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Asymmetric synthesis of (*R*)-[2,2-$^2H_2$]-1-aminocyclopropane-1-phosphonic acid (ACPP derivative) conformationally constrained ACC analogue using a chiral sulfinyl auxiliary

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ABSTRACT

The asymmetric cyclopropanation of vinylphosphonate using (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide was applied to obtain a dideuterated cyclopropyl sulfoxide. A three-step synthesis of enantiopure (+)-(1*R*)-1-amino-2,2-dideuteriocyclopropanephosphonic acid (+)-**17-d$_2$** was developed.

1. Introduction

1-Aminophosphonic acids, defined as analogues of amino acids in which the carboxylic group is replaced by a phosphonic acid moiety, are the subject of increasing interest[1] due to the tetrahedral structure of the phosphonic acid moiety since they act as 'transition-state analogues' in enzymatic hydrolysis.[2] Conformationally constrained amino acids have been the focus of both synthetic and medicinal chemistry; in particular the cyclopropane ring has served as a useful segment in peptidomimetic design.[3] This system affects the chemical and biological properties in peptides through significant conformational restrictions in the amino acid residues.[4] It has also been found that constrained amino acids can be highly potent and specific agonists since they closely mimic the bioactive conformation of natural neurotransmitters.[5] Aminocyclopropanephosphonic acids combining both unique properties (conformational restriction and isosterism) have thus motivated several research groups to study cyclopropanephosphonates as active analogues, affording improved pharmaceutical properties in certain cases.[6] Since they have not received the same attention[7,8] compared to acyclic aminophosphonic acids **1** and aminocyclopropanecarboxylic acids **2** (Fig. 1), a new approach to this type of compounds requires further investigation.

We have already reported on the synthesis of conformationally constrained analogues of bioactive amino acids based on asymmetric cyclopropanation utilizing optically active sulfinyl compounds.[9] Herein we turned our attention to 1-aminocyclopropanephosphonic acids, applying (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide **6**, designed and described by us earlier,[10] as a chiral sulfur reagent in the cyclopropanation step. In order to introduce chirality to the structure of 1-aminocyclopropanephosphonic acids, differentiation of the enantiotopic methylene groups was attained by the presence of two deuterium atoms on one of them (dideuterated ACPP). Although different syntheses of deuterium labeled 1-aminocyclopropane-1-carboxylic acid have been reported,[11] the phosphonic analogue in the deuterated version has not been described.

2. Results and discussion

Cyclopropanation of phosphoryl acrylates **7-d$_2$** and **8-d$_2$** using (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide **6** afforded a separable mixture of three diastereomers **9-d$_2$ (A–C)** and **10-d$_2$ (A–C)** in a ratio dependent on the conditions used for ylide generation (Scheme 1). Comparison of the spectroscopic data of the resulting diastereomers with those of the non-deuterated analogues described earlier[12] allowed us to determine their configuration.

In order to remove the chiral auxiliary, cyclopropane **10A-d$_2$** was subjected to sulfoxide/metal exchange, a reaction that has been widely applied for the synthesis of enantiomerically pure sulfoxides, and also as a method to generate the corresponding carbanions. Due to the presence of other reactive centers in cyclopropyl sulfoxide **10**, isopropylmagnesium chloride was used as the reagent of choice. When the reaction was performed at −10 °C in diethyl ether for 20 min, it gave confusing results: the formation of two major products with the same molecular weight. Since the desired product contains only one stereogenic center, the second product must be its regioisomer. Initially, we assumed that after the attack of the Grignard reagent on the sulfinyl group, the carbanionic species formation involved a shift of one of the deuterium atoms to the neighboring carbon atom, resulting in the formation of structure **11**.[12] This hypothesis was later discarded and the correct explanation of this phenomenon was established on the basis of our previous investigations concerning sulfinyl group removal from mono-methylated sulfinylcyclopropanes.[13] In that

