Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 4021

Convergent and enantioselective syntheses of cytosolic phospholipase $A_2\alpha$ inhibiting *N*-(1-indazol-1-ylpropan-2-yl)carbamates†

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Received 10th March 2014,
Accepted 28th April 2014

DOI: 10.1039/c4ob00535j

www.rsc.org/obc

Cytosolic phospholipase $A_2\alpha$ (cPLA$_2\alpha$) is an important enzyme of the inflammation cascade. Therefore, inhibitors of cPLA$_2\alpha$ are assumed to be promising drug candidates for the treatment of inflammatory disorders. Recently we have found that indole-5-carboxylic acid with a 3-(4-octylphenoxy)-2-(phenoxycarbonylamino)propyl substituent in position 1 is an inhibitor of cPLA$_2\alpha$. We have now synthesized a corresponding derivative with the indole heterocycle replaced by an indazole (**4**) employing an analogous reaction sequence as for the synthesis of the indole derivative. Besides, a more convergent synthesis for **4** was established using an aziridine as central intermediate. Furthermore, a chiral-pool based enantioselective synthesis was developed for the synthesis of (***R***)- and (***S***)-**4**. Starting compound for both enantiomers was the (*R*)-serine derived oxazolidine (***R***)-**25**. Compound **4** proved to be a moderate inhibitor of cPLA$_2\alpha$, with the *S*-enantiomer being twice as active as the *R*-enantiomer. The racemate **4** and the enantiomers (***R***)- and (***S***)-**4** showed a high *in vitro* metabolic stability in rat liver S9 fractions.

Introduction

Cytosolic phospholipase $A_2\alpha$ (cPLA$_2\alpha$) is an esterase that selectively cleaves the *sn*-2 position of arachidonoyl-glycerophospholipids of biomembranes to generate free arachidonic acid and lysophospholipids.[1,2] Subsequent metabolism of these products leads to a variety of inflammatory mediators including prostaglandins, leukotrienes and platelet activating factor (PAF). Mice with cPLA$_2\alpha$ deficiency display a reduced eicosanoid production and are resistant to disease in a variety of models of inflammation.[3] Therefore, cPLA$_2\alpha$ is considered as a target for the treatment of inflammatory diseases, such as rheumatoid arthritis, atopic dermatitis and Alzheimer's disease.[4–6] Today several potent inhibitors of cPLA$_2\alpha$ are known,[7,8] which show activity in diverse animal models of inflammation after systemic or local application. However, none of these agents is actually in clinical development.

We have found that certain 1-(indol-1-yl)propan-2-ones, such as compound **1** (Fig. 1), inhibit cPLA$_2\alpha$ with high potency.[9] The latter compound shows structural similarities to the propan-2-one inhibitor ARC-70484XX developed by AstraZeneca.[10] An important part of the pharmacophore of these substances is the activated electrophilic ketone moiety present in the middle part of the molecules. This structural element is supposed to form reversible covalent binding interactions with a serine residue of the active site of cPLA$_2\alpha$.

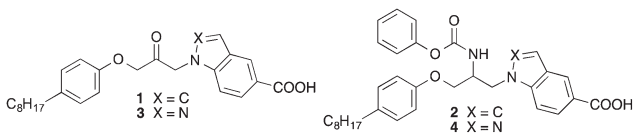

Fig. 1 Structures of known and designed inhibitors of cPLA$_2\alpha$.

Recent studies have shown that 1-(indol-1-yl)propan-2-ones are extensively metabolized *in vitro* as well as *in vivo*.[11,12] Especially, the activated ketone is reduced to an alcohol resulting in compounds, which do not inhibit cPLA$_2\alpha$ any more. Therefore, we have replaced the ketone by metabolically more stable polar moieties such as acyloxy, acylamino, urea and carbamate.[13] These variations led to a more or less pronounced drop of inhibitory potency. One of the most active compounds of the investigated substances was the carbamate substituted indole-5-carboxylic acid **2**, which possessed an IC_{50} against cPLA$_2\alpha$ in the micromolar range.

Because structure–activity relationship studies on the 1-(indol-1-yl)propan-2-ones have revealed that replacement of the indole scaffold of **1** by an indazole (**3**) led to an about five-fold increase of activity,[14] we wanted to synthesize and evaluate the corresponding carbamate-substituted indazole derivative **4**.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00535j

