-4d

0.51 g, (10%), white plates (recrystallization from hexane–ethanol, 20:1), mp 166–167 °C, $[\alpha]_D^{20} = -105.9$ (*c* 2.0, acetone). $^1$H NMR

(200 MHz, $CDCl_3$): $\delta$ 1.26 (t, 3H, $OCH_2CH_3$, $J$ = 7.1 Hz), 2.02–2.10 (br s, $4H_A$), 2.39 (s, 3H, $C_6H_4CH_3$), 2.46 (d, 1H, $J$ = 4.8 Hz), 3.20 (br s, 1H, C*H*), 4.02–4.20 (m, 2H, $OCH_2CH_3$), 7.29 and 7.57 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 13.9, 20.8, 21.3, 31.4, 33.2, 33.5, 56.9, 62.1, 124.4, 129.6, 138.6, 141.0, 166.3, 204.7. HRMS: calcd for $C_{16}H_{18}O_4S$ 306.0924. Found 306.0926.

### 4.4. 2-Hydroxy-bicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester 5

To 0.8 g (2.6 mmol) of *ent*-**4c** dissolved in EtOH (50 mL) 2 equiv of Raney nickel (freshly prepared from aluminium–nickel alloy) dissolved in dry ethanol were added portionwise. The reaction mixture was heated at 60 °C until the starting material disappeared on TLC. Then, the reaction solution was stirred for 36 h, filtered through a mixture of Celite and silica (1:1) and the precipitate was washed with ethanol. The solvent was evaporated affording the crude product **5** as a mixture of two isomers in a 3:1 ratio. Purification by column chromatography (petroleum ether/ethanol 10:1) without the separation of isomers gave 380 mg (87%) of pure **5** as a yellow oil, $[\alpha]_D^{20}$ = −19.8 (*c* 3.0, acetone). IR (KBr): 3450, 2927, 1726, 1198. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.98–1.13 (m, 1H), 1.24 (t, 3H, $OCH_2CH_3$, $J$ = 7.1 Hz), 1.66–2.43 (m, 7H), 4.10 (q, 2H, $OCH_2CH_3$, $J$ = 7.1 Hz), 4.19–4.36 (m, 1/4H, *H*–C–OH), 4.55–4.65 (m, 3/4H, *H*–C–OH). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 12.9, 18.0, 23.5, 24.1, 26.3, 27.5, 28.7, 32.0, 33.3, 34.1, 39.4, 40.4, 58.9, 59.2, 72.2, 72.6, 172.2, 172.3. HRMS: calcd for $C_9H_{14}O_3$ 170.0942. Found 170.0943.

### 4.5. Ethyl (1*S*,5*R*,6*S*)-Bicyclo[3.1.0]hexan-2-one-6-carboxylate 6

To a solution of the ester **5** (340 mg, 2 mmol) in $CH_2Cl_2$ (30 mL) were added 2 equiv of a complex ($CrO_3$/pyridine) and the reaction mixture was stirred until the reaction was judged complete by TLC. Then, a reaction solution was filtered through Celite and purified by column chromatography (acetone/petroleum ether 1:30). The product obtained was crystallized from diethyl ether to give 333 mg (98%) of **6** as white cubes (recrystallization from pentane–ethanol, 20:1), mp 64–65 °C, $[\alpha]_D^{20}$ = +64.2 (*c* 1.5, MeOH). IR (film): 2927, 1736, 1731, 1186. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.26 (t, 3H, $OCH_2CH_3$, $J$ = 7.1 Hz), 1.98–2.34 (m, 6H), 2.34–2.54 (m, 1H), 4.15 (q, 2H, $OCH_2CH_3$, $J$ = 7.1 Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 14.2, 22.5, 26.5, 29.2, 31.9, 35.8, 61.3, 170.4, 211.8. HRMS: calcd for $C_9H_{14}O_3$ 168.0782. Found 168.0786.

To a solution of the freshly prepared Grignard reagent from isopropyl chloride (1.97 g, 25 mmol) and magnesium (0.6 g, 25 mmol) in dry diethyl ether (100 mL) *ent*-**4c** (0.805 g, 2.63 mmol) was added at room temperature. The reaction mixture was stirred for 3 h and quenched with an aqeous solution of ammonium chloride. The organic layer was separated and the water phase was extracted with $CH_2Cl_2$ (5 × 15 mL). The combined organic layers were dried and evaporated in vacuum. The crude product was purified by column chromatography on silica gel using acetone/petroleum ether (1:30) as an eluent to give the white crystalline product **6**, 340 mg (77%). Mp 64–65 °C $[\alpha]_D^{20}$ = 64.0 (*c* 1.9, methanol).