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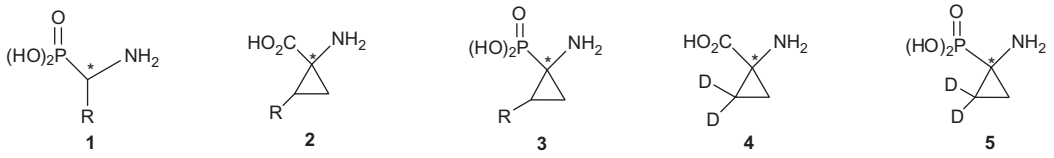
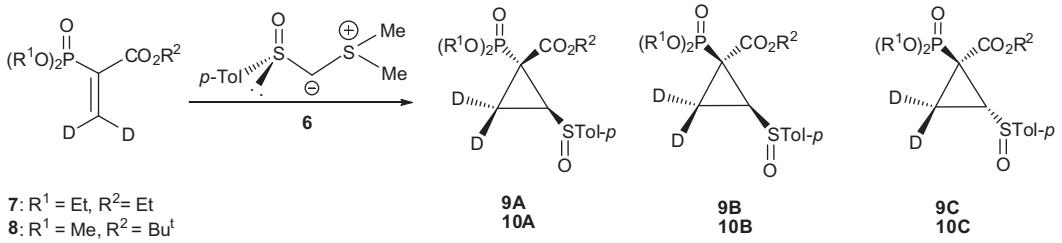


Figure 1.



entry	Reaction conditions	Product	Ratio of diast. A	B	C	D	Facial selectivity
1.	NaH/MeCN 0-20°C	**9-d$_2$**	64	23	13	-	87 : 13
2.	NaH / MeCN 0°C	**9d$_2$**	68	27	5	-	95 : 5
3.	K_2CO_3 / CH_2Cl_2 rt.	**9-d$_2$**	62	26	12	-	88 : 12
4.	NaH / MeCN 0°C	**10-d$_2$**	62	28	10	-	90 : 10
5.	K_2CO_3 / CH_2Cl_2 rt.	**10-d$_2$**	65	21	14	-	86 : 14

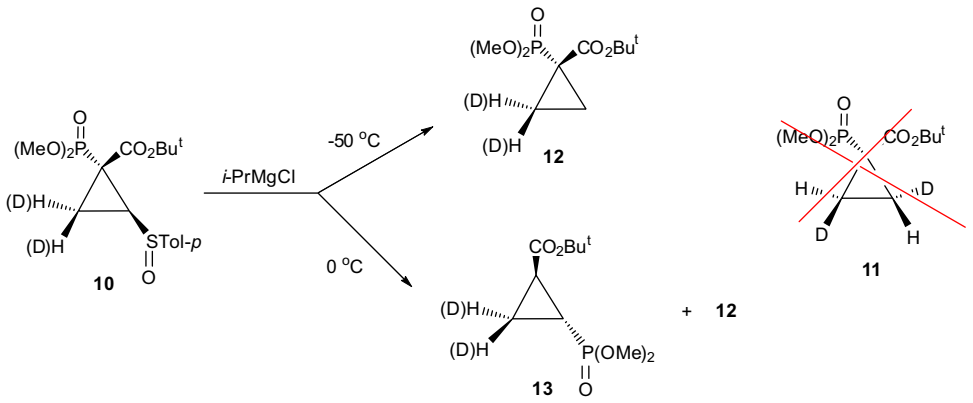
Scheme 1. Cyclopropanation of vinylphosphonates with (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide.

case, the formation of regioisomers of the desired products was explained in terms of an unprecedented 1,2-migration of a phosphoryl group on the cyclopropane ring. We found that the same rearrangement took place for cyclopropane **10**, but that the reaction course was temperature dependent. At a low temperature (−50 °C), the desulfinylated cyclopropane **12** was observed as the only product, whereas increasing the temperature and extending the reaction time led to the formation of regioisomer **13** (Scheme 2).

Taking advantage of this observation, our further investigations were performed at a lower temperature (−50 °C); due to slightly better induction during cyclopropanation, (Scheme 1 entry 2) ethyl ester **9A-d$_2$** was used for the next set of conversions. The desired desulfinylated product **14-d$_2$** was obtained exclusively in high yield.

The most typical synthetic approach to aminophosphonic acids utilizes the Curtius rearrangement,[14] where the carboxyl group can be converted into the corresponding acid chlorides and then, with sodium azide, converted into an acyl azide, which is subjected to Curtius rearrangement. Thus, the hydrolysis of the ester **14-d$_2$** with lithium hydroxide at room temperature gave acid **15-d$_2$**, which was used for the next step without purification. Since our preliminary experiment on undeuterated product **15** led to the formation of some by-products, we used the alternative procedure of the Curtius rearrangement using diphenylphosphoryl azide.[15] The reaction was carried out by boiling equimolar amounts of cyclopropanecarboxylic acid **9A-d$_2$**, diphenylphosphoryl azide, and triethylamine in *t*-BuOH and afforded the *N*-Boc-protected amino ester **16-d$_2$**. The latter, upon treating with 6 N hydrochloric acid and subsequent addition of propylene oxide and ethanol, afforded the desired aminocyclopropane-1-phosphonic acid **17-d$_2$** (Scheme 3).