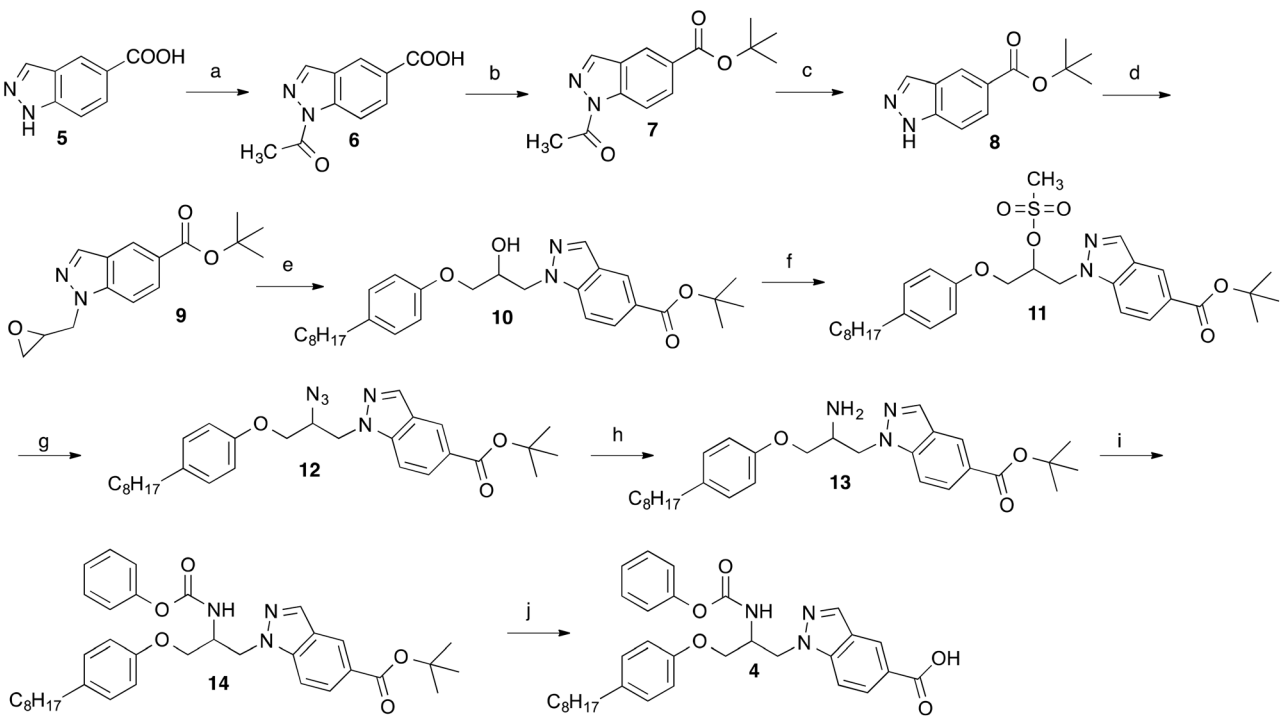
In contrast to the ketones **1** and **3**, the carbamates **2** and **4** possess a stereogenic centre resulting in *R*- and *S*-configurated products. A further aim of this study, therefore, was to develop enantioselective syntheses for the enantiomers of **4** and to determine the influence of the configuration of this compound on $cPLA_2\alpha$ inhibition.

Results and discussion

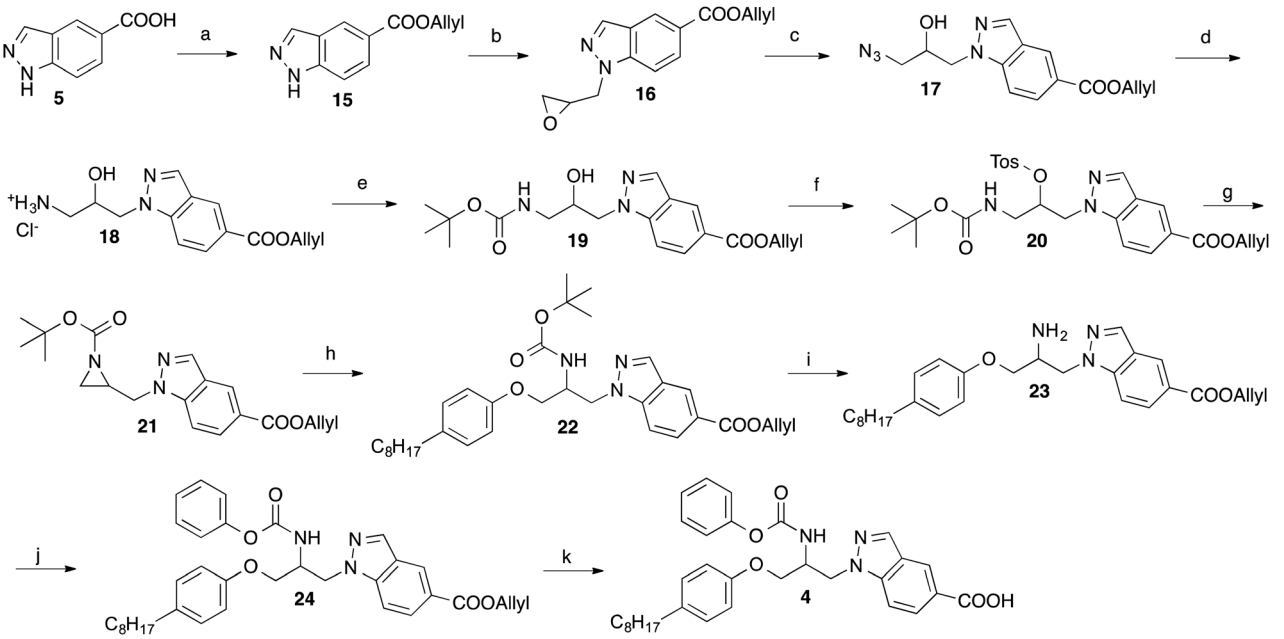
Chemistry

For the preparation of the indazole **4** the synthetic route developed for the synthesis of the corresponding indole **2**[13] was used (Scheme 1). Starting material was indazole-5-carboxylic acid (**5**), which first was converted into its *tert*-butyl-ester **8** employing a reaction sequence published for the synthesis of *tert*-butyl benzotriazole-5-carboxylate.[15] Treatment of **8** with epichlorohydrin in presence of KOH and tetrabutylammonium bromide led to **9**, which was reacted with 4-octylphenol to obtain the secondary alcohol **10**. The alcohol functionality of this compound was converted to a mesylate (**11**) by reaction with methanesulfonyl chloride. From the latter intermediate the azide **12** was obtained by treatment with trimethylsilyl azide and tetrabutylammonium fluoride. Catalytic hydrogenation of the azide group of **12** with Pd on charcoal led to the amine-substituted compound **13**. Reaction of this with phenyl chloroformate in presence of an amine base followed by hydrolysis of the *tert*-butyl ester with trifluoroacetic acid gave the desired target compound **4**.