### 4.6. (1*S*,2*S*,5*R*,6*S*)-Ethyl 2-spirohydantoin-bicyclo[3.1.0]hexane-6-carboxylate 7

A mixture containing 270 mg (1.6 mmol) of **4**, 119 mg (1.8 mmol) of KCN and 173 mg, (1.8 mmol) of $(NH_4)_2CO_3$ in EtOH (30 mL) and $H_2O$ (30 mL) was stirred at 35 °C for 15 h. The reaction mixture was cooled to 0 °C and $H_2O$ was added. After 3 h at 0 °C the precipitate was isolated by filtration and dried to give **7** as white plates (280 mg, 73%) (recrystallization from EtOH), mp 219–221 °C, $[\alpha]_D^{20}$ = −24 (*c* 2.0, MeOH). IR (KBr): 3209, 2961, 1780, 1755, 1413. $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 1.17 (t, 3H, $OCH_2CH_3$, $J$ = 7.1 Hz), 1.17–1.49 (m, 2H), 1.50–2.23 (m, 5H), 4.04 (q, 2H, $OCH_2CH_3$, $J$ = 7.1 Hz), 8.13 (s, 1H, N–*H*), 10.57 (s, 1H, N–H). $^{13}$C NMR (50 MHz, DMSO-$d_6$): $\delta$ 14.06, 20.1, 25.6, 27.5, 29.5, 33.3, 60.1, 68.7, 171.9, 179.5. HRMS: calcd for $C_9H_{14}O_3$ 238.0956. Found 238.0954.

### 4.7. (1*S*,2*S*,5*R*,6*S*)-2-Amino-bicyclo[3.1.0]hexane-2, 6-dicarboxylic acid 1

A mixture containing hydantoin **7** (150 mg, 0.63 mmol) and 3 N NaOH (5 mL) was refluxed for 28 h. Then, the solution was cooled to room temperature, filtered and acidified to pH 3.0 with concentrated HCl. The reaction mixture was stirred for 1 h at room temperature and for 2 h at 0 °C. Then water was evaporated and the product **1** was purified by ion exchange resin (Amberlyst A-21 and Dowex 50W) to give 100 mg of **5** (85%) as a white powder, mp 270–271 °C, $[\alpha]_D^{20}$ = +37.1 (*c* 1.7, 0.1 N HCl). $^1$H NMR (200 MHz, $D_2O$ + KOD): $\delta$ 1.37–1.68 (m, 2H), 1.70–2.35 (m, 8H), 2.55–2.72 (m, 1H). $^{13}$C NMR (50 MHz, $D_2O$ + KOD): $\delta$ 25.01, 27.5, 29.5, 31.3, 33.3, 67.8, 176.5, 180.2. Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99. Found: C, 51.62; H, 6.09.

### 4.8. Cyclopropanation of (−)-(*S*)-(*p*-tolylsulfinyl)cyclopent-2-enone 3 with phosphorus stabilized sulfonium ylides

#### 4.8.1. 1-(*p*-Tolylsulfinyl)-6-(dimethoxyphosphoryl)bicyclo-[3.1.0]hexan-2-one 9

To a mixture of (dimethoxyphosphorylmethyl)dimethyl sulfonium perchlorate (2.5 g, 11 mmol) and DBU (1.7 mL, 11 mmol) in $CH_2Cl_2$ (50 mL) 2.2 g (10 mmol) of (−)-(*S*)-**3** (2.2 g, 10 mmol) was slowly added. The reaction mixture was allowed to stir for 12 h and then $H_2O$ (20 mL) was added. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuum. The crude product was obtained as a mixture of two *endo* isomers in a 4:1 ratio. Column chromatography (hexane/acetone, 12:1) afforded pure **9** as a colourless oil, 2.32 g (96%). The isomers **9a** and **9b** were separated by HPLC (isopropanol–hexane, 1:15).