Examination of the ^{1}H NMR spectra of the deuterated compounds obtained for each step of the synthesis, confirmed the substitution of the methylenic protons by deuterium, since the resonances corresponding to these protons were absent. Even



Scheme 2. Sulfinyl exchange.

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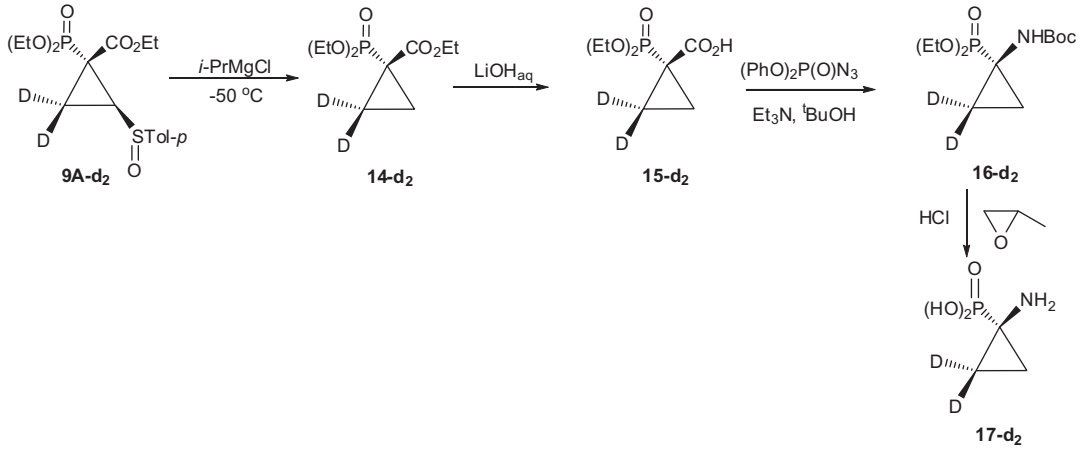

Scheme 3.

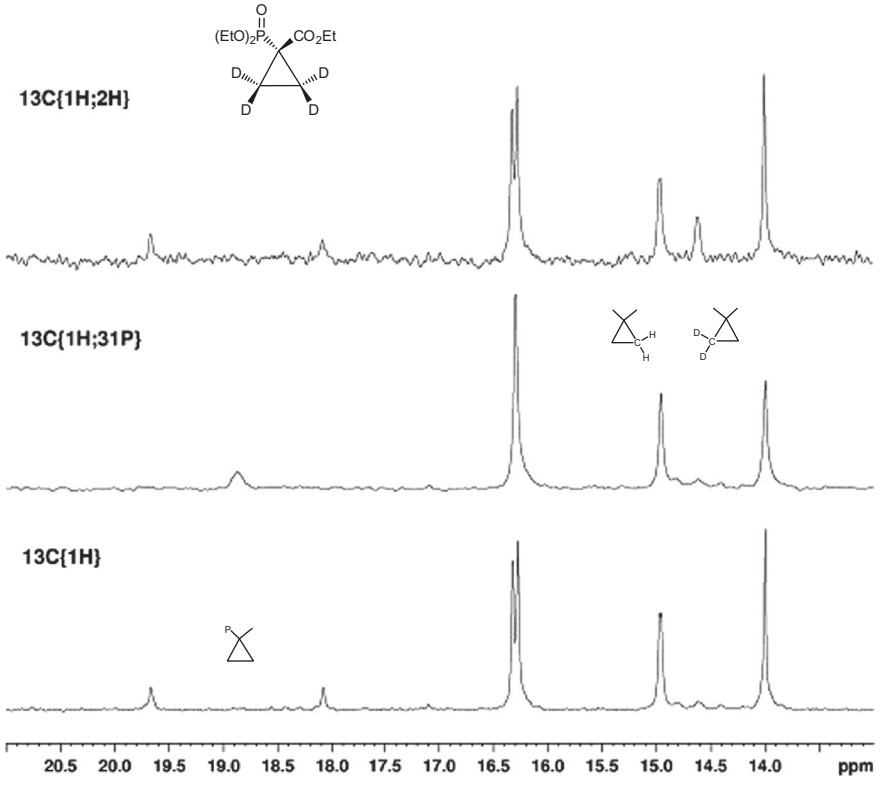

Figure 2. ^{13}C NMR of (−)-(1*R*)-ethyl-1-diethylphosphono-2,2-$^{2}H_2$-cyclopropanecarboxylate **14-d$_2$**.

more diagnostic was ^{13}C NMR, where both methylene carbons were different (CH_2 vs CD_2). However, to make it more visible in some cases, deuterium decoupling was required (Fig. 2).