In Scheme 2, an alternative approach for the synthesis of **4** is outlined, which is more convergent in respect of the variation of the octylphenoxy-part of **4** during the course of structure–activity studies. This synthetic route started from indazole-5-carboxylic acid, which was converted into its allyl ester (**15**) by reaction with allyl bromide in presence of K_2CO_3. Using Cs_2CO_3 as base, the indazole ester **15** was alkylated with epichlorohydrin in position **1** yielding the oxiranylmethylindazole derivative **16**. The oxiranyl ring of **16** was opened to a azidoalcohol by reaction with sodium azide.[16] Then the azido group of **17** was transformed to an amine (**18**) by treatment with triphenylphosphine, which in turn was protected with BOC using di-*tert*-butyl dicarbonate. The alcohol group of obtained compound **19** was reacted with tosyl chloride in presence of 4-dimethylaminopyridine to give the tosylate **20**. Cyclization to the aziridine **21** was accomplished by treatment of **20** with powdered KOH and tetrabutylammonium hydrogensulfate in CH_2Cl_2. Ring opening of the BOC-protected aziridine **21** with 4-octylphenol was achieved in methylene chloride with catalytical amounts of BF_3-etherate.[17] The BOC group of **22** was removed by trifluoroacetic acid. Reaction of the generated amine **23** with phenyl chloroformate led to the carbamate **24**. Finally, the allyl ester of the indazole heterocycle of **24** was cleaved with tetrakis(triphenylphosphine)palladium(0) to afford the desired target compound **4**. By this way, derivatives



Scheme 1 Reagents and conditions: (a) acetic anhydride, reflux, 2 h; (b) *tert*-butyl 2,2,2-trichloroacetimidate, cyclohexane, THF, BF_3-etherate, room temp., 2 h; (c) 1 M aqueous NaOH, ethanol, room temp., 1 h; (d) epichlorohydrin, powdered KOH, tetrabutylammonium bromide, room temp., 4 h; (e) 4-octylphenol, 4-dimethylaminopyridine, 120 °C, 2 h; (f) methanesulfonyl chloride, pyridine, room temp., 3.5 h; (g) trimethylsilyl azide, tetrabutylammonium fluoride, THF, reflux, 72 h; (h) Pd/C, H_2, THF, room temp., 6 h; (i) phenyl chloroformate, ethyl(diisopropyl)amine, THF, room temp., 45 min; (j) trifluoroacetic acid, CH_2Cl_2, room temp., 12 h.



Scheme 2 Reagents and conditions: (a) allyl bromide, K_2CO_3, DMF, room temp., 6 h; (b) epichlorohydrin, Cs_2CO_3, DMF, room temp., 14 h; (c) NaN_3, NH_4Cl, methanol, H_2O, 80 °C, 18 h; (d) triphenylphosphine, acetonitrile, reflux, overnight; (e) di-*tert*-butyl dicarbonate, triethylamine, diethyl ether, methanol, 0 °C, 2 h; (f) *p*-toluenesulfonyl chloride, powdered KOH, THF, room temp., 4 h; (g) KOH powder, tetrabutylammonium hydrogen sulfate, CH_2Cl_2, room temp., 6 h; (h) 4-octylphenol, BF_3-etherate, CH_2Cl_2, room temp., 1 min; (i) trifluoroacetic acid, CH_2Cl_2, room temp., 2 h; (j) phenyl chloroformate, triethylamine, THF, room temp., 2 h; (k) tetrakis(triphenylphosphine)palladium(0), acetic acid, THF, room temp., 6 h.

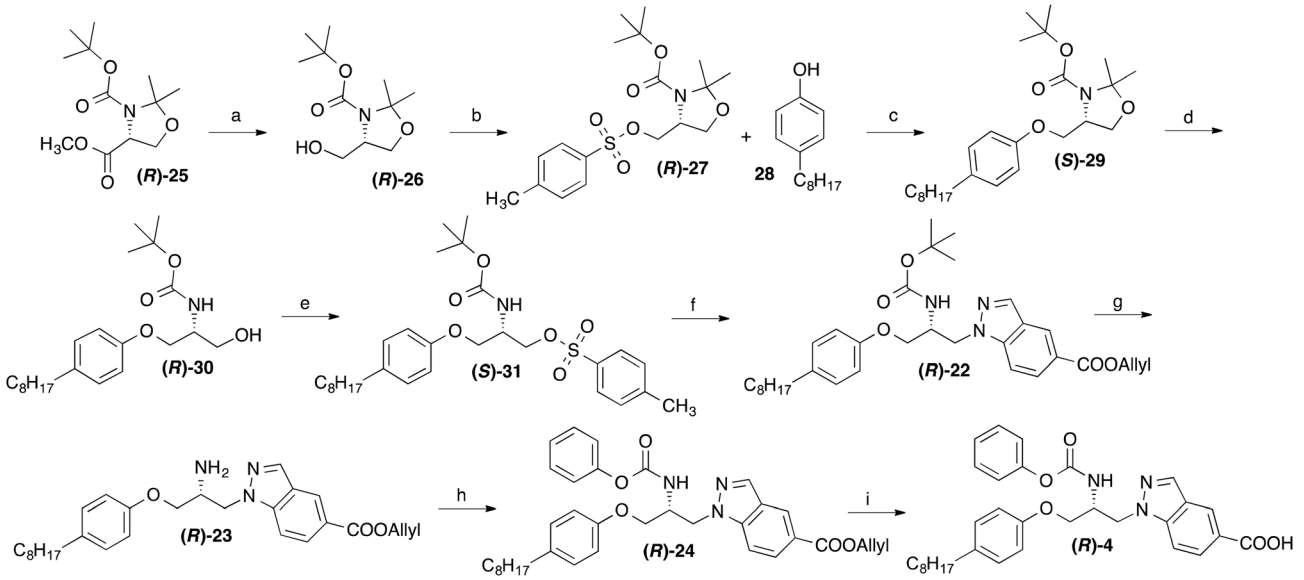
with varying substituents at the phenoxy-residue can be obtained from a common intermediate (here **21**) in only four steps instead of six necessary in the synthesis described above (Scheme 1).