**4.8.1.1. Major *endo*-(1R,5R,6S,$S_S$)-9a.** $[\alpha]_D^{20}$ = 56.4 (*c* 2.2, acetone). $^{31}$P NMR (81 MHz, $CDCl_3$): $\delta$ 23.4. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.95–1.87 (m, 1H), 2.03 (ddd, $1H_D$, $J$ = 3.6, 11.6, 19.5 Hz), 2.22 (dd, 1H, $J$ = 3.6, 9.2 Hz), 2.25 (d, 1H, $J$ = 9.5 Hz), 2.39 (s, 3H, $C_6H_4CH_3$), 2.68 (dd, 1H, $J$ = 6.2, 9.2 Hz), 2.74–2.68 (m, 1H), 3.74 (d, 3H, $OCH_3$, $J$ = 8.0 Hz), 3.79 (d, 3H, $OCH_3$, $J$ = 8.0 Hz), 7.28 and 7.47 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 19.0, 21.4, 23.4 (d, $J$ = 190 Hz), 30.1, 38.6, 52.8, 60.4, 124.6, 129.9, 138.6, 142.5, 208.1. Anal. Calcd for $C_{15}H_{19}O_5PS$: C, 52.63; H, 5.59; S 9.36. Found: C, 52.71; H, 5.68; S 9.17.

**4.8.1.2. Minor *endo*-(1S,5S,6R,$S_S$)-9b.** $[\alpha]_D^{20}$ = −11.9 (*c* 2.0, acetone). $^{31}$P NMR (81 MHz, $CDCl_3$): $\delta$ 22.8. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 2.09 (d, 1H, $J$ = 9.5 Hz), 2.37–2.27 (m, $2H_D$), 2.39 (s, 3H, $C_6H_4CH_3$), 2.55 (ddd, 1H, $J$ = 3.7, 10.6, 19.5 Hz), 2.96- 2.89 (m, 2H), 3.05 (d, 3H, $OCH_3$, $J$ = 11.0 Hz), 3.61 (d, 3H, $OCH_3$, $J$ = 11.0 Hz), 7.32 and 7.72 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 19.0 (d, $J$ = 126 Hz), 19.3, 21.3, 35.2, 38.6, 52.3, 58.4, 124.4, 129.6, 139.2, 141.9, 207.6. HRMS: calcd for $C_{15}H_{19}O_5PS$ 342.0690. Found 342.0692.

#### 4.8.2. (*S*)-1-(*p*-Tolylsulfinyl)-6-[5,5-dimethyl-2-oxo-2-(1,3,2)-dioxaphosphorinanyl]bicyclo[3.1.0]hexan-2-one 10

Reaction of 190 mg (0.5 mmol) of (5,5-dimethyl-2-oxo-2λ5-[1,3.2]-dioxaphosphinan methylene)dimethyl sulfonium perchlorate and 110 mg (0.5 mmol) of 2-[(*S*)-(4-methylphenyl)sulfinyl]cyclopenten-2-one according to procedure A gave the desired product **8** as a mixture of two *endo*-isomer in a ratio of 10:1.

Purification by column chromatography allowed the separation of both isomers.

**4.8.2.1. (1*R*,5*R*,6*S*,$S_S$) 1-(*p*-Tolylsulfinyl)-6-[5,5-dimethyl-2-oxo-(1,3,2)dioxaphosphorinanyl] (*p*-tolylsulfinyl)bicyclo(3.1.0)hexan-2-one 10a.** The major isomer (68 mg, 31% yield), white needles (recrystallization from $Et_2O$), mp = 153–154 °C; $[\alpha]_D^{20}$ = +64.8 (*c* 3.2, acetone). $^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta$ 13.8. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.20 (s, 3H, $CH_3$), 1.01 (s, 3H, $CH_3$), 1.92 (dt, $1H_D$, *J* = 6.5, 13.0 Hz), 2.26–2.10 (m, 2H), 2.39 (s, 3H, $C_6H_4CH_3$), 2.55–2.35 (m, 2H), 2.91–2.61 (m, 2H), 4.25–3.87 (m, 4H, $OCH_2$), 7.30 and 7.47 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 17.8 (d, *J* = 103 Hz), 19.4, 20.5, 21.3, 32.1, 35.7, 37.8, 58.8 (d, *J* = 4 Hz), 124.8, 129.8, 139.3, 141.8, 207.4 (d, *J* = 3.2 Hz). Anal. Calcd for $C_{18}H_{23}O_5PS$: C, 56.64; H, 6.06; S, 8.38. Found: C, 56.62; H, 6.18; S, 8.22.