3. Conclusion

In conclusion, we have reported on the asymmetric synthesis of cyclopropyl phosphonates using the (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide **6** and reaction sequences that demonstrate that these products are well-suited to the synthesis of the cyclopropyl analogues of aminophosphonic acids. An elaborated procedure of desulfinylation allowed us to avoid 1,2-migration of a phosphoryl group on a cyclopropane ring and obtain the cyclopropyl phosphonate with the retained structure and configuration. Employment of a Curtius procedure resulted in the formation of enantiopure (+)-(1*R*)-1-amino-2,2-dideuteriocyclopropanephosphonic acid (+)-**17-d$_2$**, which is the first approach to this deuterium labeled analogue.

4. Experimental

4.1. General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker Avance III 600, Bruker Avance III 500, and Bruker AC 200 Spectrometer, using deuterochloroform as solvent. Mass spectra were recorded on Finnigan MAT95. IR spectra were recorded on Ati Mattson FTIR Spectrometer. The optical rotations were measured on a Perkin–El-

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mer 241 MC photopolarimeter in acetone solution. The microanalyses were performed on 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

To a round-bottomed flask equipped with a magnetic stirrer bar were added 2 mmol (0.48 g) of ethyl-1-diethylphosphono-2,2-dideuteroacrylate and 2 mmol (0.6 g) of (*S*)-dimethyl sulfonium-(*p*-tolylsulfinyl)methyl tetrafluoroborate placed in 10 mL of CH_2Cl_2. To this suspension was added 0.3 g of K_2CO_3 and the mixture was stirred vigorously overnight. Filtration and evaporation of the solvent afforded a crude residue in 95% yield. Separation of the diastereomers was achieved by chromatography on silica (hexane/acetone 2:1).

4.2.1. (+)-(1*R*,2*S*,*Ss*)-Ethyl-1-diethylphosphono-2-*p*-tolylsulfinyl-3,3-$^2H_2$-cyclopropanecarboxylate 9A-d_2

Yield 53%; yellowish oil; $[\alpha]_D^{20} = +79$ (*c* 13.6, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ: 18.8; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.0 Hz), 1.28 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.0 Hz), 1.32 (t, 3H, $COCH_2CH_3$, J_{HH} = 7.1 Hz), 2.42 (s, 3H, $C_6H_4CH_3$), 2.90 (d, 1H, J_{PH} = 15.2 Hz, *CHS*(O)), 3.89–3.94 (m, 1H, $POCHHCH_3$), 4.0–4.03 (m, 1H, $POCHHCH_3$), 4.07–4.14 (m, 2H, $POCH_2CH_3$), 4.26 (q, 2H, $COCH_2CH_3$, J_{HH} = 7.1 Hz), 7.32 and 7.58 (A_2B_2, 4H, $C_6H_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 12.7 (m, *C*D_2), 14.1 (CH_3CH_2OC), 16.3 (m, CH_3CH_2OP), 21.5 ($C_6H_4CH_3$), 27.5 (*C*P, d, J_{CP} = 181.0 Hz), 44.6 (*C*HSO), 62.5 (CH_3CH_2OC), 63.1 (d, J_{CP} = 6.0 Hz, CH_3CH_2OP), 63.4 (d, J_{CP} = 6.7 Hz, CH_3CH_2OP), 124.3, 130.0, 140.8, 142.1, 165.7 (d, J_{CP} = 7.7 Hz); MS(CI) *m*/*z* 391 $(M+H)^+$; HR MS(ES) 413.1133 calcd for $C_{17}{}^1H_{23}{}^2H_2O_6NaPS$ $[M+Na]^+$ found: 413.1128.