Due to the chiral centre present in **4**, this compound exists as two enantiomers. For the determination of their eudismic ratio, additionally an enantioselective, chiral-pool based synthetic approach was established. The synthesis of the *R*-configurated enantiomer of **4** started from the commercially availably, (*R*)-serine derived oxazolidine (***R***)-**25**,[18] which was converted to the tosylate (***R***)-**27** as previously described (Scheme 3).[19,20] This central intermediate was reacted with 4-octylphenol to yield the phenol ether (***S***)-**29**. The acetone protecting group was removed by reaction with *p*-toluenesulfonic acid and the alcohol moiety of (***R***)-**30** was converted to a tosyl ester with *p*-toluenesulfonyl chloride. Treatment of obtained compound (***R***)-**31** with allyl indazole-5-carboxylate in DMF in presence of NaH afforded the BOC protected 1-(2-aminopropyl)indazole derivative (***R***)-**22**. After deprotection of the BOC group, the amine moiety of resulting compound (***R***)-**23** was reacted with phenyl chloroformate in presence of an amine base. Subsequent cleavage of the allyl ester group of resulting compound (***R***)-**24** using Pd(0) catalysis led to the desired target compound (***R***)-**4**.

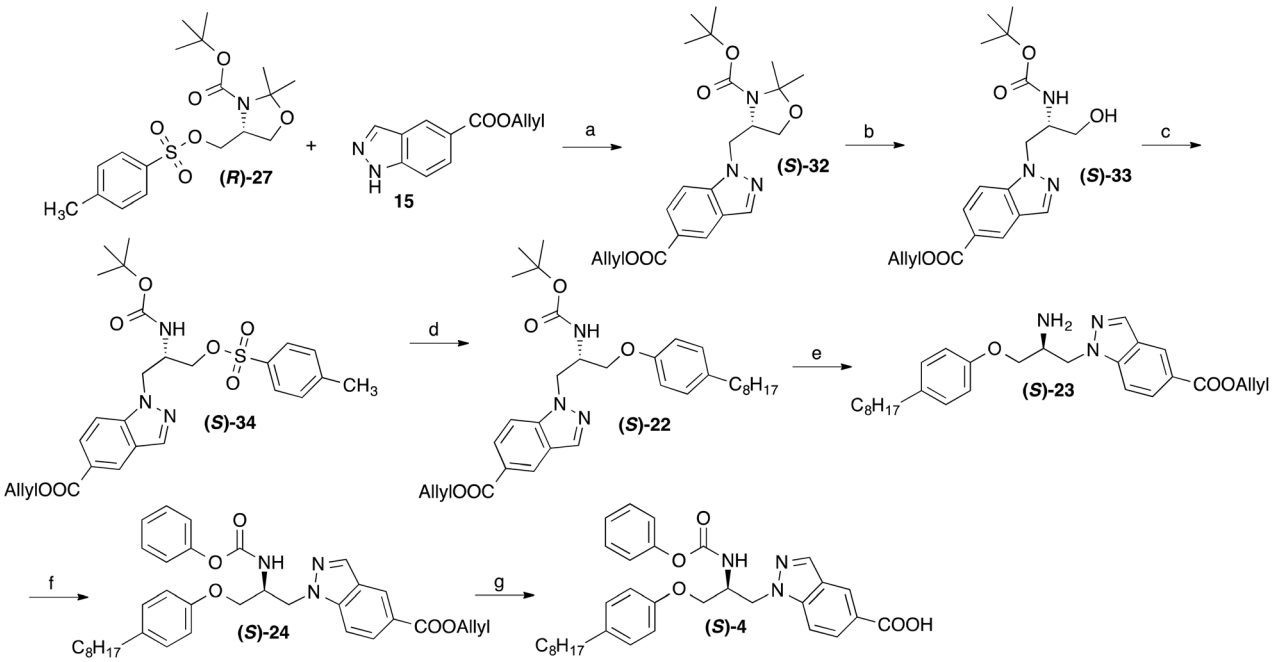
The synthesis of the *S*-enantiomer of **4** is outlined in Scheme 4. With (***R***)-**27**, the identical central chiral intermediate was used as for the synthesis of the *R*-enantiomer. To get the antipodal configuration in the target compound, here the indazole heterocycle and not the 4-octylphenoxy residue was introduced at first into the molecule. After removing the acetone protection group of obtained compound (***S***)-**32**, the free alcohol moiety was esterified with tosyl chloride and the tosylate group substituted by a 4-octylphenoxy residue to afford (***S***)-**22**. From this compound (***S***)-**4** was synthesized employing the same procedure as for the synthesis of (***R***)-**4** from (***R***)-**22**. Chiral HPLC on a Chiralpak® IA column revealed that (***R***)-**4** and (***S***)-**4** were formed with 93% ee and 100% ee, respectively (for chromatograms see ESI†).

Biological evaluation

The target compounds were evaluated for $cPLA_2\alpha$ inhibition in an assay using $cPLA_2\alpha$ isolated from porcine platelets.[21] When measuring the inhibitory potency of **4**, (***S***)-**4** and (***R***)-**4** it became evident that the data were strongly influenced by small impurities of the extreme potent indazolylpropan-2-one **3** (IC_{50}: 0.0045 μM) present in the substances. The highest amounts of **3** (about 1% measured by HPLC/UV and MS) were found in **4** synthesized *via* the route shown in Scheme 1. The spectral data of the intermediates of the synthesis revealed that the ketone group was introduced into the molecule during the reduction of the azide **12** to the amine **13**, and that the ketone impurity could not be separated in the following steps. The compounds synthesized by the sequences outlined in Schemes 2–4 contained smaller amounts of **3** (less than 0.1%). However, their inhibition values were also impaired by this substance. Therefore, all target compounds were purified by reversed phase HPLC. By this way, impurity **3** could be totally removed.