**4.8.2.2. (1*S*,5*S*,6*R*,$S_S$) 1-(*p*-Tolylsulfinyl)-6-[5,5-dimethyl-2-oxo-2-(1,3,2)dioxaphosphorinanyl]bicyclo[3.1.0]hexan-2-one 10b.** The minor isomer 7 mg, 3% yield, white needles (recrystallization from $C_6H_6$), mp 141–142 °C. $[\alpha]_D^{20}$ = 58 (*c* 2.2, acetone). $^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta$ 14.3. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.63 (s, 3H, $CH_3$),1.01 (s, 3H, $CH_3$), 2.13 (d, $1H_D$, *J* = 9.4 Hz), 2.69–2.10 (m, 3H), 2.38 (s, 3H, $C_6H_4CH_3$), 3.41–2.81 (m, 2H), 3.65–3.44 (m, 3H, $OCH_2$), 3.95–3.81 (m, 1H, $OCH_2$), 7.32 and 7.76 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 17.8 (d, *J* = 186 Hz), 19.3, 20.5, 21.3, 32.1 (d, *J* = 7.5 Hz), 35.7 (d, *J* = 3.5 Hz), 37.9, 58.8 (d, *J* = 4.1 Hz), 75.9, 124.8, 129.8, 139.3, 141.8, 207.4 (d, *J* = 3.2 Hz). Anal. Calcd for $C_{18}H_{23}O_5PS$: C, 56.62; H, 6.06. Found: C, 56.78; H, 6.32.

**4.8.3. 1-(*p*-Tolylsulfinyl)-6-(diisopropoxyphosphoryl) bicyclo[3.1.0]hexan-2-one 11**

To a mixture of (diisopropoxyphosphorylmethyl)dimethyl sulfonium perchlorate (2.5 g, 11 mmol) and $K_2CO_3$ (1.7 mg, 24 mmol) in $CH_2Cl_2$ (50 mL) was added slowly (−)-(*S*)-**3** (2.2 g, 10 mmol). The reaction mixture was stirred for 12 h and then $H_2O$ (20 mL) added. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuum. The crude product was obtained as mixture of two *endo* isomers in a 3:1 ratio (8.4 g 96% yield). Purification and isomer separation were done by column chromatography using silica gel and diethyl ether/hexane, 3:1 as eluent.

**4.8.3.1. Major (1*R*,5*R*,6*S*,$S_S$)-11a.** 6.3 g (72%) of white needles (recrystallization from pentane–ethanol, 15:1), mp 84–85 °C; $[\alpha]_D^{20}$ = +49 (*c* 8.2, acetone). $^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta$ 17.7 $^1H$ NMR (200 MHz, $CDCl_3$): 1.34–1.28 (m, 12H, $CH_3CH$), 1.97–1.62 (m, 2H), 2.41–2.03 (m, 2H), 2.36 (s, 3H, $C_6H_4CH_3$), 2.80–2.45 (m, 2H), 4.77–4.58 (m, 2H, OC*H*), 7.24 and 7.44 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 20.1 (d, *J* = 169 Hz), 21.3, 23.7, 27.5, 29.4 (d, *J* = 3.4 Hz), 38.8, 60.4 (d, *J* = 3.0 Hz), 71.5 (d, *J* = 6.4 Hz), 71.2 (d, *J* = 6.4 Hz), 124.5, 129.8, 138.8, 142.3, 208.3 (d, *J* = 3.2 Hz). Anal. Calcd for $C_{19}H_{27}O_5PS$: C, 57.27; H, 6.83; P, 7.77. Found: C, 57.05; H, 6.74; P, 7.78.