4.2.2. (+)-(1*S*,2*R*,*Ss*)-Ethyl-1-diethylphosphono-2-*p*-tolylsulfinyl-3,3-$^2H_2$-cyclopropanecarboxylate 9C-d_2

Yield 8%; yellowish oil; $[\alpha]_D^{20} = +120$ (*c* 10.1, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ: 18.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.0 Hz), 1.34 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.0 Hz), 1.37 (t, 3H, $COCH_2CH_3$, J_{HH} = 7.1 Hz), 2.43 (s, 3H, $C_6H_4CH_3$), 3.08 (d, 1H, J_{PH} = 13.9 Hz, *CHS*(O)), 4.07–4.14 (m, 4H, $POCH_2CH_3$), 4.4 (m, 2H, $COCH_2CH_3$), 7.33 and 7.58 (A_2B_2, 4H, $C_6H_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 14.0 (CH_3CH_2OC), 14.9 (m, *C*D_2), 16.3 (d, J_{CP} = 5.8 Hz, CH_3CH_2OP);16.4 (d, J_{CP} = 6.7 Hz, CH_3CH_2OP), 21.4 ($C_6H_4CH_3$), 27.0 (d, J_{CP} = 181.9 Hz), 48.0 (*C*HSO), 62.7 (CH_3CH_2OC), 63.4 (m, CH_3CH_2OP), 124.2, 130.1, 140.8, 142.0, 166.2 (d, J_{CP} = 5.2 Hz); MS(CI) *m*/*z* 391 $(M+H)^+$; HR MS(ES) 413.1133 calcd for $C_{17}{}^1H_{23}{}^2H_2O_6NaPS$ $[M+Na]^+$ found: 413.1135.

4.2.3. (−)-(1*S*,2*S*,*Ss*)-Ethyl-1-diethylphosphono-2-*p*-tolylsulfinyl-3,3-$^2H_2$-cyclopropanecarboxylate 9B-d_2

Yield: 20%; yellowish oil; $[\alpha]_D^{20} = -32$ (*c* 7.4, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ: 17.3 ppm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.2 Hz), 1.31 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.0 Hz), 1.34 (t, 3H, $COCH_2CH_3$, J_{HH} = 7.0 Hz), 2.38 (s, 3H, $C_6H_4CH_3$), 3.00 (d, 1H, *SCH*, J_{PH} = 9.0 Hz), 4.09–4.26 (m, 6H, OCH_2CH_3), 7.29 and 7.74 (A_2B_2 aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): 13.8 (CH_3CH_2OC), 16.3 (m, CH_3CH_2OP), 18.1 (m, *C*D_2), 21.3 ($C_6H_4CH_3$), 27.6 (d, J_{CP} = 195.7 Hz), 49.7 (*C*HSO), 62.4 (CH_3CH_2OC), 62.9 (d, J_{CP} = 6.2 Hz, CH_3CH_2OP), 63.4 (d, J_{CP} = 6.5 Hz, CH_3CH_2OP), 124.5, 129.9, 141.6, 142.1, 167.5 (d, J_{CP} = 7.7 Hz); MS(CI) *m*/*z* 391 $(M+H)^+$.

4.2.4. (+)-(1*R*,2*S*,*Ss*)-*t*-Butyl-1-dimethylphosphono-2-*p*-tolylsulfinyl-3,3-$^2H_2$-cyclopropanecarboxylate 10A-d_2

Yield: 50%; white solid; mp 92–94 °C; $[\alpha]_D^{20} = +86.8$ (*c* 1.0, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ 22.5; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 9H, $COC(CH_3)_3$), 2.41 (s, 3H, $C_6H_4CH_3$), 2.87 (d, 1H, J_{PH} = 15.4 Hz, *CHS*(O)), 3.64 and 3.77 (2 × d, 6H, $POCH_3$, J_{PH} = 11.1 - Hz), 7.32 and 7.75 (AB, 4H, $C_6H_4CH_3$, J_{HH} = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 12.1 (*C*D_2, quint. J_{CD} = 25.5 Hz), 21.2 ($C_6H_4CH_3$), 27.6 ($(CH_3)_3C$, 27.7 (d, J_{CP} = 180.4 Hz), 44.0 (*C*HS, d, J_{CP} = 3.2 Hz), 53.3 (d, J_{CP} = 6.0 Hz), 53.5 (d, J_{CP} = 6.0 Hz), 83.6 ($(CH_3)_3C$, 124.1, 129.9, 140.6, 141.8, 164.0 (C=O, d, J_{CP} = 4.8 Hz); MS(CI) *m*/*z* 391 $(M+H)^+$. HR MS(FAB) 390.1235 calcd for $C_{17}{}^1H_{23}{}^2H_2O_6PS$ $[M]^+$ Found 390.1239.