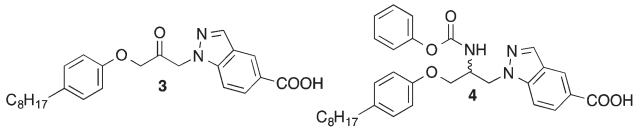
Scheme 3 Reagents and conditions: (a) $LiBH_4$, THF, 0 °C, 3 h; (b) *p*-toluenesulfonyl chloride, 4-dimethylaminopyridine, triethylamine, CH_2Cl_2, room temp., overnight; (c) NaH (dispersion in mineral oil), DMF, 70 °C, 3 h; (d) *p*-toluenesulfonic acid, room temp., 4 h; (e) *p*-toluenesulfonyl chloride, 4-dimethylaminopyridine, triethylamine, CH_2Cl_2, room temp., overnight; (f) allyl indazole-5-carboxylate (**15**), NaH (dispersion in mineral oil), DMF, 80 °C, 3 h; (g) trifluoroacetic acid, CH_2Cl_2, room temp., 2 h; (h) phenyl chloroformate, triethylamine, THF, room temp.; (i) tetrakis(triphenylphosphine)palladium(0), acetic acid, THF, room temp., 6 h.



Scheme 4 Reagents and conditions: (a) NaH, DMF, 80 °C, 3 h; (b) 1. 1 M HCl, THF, 70 °C, 3 h; 2. di-*tert*-butyl dicarbonate, triethylamine, methanol, room temp., 12 h; (c) *p*-toluenesulfonyl chloride, 4-dimethylaminopyridine, triethylamine, CH_2Cl_2, room temp., 12 h; (d) 4-octylphenol, NaH, DMF, 80 °C, 3 h; (e) trifluoroacetic acid, CH_2Cl_2, room temp., 2 h; (f) phenyl chloroformate, triethylamine, THF, room temp., 2 h; (g) tetrakis(triphenylphosphine)palladium(0), acetic acid, THF, room temp., 6 h.

The previously published lead compound **2** was newly synthesized from racemic **25** and allyl indole-5-carboxylate following the route outlined in Scheme 4 for the synthesis of (***S***)-**4** (see ESI†). After cleaning up by reversed phase HPLC, for **2** an IC_{50} value against $cPLA_2\alpha$ of 26 μM was evaluated. In contrast to the ketones **1** and **3**, the replacement of the indole heterocycle by an indazole did not increase inhibitory potency in case of the carbamates. With an IC_{50} of 29 μM **4** was as active

Table 1 Inhibition of $cPLA_2\alpha$ and metabolic stability



Compound	Inhibition of $cPLA_2\alpha$ IC_{50} [a] (μM)	Metabolic stability[b] (%)
3	0.0045	8
4 (racemate)	29	84
(***R***)-**4**	34	89
(***S***)-**4**	18	81

[a] Values are the means of at least two independent determinations, errors are within ±20%; IC_{50} value of reference inhibitor ARC-70484XX: 0.0065 μM.[10,21] [b] Percentage of parent compound remaining after metabolism by rat liver S9 fractions in presence of NADPH; values are the means of at least two independent determinations. Metabolic stability of reference inhibitor 3-(5-carboxypentanoyl)-1-[3-(4-octylphenoxy)-2-oxopropyl]indole-5-carboxylic acid:[12] 63 ± 6.7% (n = 9). Calculated log P values for **3** and **4** using Advanced Chemistry Development (ACD/Labs) Software V11.02: 6.5 and 8.4, respectively.

as **2** (Table 1). The two enantiomers of **4** showed a slight but significant difference in their IC_{50} values: the *S*-enantiomer was about two-fold more active than the *R*-enantiomer.

As mentioned above, a drawback of the indazolylpropan-2-one **3** is its metabolic liability. In *in vitro* experiments it could be shown that the carbamate **4** is much more stable against metabolism by rat liver homogenate than **3**. After incubation of **3** in presence of the co-factor NADPH only 8% of the parent compound could be recovered, under the same conditions still 80–90% of **4**, (***S***)-**4** and (***R***)-**4** were present in the incubation mixture.

Conclusions

Taken together, we have developed new effective synthetic approaches for the synthesis of **4** as well as for its enantiomers (***S***)-**4** and (***R***)-**4**. The biological evaluation of these compounds revealed that the increase of metabolic stability achieved by replacement of the ketone function of **3** by a carbamate moiety is accompanied by a drastic loss of $cPLA_2\alpha$ inhibitory potency. The aim of further studies will be to improve $cPLA_2\alpha$ inhibitory potency of **4** by structural variations.