**4.8.3.2. Minor (1*S*,5*S*,6*R*,$S_S$)-11b.** 2.1 g (24%), $[\alpha]_D^{20}$ = −23 (*c* 2.2, acetone). $^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta$ 19.0. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.88 (d, 3H, $CH_3CH$, *J* = 6.1 Hz), 1.03 (d, 3H, $CH_3CH$, *J* = 6.1 Hz), 1.22 (d, 3H, $CH_3CH$, *J* = 6.1 Hz), 1.24 (d, 3H, $CH_3CH$, *J* = 6.1 Hz), 2.10 (d, 1H, *J* = 9.5 Hz), 2.48–2.29 (m, 2H), 2.39 (s, 3H, $C_6H_4CH_3$), 2.70–2.52 (m, 1H), 3.02–2.80 (m, 2H), 4.23 (dq, 1H, OC*H*, *J* = 6.5, 13.4 Hz), 4.56 (dq, 1H, OC*H*, *J* = 6.5, 13.4 Hz), 7.28 and 7.71 (AA′BB′, 4H, $C_6H_4CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 20.0 (d, *J* = 175 Hz), 21.8, 23.7 (d, *J* = 5.1 Hz), 27.4, 29.4 (d, *J* = 3.5 Hz), 38.6, 60.4 (d, *J* = 2.9 Hz), 71.5 (d, *J* = 6.2 Hz), 71.1 (d, *J* = 6.1 Hz), 124.5, 129.8, 138.7, 142.3, 208.3 (d, *J* = 3.8 Hz). Anal. Calcd for $C_{19}H_{27}O_5PS$: C, 57.27; H, 6.83. Found: C, 5.42; H, 6.69.

**4.9. (1*S*,5*S*,6*S*)-6-(Diisopropoxyphosphoryl)bicyclo[3.1.0]hexan-2-one 12**

To a solution of the freshly prepared Grignard reagent from isopropyl chloride (1.97 g, 25 mmol) and magnesium (0.6 g, 25 mmol) in dry diethyl ether (100 mL) sulfoxide **9** (1 g, 2.5 mmol) was added at room temperature. The reaction mixture was stirred for 3 h and quenched with an aqeous solution of ammonium chloride. The organic layer was separated and the water fraction was extracted with $CH_2Cl_2$ (5 × 15 mL). The combined organic fractions were dried and evaporated in vacuum. The crude product was purified by column chromatography on silica gel using diethyl ether as an eluent to give a yellow oil, 470 mg (72% yield). $[\alpha]_D^{20}$ = +10.8 (*c* 2.3, acetone). $^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta$ 22.3. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.27–1.35 (m, 12H, $CH_3$), 1.34–1.52 (m, 1H), 2.09 −2.40 (m, 5H), 2.61–2.84 (m, 1H), 4.68 (dq, 2H, OC*H*, *J* = 6.5, 13.6 Hz). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 20.4 (d, *J* = 5.1 Hz), 21.3 (d, *J* = 196 Hz), 23.8, (d, *J* = 9.6 Hz), 28.2 (d, *J* = 2.8 Hz), 33.0 (d, *J* = 3.2 Hz), 36.4, 70.6 (d, *J* = 6.1 Hz), 70.9 (d, *J* = 5.8 Hz), 213.5 (d, *J* = 4.2 Hz). Anal. Calcd for $C_{12}H_{21}O_4P$: C, 55.38; H, 8.13. Found: C, 55.62; H, 8.04.

**4.10. 6-(Diisopropoxyphosphoryl)-2-spirohydantoinbicyclo-[3.1.0]hexane 13**

Sodium cyanide (130 mg, 0.2 mmol), ammonium carbonate (240 g, 0.24 mmol) and ketone (**12**) (312 mg, 0.12 mmol) were dissolved in 10 mL of a mixture of ethanol and water in a ratio of 1:1. The reaction mixture was heated at 35 °C for 3 days. The solvent was evaporated and $H_2O$ (10 mL) was added. This solution was extracted with $CH_2Cl_2$ (5 × 10 mL). The extract was dried over $MgSO_4$ and concentrated, giving a yellow oil. Purification by column chromatography on silica gel, hexane/acetone (10:1) gave 388 mg (98%) of a colourless oil, $[\alpha]_D^{20}$ = +92 (*c* 6.4, acetone). $^{31}P$ NMR (81 MHz, $CDCl_3$): $\delta$ 27.7. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.01 (ddd, 1H, *J* = 4.2, 8.7, 8.7 Hz), 1.32 (d, 6H, $CH_3CHO$, *J* = 6.1 Hz), 1.34 (d, 6H, $CH_3CHO$, *J* = 6.1 Hz), 2.37–1.92 (m, 6H), 4.81–4.59 (m, 2H, OC*H*), 7.23 (br s, 1H, N–*H*), 8.81 (br s, 1H, N–*H*). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 16.2 (d, *J* = 194 Hz), 23.8, 24.7, 26.3 (d, *J* = 5.5 Hz), 31.0 (d, *J* = 6.4 Hz), 31.1, 69.5 (d, *J* = 5.2 Hz), 70.6 (d, *J* = 5.9 Hz), 71.2 (d, *J* = 7.1 Hz), 155.6, 177.8. Anal. HRMS: calcd for $C_{14}H_{23}PN_2O_5$ 330.1345. Found 330.1344.