4.2.5. (−)-(1*S*,2*S*,*Ss*)-*t*-Butyl-1-dimethylphosphono-2-*p*-tolylsulfinyl-3,3-$^2H_2$-cyclopropanecarboxylate 10C-d_2

Yield: 21%; yellowish oil; $[\alpha]_D^{20} = -38.7$ (*c* 3.1 acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ 20.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (s, 9H, $COC(CH_3)_3$), 2.40 (s, 3H, $C_6H_4CH_3$), 2.91 (d, 1H, J_{HH} = 9.4 Hz, *CHS*(O)), 3.79 and 3.82 (2 × d, 6H, $POCH_3$, J_{HH} = 11.1 Hz), 7.32 and 7.75 (A_2B_2, 4H, $C_6H_4CH_3$, J_{HH} = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 17.1 (quint. J_{CD} = 25.5 Hz), 21.2, 27.6, 28.9 (d, J_{CP} = 196.0 Hz), 48.8 (d, J_{CP} = 3.2 Hz), 53.0 (d, J_{CP} = 6.1 Hz), 53.5 (d, J_{CP} = 6.9 Hz), 83.45, 124.2, 129.8, 141.3, 141.4, 165.8 (d, J_{CP} = 6.8 Hz); MS(CI) *m*/*z* 391 $(M+H)^+$; HR MS(FAB) 390.1235 calcd for $C_{17}{}^1H_{23}{}^2H_2O_6PS$ $[M]^+$ found: 390.1230.

4.3. Sulfinyl exchange

At the indicated temperature under nitrogen, to a stirred solution of (+)-**9A-d_2** or (+)-**10A-d_2** (0.2 mmol) in anhydrous Et_2O (3.0 mL), *i*-PrMgCl (2.0 M in Et_2O, 1 mmol, 0.11 mL), was added and the mixture was stirred at −50 °C for 1 h. The reaction was quenched by NH_4Cl, and extracted with Et_2O (3 x 5 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification was performed by plate chromatography (hexane/acetone 3:1)

4.3.1. (−)-(1*R*)-Ethyl-1-diethylphosphono-2,2-$^{22}H_2$-cyclopropanecarboxylate 14-d_2

Yield: 83%; yellowish oil; $[\alpha]_D^{20} = -4.5$ (*c* 6.7, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ 23.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (t, 3H, $POCH_2CH_3$, J_{HH} = 7.1 Hz), 1.29 (t, 6H, $COCH_2CH_3$, J_{HH} = 7.0 Hz), 1.39–1.43 (m, 2H, *CH*$_2$), 4.12–4.18 (m, 6H, OCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 14.0 (CH_3CH_2OC), 14.6 (*C*D_2), 14.9 (*CH*$_2$), 16.2 (CH_3CH_2OP), 16.3 (d, J_{CP} = 6.0 Hz, CH_3CH_2OP), 19.1 (d, J_{CP} = 199.4 Hz) 61.4 (CH_3CH_2OC), 62.5 (d, J_{CP} = 6.0 Hz, CH_3CH_2OP), 62.6 (CH_3CH_2OP), 170.1 (*C*=O); MS(CI) *m*/*z* 253 $(M+H)^+$; MS(ES) 275.0993 calcd for $C_{10}{}^1H_{17}{}^2H_2O_5PNa$ $[M+Na]^+$ found: 275.0992

4.3.2. (+)-(1*R*)-*t*-Butyl-1-dimethylphosphono-2,2-$^2H_2$-cyclopropanecarboxylate 12-d_2

Yield: 82%; yellowish oil; $[\alpha]_D^{20} = +1.7$ (*c* 1.0, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ 28.3; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31–1.40 (m, 2H, *CH*$_2$), 1.45 (s, 9H, $(CH_3)_3CO$), 3.78 (d, 6H, $POCH_3$, J_{PH} = 11.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 13.9 (quint. J_{CD} = 25.4 Hz), 14.4, 19.2 (d, J_{CP} = 198.8 Hz), 27.9, 53.3 (d, J_{CP} = 6.2 Hz), 82.0, 168.8 (d, J_{CP} = 8.3 Hz); MS(CI) *m*/*z* 253 $(M+H)^+$; MS(FAB) 252.1096 calcd for $C_{10}{}^1H_{17}{}^2H_2O_5P$ $[M]^+$ found: 252.1105