Experimental section

Chemistry

General. Column chromatography was performed on silica gel 60, particle size 0.040–0.063 mm, from Macherey & Nagel. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer (400 MHz), a Varian Unity Plus 600 spectrometer (600 MHz) or an Agilent VNMRS-600 spectrometer (600 MHz). ^{13}C NMR spectra were measured on a Varian Mercury Plus 400 spectrometer (101 MHz) or an Agilent VNMRS-600 spectrometer (151 MHz). Electron ionization (EI) mass spectra were obtained on a Finnigan GCQ apparatus. The high resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF-Q II spectrometer using electro spray chemical ionization (ESI) or atmospheric pressure chemical ionization (APCI). Preparative reversed phase HPLC was performed using a Knauer pump P2.1L and a Shimazu SPD-6A UV detector. Chromatograms were recorded with MacDAcq32 Control Software from Bischoff. As stationary phase a Knauer RP18 Eurospher II 5 μm column (20 mm (I.D.) × 250 mm) with a RP18 Eurospher II 5 μm guard column (20 mm (I.D.) × 30 mm) was used. The mobile phase consisted of acetonitrile–water–formic acid (80 : 20 : 0.1, v/v/v). The flow rate was 25 mL min^{-1}. The compounds were dissolved in DMSO and the injected sample volume was 0.5–1 mL. The detection wavelength was set to 254 nm. The substances were obtained as solids after distilling off the organic solvent and freeze-drying the remaining aqueous phase using a Christ alpha 1-2 LD plus apparatus. Chiral HPLC-analysis was performed on a Daicel Chiralpak® IA 5 μm column (4.6 mm (I.D.) × 250 mm) using isohexane–methanol–isopropanol–formic acid (90 : 8.75 : 1.25 : 0.1, v/v/v/v) as mobile phase at a flow rate of 1 mL min^{-1}. The detection wavelength was 254 nm.

Allyl indazole-5-carboxylate (15). To a stirring suspension of potassium carbonate (0.52 g, 3.76 mmol) in dry DMF (4 mL) were added allyl bromide (2.2 mL, 13 mmol) and indazole-5-carboxylic acid (0.150 g, 0.93 mmol) and the obtained mixture was stirred at room temperature for 3 h. After addition of water (15 mL), the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 8 : 2) to yield **15** as a solid (0.175 g, 94%). Mp: 112–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.87 (dt, J = 5.6 Hz and 1.4 Hz, 2H), 5.31 (dq, J = 10.4 Hz and 1.3 Hz, 1H), 5.44 (dq, J = 17.2 Hz and 1.6 Hz, 1H), 6.07 (ddt, J = 17.2 Hz, 10.5 Hz and 5.6 Hz, 1H), 7.55 (dd, J = 8.9 Hz and 0.8 Hz, 1H), 8.12 (dd, J = 8.8 Hz and 1.5 Hz, 1H), 8.22 (s, 1H), 8.59 (dd, J = 1.4 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 65.8, 109.8, 118.4, 123.1, 123.7, 124.7, 128.1, 132.4, 136.3, 142.1, 166.5; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 203.0815, found: 203.0819.

Allyl 1-(oxiran-2-ylmethyl)indazole-5-carboxylate (16). To a solution of **15** (0.070 g, 0.35 mmol) in DMF (5 mL) was added cesium carbonate (0.337 g, 1.03 mmol) followed by epichlorohydrin (0.190 mL, 1.74 mmol). The mixture was stirred at room temperature for 14 h. After addition of water (10 mL), the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1) to yield **16** as an oil (0.063 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (dd, J = 4.7 Hz and 2.6 Hz, 1H), 2.84 (dd, J = 4.7 Hz and 4.0 Hz, 1H), 3.37 (dddd, J = 5.7 Hz, 3.9 Hz, 3.2 Hz and 2.5 Hz, 1H), 4.44 (dd, J = 15.2 Hz and 5.6 Hz, 1H), 4.72 (dd, J = 15.2 Hz and 3.3 Hz, 1H), 4.84 (dt, J = 5.6 Hz and 1.4 Hz, 2H), 5.29 (dq, J = 10.5 Hz and 1.3 Hz, 1H), 5.42 (dq, J =

17.2 Hz and 1.6 Hz, 1H), 6.05 (ddt, J = 17.2 Hz, 10.4 Hz and 5.6 Hz, 1H), 7.50 (dt, J = 8.9 Hz and 0.9 Hz, 1H), 8.07 (dd, J = 8.9 Hz and 1.5 Hz, 1H), 8.10 (d, J = 1.0 Hz, 1H), 8.52 (dd, J = 1.5 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 45.4, 50.7, 51.3, 65.6, 109.3, 118.2, 123.3, 123.9, 124.7, 127.5, 132.5, 135.4, 142.1, 166.4; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 259.1077, found: 259.1093.

Allyl 1-(3-azido-2-hydroxypropyl)indazole-5-carboxylate (17). Sodium azide (0.076 g, 1.17 mmol) and ammonium chloride (0.025 g, 0.47 mmol) were added to a suspension of **16** (0.060 g, 0.23 mmol) in methanol–water (9 : 1) (4.5 mL). The mixture was heated at 80 °C for 18 h. After cooling, the suspension was exhaustively extracted with diethyl ether. The combined organic phases were dried with Na_2SO_4 and concentrated to give **17** as a solid (0.067 g, 96%). Mp: 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (s, 1H), 3.38 (dd, J = 5.5 Hz and 1.9 Hz, 2H), 4.31 (dtd, J = 6.4 Hz, 5.5 Hz and 4.2 Hz, 1H), 4.45 (dd, J = 14.2 Hz and 6.2 Hz, 1H), 4.50 (dd, J = 14.2 Hz and 4.3 Hz, 1H), 4.85 (dq, J = 5.6 Hz and 1.4 Hz, 2H), 5.31 (dq, J = 10.5 Hz and 1.3 Hz, 1H), 5.43 (dq, J = 17.2 Hz and 1.5 Hz, 1H), 6.07 (ddtd, J = 17.2 Hz, 10.4 Hz, 5.6 Hz and 1.2 Hz, 1H), 7.47 (dt, J = 8.9 Hz and 1.0 Hz, 1H), 8.11 (dd, J = 8.9 Hz and 1.5 Hz, 1H), 8.13 (d, J = 1.0 Hz, 1H), 8.54 (dd, J = 1.5 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 51.3, 53.9, 65.8, 70.1, 109.0, 118.4, 123.5, 123.6, 124.9, 127.9, 132.4, 135.7, 142.2, 166.4; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 302.1248, found: 302.1269.