**4.11. (1*S*,2*R*,5*S*,6*S*)-2-Amino-6-phosphonobicyclo[3.1.0]hexane-2-carboxylic acid 2**

Hydantoin **13** (200 mg, 0.7 mmol) was heated in 10 mL of 6 N HCl at a temperature of 86 °C for 48 h. The acid was removed by rotaevaporation and the remaining oil was diluted with $H_2O$ (5 mL). The solution was chromatographed on a column by ion exchange resin of Dowex 50×8 ($H^+$ form). The product was eluted with water. The fractions were collected and evaporated to give **2** (87 mg 65%) as a colourless oil, $[\alpha]_D^{20}$ = +82.5 (*c* 4.2, methanol). $^{31}P$ NMR (81 MHz, $CD_3OD$): $\delta$ 26.6. $^1H$ NMR (200 MHz, $CD_3OD$): $\delta$ 1.21 (ddd, 1H, *J* = 3.8, 8.7, 8.7 Hz), 2.12–1.92 (m, 4H), 2.36–2.12 (m, 2H). $^{13}C$ NMR (50 MHz, $CD_3OD$): $\delta$ 17.3 (d, *J* = 188 Hz), 25.8 (d, *J* = 4.8 Hz), 26.9 (d, *J* = 4.8 Hz), 32.0 (d, *J* = 5.2 Hz), 32.2, 71. 1 (d, *J* = 5.5 Hz), 71.7 (d, *J* = 5.5 Hz, 180.3. Anal. Calcd for $C_7H_{12}NO_5P$: C, 38.02; H, 5.47. Found: C, 37.89; H, 5.61.

## 5. Crystallographic data

Intensity data for the crystals of (+)-**10b** and (+)-**11a** were collected on a Bruker AXS Smart APEX CCD 3-circle diffractometer with MonoCap capillary and monochromated Mo Kα radiation

($\lambda$ = 0.71073 Å, 50 kV, 40 mA) at temperatures of 100 K and 90 K, respectively. In both experiments 6000 frames were measured at ω-scans with 0.3° intervals with a counting time of 20 s per frame exposure. Data collection and data reduction were done with the SMART and SAINT-PLUS programs.[21] The structures were solved by direct methods using the SHELXS-97 program.[22] All non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on $F^2$ using the SHELXL-97 program[22] and the complete set of reflections. All hydrogen atoms were located from Fourier difference maps, assigned isotropic thermal parameters 1.2 times those of their parent non-H and were included in the refinements as riding atoms.

(+)-**10b**: Molecular formula: $C_{18}H_{23}O_5PS$. Formula weight: Mr = 382.40. Crystallographic system: orthorhombic. Space group: $P2_12_12_1$; $a$ = 6.9592(2) Å, $b$ = 9.2949(3) Å, $c$ = 27.8869(9) Å, $V$ = 1803.87(10) Å$^3$, $Z$ = 4, $D_x$ = 1.408 Mg m$^{-3}$. Mo Kα radiation. $\mu$ = 0.294 mm$^{-1}$, $T$ = 100 K. Final residuals for 229 parameters were $R_1$ = 0.0293, $wR_2$ = 0.0798 for 3153 reflections with $I > 2\sigma(I)$, and $R_1$ = 0.0293, $wR_2$ = 0.0799 for all 3168 reflections.

(+)-**11a**: Molecular formula: $C_{19}H_{27}O_5PS$. Formula weight: Mr = 398.45. Crystallographic system: orthorhombic. Space group: $P2_12_12_1$; $a$ = 5.9690(4) Å, $b$ = 9.3529(6) Å, $c$ = 37.123(2) Å, $V$ = 2072.5(2) Å$^3$, $Z$ = 4, $D_x$ = 1.277 Mg m$^{-3}$. Mo Kα radiation. $\mu$ = 0.259 mm$^{-1}$, $T$ = 90 K. Final residuals for 240 parameters were $R_1$ = 0.0226, $wR_2$ = 0.0587 for 3620 reflections with $I > 2\sigma(I)$, and $R_1$ = 0.0227, $wR_2$ = 0.0588 for all 3633 reflections.

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary data no. CCDC 760177 (**10b**) and 760178 (**11a**). Copies of the data can be obtained free of charge by applying to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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