4.3.3. (+)-(1*S*,2*R*)-*t*-Butyl-3,3-$^2H_2$-2-dimethylphosphonocyclopropanecarboxylate 13-d_2

Yield: 48%; yellowish oil; $[\alpha]_D^{20} = -124.2$ (*c* 1.7, acetone); ^{31}P NMR (202 MHz, $CDCl_3$) δ: 30.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ: (dd, 1H, CH*trans*, J_{HH} = 4.8, 5.0 Hz), 1.43 (s, 9H, $(CH_3)_3CO$), 2.05 (dd, 1H, CH*cis*, J_{HH} = 4.8, J_{PH} = 14.8 Hz), 3.74 and 3.75 (2 × d, 6H, $POCH_3$, J = 10.8 Hz) ^{13}C NMR (125 MHz, $CDCl_3$): 10.7 (*C*D_2, quint. J_{CD} = 25.5 Hz), 12.0 (*C*P=O, d, J_{CP} = 195.5 Hz), 18.6, 28.0 ($(CH_3)_3CO$), 52.7 (t, J_{CP} = 5.7 Hz), 81.4, 171.0 (d, J_{CP} = 10.8 Hz); MS(CI) *m*/*z* 253

$(M+H)^+$; MS(FAB) 252.1096 calcd for $C_{10}{}^1H_{17}{}^2H_2O_5P$ $[M]^+$ found: 252.1098.

4.4. (−)-(1*R*)-1-Diethylphosphono-2,2-$^2H_2$-cyclopropane-*tert*-butoxycarbonylamine

At first, 76 mg of ethyl ester **14-d$_2$** (0.3 mmol) was dissolved in 5 mL of aqueous solution of LiOH. The mixture was then stirred for 1 h at room temperature. Next to the solution was added 5% HCl. The water phase was extracted with $CHCl_3$ (5 × 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The crude carboxylic acid derivative (62 mg, 0.28 mmol) and NEt_3 (40 μL, 0.28 mmol) were mixed with dry *t*-BuOH (5 mL) at 25 °C under N_2. Diphenylphosphoryl azide (76 mg, 0.28 mmol) was then added, and the reaction mixture was refluxed with stirring for 12 h. The reaction solution was concentrated, and the crude product extracted with ether. After being washed with 1 M HCl and saturated $NaHCO_3$(aq) and dried, the product was purified by chromatography on silica (hexane/acetone 4:1). Yield: 88%; colorless oil; $[\alpha]_D^{20} = -0.3$ (*c* 2.6, acetone); ^{31}P NMR (81 MHz, $CDCl_3$) δ 25.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (2 × t, 6H, $POCH_2CH_3$, J_{HH} = 7.0 Hz), 1.35–1.50 (m, 2H, CH_2), 1.42 (s, 9H, $COC(CH_3)_3$), 4.12–4.19 (m, 4H, $POCH_2CH_3$), 4.95 (s, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): 12.9 (CH_2), 14.1 (CD_2), 16.3 (CH_3CH_2OP), 16.4 (d, J_{CP} = 6.2 Hz, CH_3CH_2OP), 25.2, 27.0 (d, J_{CP} = 221.1 Hz), 28.2 ($COC(CH_3)_3$), 61.6 (CH_3CH_2OC), 62.5 (CH_3CH_2OP), 62.6 (d, J_{CP} = 5.5 Hz, CH_3CH_2OP), 79.8 ($COC(CH_3)_3$), 155.0 (*C*=O) MS(CI) *m*/*z* 297 $(M+H)^+$; HR MS(FAB) 296.1596 calcd for $C_{12}{}^1H_{23}{}^2H_2O_5NP$ $[M]^+$ found: 296.1586.

4.5. (−)-(1*R*)-1-Amino-[2,2-$^2H_2$]-cyclopropane-1-phosphonic acid 17-d$_2$

A solution of *N*-Boc-protected cyclopropylamine **16-d$_2$** (27 mg) in 2 mL of 6 N HC1 was heated at 100 °C for 24 h and then concentrated under vacuum. The residue was dissolved in absolute ethanol (0.5 mL) and then treated with propylene oxide (0.04 mL). After standing overnight at room temperature, the mixture was filtered to afford a white solid. $[\alpha]_D^{20} = -1.3$ (*c* 1.2, H_2O); ^{31}P NMR (81 MHz, D_2O) δ 12.4 ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.02–1.11 (m, 2H, CH_2), ^{13}C NMR (125 MHz, D_2O): 8.8 (CD_2), 8.9 (CH_2), 30.4 (d, J_{CP} = 191.3 -Hz) (lit.[16] for undeuterated acid δ 30.9, d, J_{CP} = 193.5 Hz); MS(FAB) *m*/*z* 139 M^+.