Allyl 1-(3-amino-2-hydroxypropyl)indazole-5-carboxylate hydrochloride (18). A solution of **17** (1.50 g, 4.98 mmol) in acetonitrile (12 mL) was treated with triphenylphosphine (1.31 g, 4.99 mmol) and stirred at room temperature for about 30 min until the development of nitrogen could be observed. Then the mixture was heated under reflux overnight. After cooling and evaporation of the solvent, the residue was dissolved in 1 M HCl and washed with ethyl acetate. The aqueous phase was concentrated to dryness and dissolved in a small volume of CH_2Cl_2. Addition of etheric HCl led to the formation of a precipitate. Finally, the solvent was removed *in vacuo* to yield **18** as a solid (1.55 g, 100%). Mp: 55–56 °C; ^{1}H NMR (400 MHz, DMSO-D_6): δ 2.71–2.85 (m, 1H), 2.90–3.04 (m, 1H), 4.12–4.30 (m, 1H), 4.53 (d, J = 5.6 Hz, 2H), 4.83 (dt, J = 5.4 Hz and 1.5 Hz, 2H), 5.29 (dq, J = 10.6 Hz and 1.5 Hz, 1H), 5.42 (dq, J = 17.2 Hz and 1.7 Hz, 1H), 5.81 (s, 1H), 6.08 (ddt, J = 17.2 Hz, 10.6 Hz and 5.4 Hz, 1H), 7.83 (dt, J = 8.9 Hz and 0.9 Hz, 1H), 7.97 (dd, J = 8.9 Hz and 1.6 Hz, 1H), 8.05 (s, 3H), 8.31 (d, J = 0.9 Hz, 1H), 8.52 (dd, J = 1.6 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-D_6): δ 42.2, 52.2, 64.9, 66.8, 110.5, 117.8, 122.0, 123.2, 124.1, 126.2, 132.8, 135.2, 142.0, 165.6; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 276.1343, found: 276.1372.

Allyl 1-{3-[(*tert*-butoxycarbonyl)amino]-2-hydroxypropyl}-indazole-5-carboxylate (19). A solution of **18** (0.220 g, 0.71 mmol) in diethyl ether (10 mL) and methanol (6 mL) was treated at 0 °C with triethylamine (0.11 mL, 0.79 mmol). Then di-*tert*-butyl dicarbonate (0.174 g, 0.80 mmol) was added and the mixture was stirred at room temperature for 2 h, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1 to 6 : 4) to afford **19** as an oil (0.256 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.59 (s, 1H), 3.16 (dd, J = 14.8 Hz and 4.2 Hz, 1H), 3.40 (d, J = 14.4 Hz, 1H), 4.18–4.27 (m, 1H), 4.40 (dd, J = 14.2 Hz and 6.7 Hz, 1H), 4.50 (dd, J = 14.3 Hz and 4.6 Hz, 1H), 4.86 (dt, J = 5.7 Hz and 1.4 Hz, 2H), 5.10 (s, 1H), 5.31 (dq, J = 10.4 Hz and 1.3 Hz, 1H), 5.43 (dq, J = 17.2 Hz and 1.6 Hz, 1H), 6.07 (ddt, J = 17.2 Hz, 10.5 Hz and 5.6 Hz, 1H), 7.47 (dt, J = 8.9 Hz and 0.9 Hz, 1H), 8.07–8.13 (m, 2H), 8.54 (dd, J = 1.5 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 28.5, 44.2, 51.8, 65.7, 71.0, 80.3, 109.2, 118.4, 123.5, 123.6, 124.9, 127.8, 132.5, 135.4, 142.1, 157.4, 166.4; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 376.1867, found: 376.1875.

Allyl 1-{3-[(*tert*-butoxycarbonyl)amino]-2-(tosyloxy)propyl}-indazole-5-carboxylate (20). To a solution of **19** (1.70 g, 4.53 mmol) in dry THF (40 mL) were added tosyl chloride (1.76 g, 9.23 mmol) and freshly powdered potassium hydroxide (88%) (1.08 g, 17 mmol). The mixture was stirred at room temperature for 4 h, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 8 : 2) to yield **20** as an oil (2.25 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.32 (s, 3H), 3.51 (t, J = 4.6 Hz, 2H), 4.55 (dd, J = 15.5 Hz and 7.2 Hz, 1H), 4.61 (dd, J = 15.1 Hz and 3.8 Hz, 1H), 4.87 (dt, J = 5.7 Hz and 1.4 Hz, 2H), 4.94–5.01 (m, 1H), 5.07 (t_{broad}, J = 6.4 Hz, 1H), 5.33 (dq, J = 10.4 Hz and 1.3 Hz, 1H), 5.45 (dq, J = 17.2 Hz and 1.5 Hz, 1H), 6.09 (ddt, J = 17.3 Hz, 10.5 Hz and 5.6 Hz, 1H), 6.97 (d, J = 8.3 Hz, 2H), 7.29–7.37 (m, 3H), 7.90 (s, 1H), 8.00 (d, J = 8.9 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.7, 28.5, 42.4, 50.2, 65.8, 80.0, 80.2, 109.2, 118.5, 123.3, 123.8, 124.5, 127.4, 127.6, 129.6, 132.5, 132.5, 135.6, 142.1, 144.9, 156.0, 166.4; HRMS (ESI+) $[M + H]^+$ calculated: 530.1955, found: 530.1956.