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References

1. For a recent review see (a) Mucha, A.; Kafarski, P.; Berlicki, Ł. *J. Med. Chem.* **2011**, *54*, 5955–5980; (b) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17*, 264–289; (c) Ordonez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17–49; (d) Berlicki, Ł.; Kafarski, P. *Curr. Org. Chem.* **2005**, *9*, 1829–1850.
2. Jacobsen, N. E.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 654–657.
3. (a) Brackmann, F.; de Mejere, A. *Chem. Rev.* **2007**, *107*, 4493–4537; (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
4. For example employing cyclopropane ring constraint in a peptides, see (a) Burgess, K.; Ho, K.-K.; Pettitt, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 54–65; (b) Burgess, K.; Ke, C.-Y. *J. Org. Chem.* **1996**, *61*, 8627–8631.
5. (a) Pellicciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2259–2269; (b) Pellicciari, R.; Marinozzi, M.; Camaioni, E.; Nunez, M.; Costantino, G.; Gasparini, F.; Giorgi, G.; Macchiarulo, A.; Subramanian, N. *J. Org. Chem.* **2002**, *67*, 5497–5507.
6. (a) Pompei, M.; Di Francesco, M. E.; Koch, U.; Liverton, N. J.; Summa, V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2574–2578; (b) Sheng, X. C.; Pyun, H.; Chaudhary, K.; Wang, J.; Doerffler, E.; Fleury, M.; McMurtrie, D.; Chen, X.; Delaney, I. W. E.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3453–3457; (c) Pyun, H.-J.; Clarke, M. O.; Cho, A.; Casarez, A.; Ji, M.; Fardis, M.; Pastor, R.; Sheng, X. C.; Kim, C. U. *Tetrahedron Lett.* **2012**, *53*, 2360–2363.
7. Gulyukina, N. S.; Makukhin, N. N.; Beletskaya, I. P. *Zh. Org. Khim.* **2011**, *47*, 633–648. and references cited therein.
8. (a) Wąsek, K.; Kędzia, J.; Krawczyk, H. *Tetrahedron: Asymmetry* **2010**, *21*, 2081–2086; (b) Hercouet, A.; Le Corre, M.; Carboni, B. *Tetrahedron Lett.* **2000**, *41*, 197–199; (c) Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267–2276.
9. (a) Midura, W. H.; Mikołajczyk, M. *Tetrahedron Lett.* **2002**, *43*, 3061–3065; (b) Krysiak, J.; Midura, W. H.; Wieczorek, W.; Sieroń, L.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1486–1493; (c) Midura, W. H.; Krysiak, J. A.; Rzewnicka, A.; Supeł, A.; Łyżwa, P. *Tetrahedron* **2013**, *69*, 730–737.
10. (a) Midura, W. H. *Synlett* **2006**, 733–736; (b) Midura, W. H. *Tetrahedron Lett.* **2007**, *48*, 3907–3910; (c) Midura, W. H.; Cypryk, M. *Tetrahedron: Asymmetry* **2010**, *21*, 177–186.
11. (a) Hill, R. H.; Prakash, S. R.; Wiesendanger, R.; Angst, W.; Martinoni, B.; Arigoni, D.; Liu, H. W.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 795–796; (b) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 87; (c) Buñuel, E.; Bull, S. D.; Davies, S. G.; Christopher Garner, A. C.; Savory, E. D.; Smith, A. D.; Richard, J.; Vickers, R. J.; Watkin, D. *J. Org. Biomol. Chem.* **2003**, *1*, 2531–2542.
12. Midura, W. H. *Phosphorus, Sulfur and Silicon* **2011**, *186*, 1189–1192.
13. Midura, W. H.; Sobczak, A.; Paluch, P. *Tetrahedron Lett.* **2013**, *54*, 223–226.
14. Moore, J. D.; Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2002**, *67*, 8123–8129.
15. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, 6203–6205.
16. Fadel, A. *J. Org. Chem.* **1999**, *64*, 4953–4955.