Allyl 1-{[1-(*tert*-butoxycarbonyl)aziridine-2-yl]methyl}indazole-5-carboxylate (21). To a solution of **20** (2.25 g, 4.25 mmol) in CH_2Cl_2 (40 mL) were added tetrabutylammonium hydrogen sulfate (0.231 g, 0.68 mmol) and freshly powdered potassium hydroxide (88%) (1.08 g, 17 mmol). The mixture was stirred at room temperature for 6 h. After addition of diethyl ether (100 mL), the mixture was filtered and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9 : 1) to yield **21** as an oil (1.26 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 2.12 (d, J = 3.6 Hz, 1H), 2.37 (d, J = 6.2 Hz, 1H), 2.83 (tdd, J = 6.1 Hz, 4.8 Hz and 3.5 Hz, 1H), 4.48 (dd, J = 14.8 Hz and 6.0 Hz, 1H), 4.55 (dd, J = 14.8 Hz and 4.8 Hz, 1H), 4.86 (dt, J = 5.6 Hz and 1.4 Hz, 2H), 5.30 (dq, J = 10.4 Hz and 1.3 Hz, 1H), 5.43 (dq, J = 17.2 Hz and 1.5 Hz, 1H), 6.07 (ddt, J = 17.1 Hz, 10.5 Hz and 5.6 Hz, 1H), 7.54 (dt, J = 8.8 Hz and 0.8 Hz, 1H), 8.08 (dd, J = 8.8 Hz and 1.5 Hz, 1H), 8.11 (d, J = 0.9 Hz, 1H), 8.53 (dd, J = 1.5 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 27.8, 30.3, 36.4, 51.4, 65.7, 81.6, 109.7, 118.3, 123.2, 124.0, 124.7, 127.4, 132.5, 135.4, 142.0, 161.6, 166.6; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 358.1761, found: 358.1749.

Allyl 1-{2-[(*tert*-butoxycarbonyl)amino]-3-(4-octylphenoxy)-propyl}indazole-5-carboxylate (22). A solution of **21** (0.050 g,

0.14 mmol) in CH_2Cl_2 (10 mL) was treated with 4-octylphenol (0.044 g, 0.21 mmol). After addition of 2 drops of BF_3-etherate, the mixture was stirred at room temperature for 1 min, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1 to 8 : 2) to yield **22** as an oil (0.016 g, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.6 Hz, 3H), 1.22–1.35 (m, 10H), 1.41 (s, 9H), 1.50–1.57 (m, 2H), 2.49–2.58 (m, 2H), 3.78 (dd, J = 9.5 Hz and 5.6 Hz, 1H), 3.95 (dd, J = 9.5 Hz and 3.3 Hz, 1H), 4.36–4.50 (m, 1H), 4.66 (dd, J = 14.2 Hz and 5.8 Hz, 1H), 4.76 (dd, J = 14.3 Hz and 5.2 Hz, 1H), 4.85 (d, J = 5.6 Hz, 2H), 5.31 (dd, J = 10.4 Hz and J = 1.2 Hz, 1H), 5.37–5.49 (m, 2H), 6.07 (ddt, J = 17.1 Hz, 10.8 Hz and 5.6 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.9 Hz, 1H), 8.03 (dd, J = 8.9 Hz and 1.3 Hz, 1H), 8.13 (s, 1H), 8.53 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2, 22.8, 28.4, 29.4, 29.6, 31.8, 32.0, 35.2, 49.1, 50.3, 65.7, 66.7, 80.1, 109.2, 114.5, 118.3, 123.3, 123.7, 124.7, 127.6, 129.5, 132.5, 135.6, 136.1, 142.3, 155.3, 156.2, 166.5; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 564.3432, found: 564.3505.

Allyl 1-[2-amino-3-(4-octylphenoxy)propyl]indazole-5-carboxylate (23). A solution of **22** (0.108 g, 0.19 mmol) in CH_2Cl_2 (8 mL) was treated with several drops of trifluoroacetic acid (0.57 mL, 7.4 mmol) and stirred at room temperature for 2 h. Then the reaction mixture was evaporated. The residue was treated with ethyl acetate and washed with 2 M aqueous NaOH solution. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to yield **23** as an oil (0.089 g, 100%). ^{1}H NMR (400 MHz, DMSO-D_6): δ 0.83 (t, J = 6.6 Hz, 3H), 1.29–1.14 (m, 10H), 1.49 (t, J = 7.9 Hz, 2H), 2.38–2.45 (m, 2H), 3.96 (dd, J = 10.3 Hz and 4.9 Hz, 1H), 4.06 (s, 1H), 4.15 (dd, J = 10.5 Hz and 3.5 Hz, 1H), 4.85–4.75 (m, 4H), 5.27 (dq, J = 10.5 Hz and 1.5 Hz, 1H), 5.40 (dq, J = 17.2 Hz and 1.7 Hz, 1H), 6.05 (ddt, J = 17.6 Hz, 10.5 Hz and 5.3 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.8 Hz, 1H), 7.97 (dd, J = 8.8 Hz and 1.6 Hz, 1H), 8.39 (s, 1H), 8.53 (d, J = 1.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-D_6): δ 14.4, 22.5, 29.0, 29.1, 29.3, 31.6, 31.7, 34.7, 51.4, 51.9, 65.4, 70.3, 110.6, 114.7, 118.2, 122.4, 123.6, 124.6, 126.6, 129.5, 133.3, 134.9, 135.5, 142.2, 156.8, 166.0; MS (EI 70 eV) m/z (%): 463 (3) M^+, 258 (16), 248 (50), 107 (100).

Allyl 1-{3-(4-octylphenoxy)-2-[(phenoxycarbonyl)amino]propyl}-indazole-5-carboxylate (24). To a solution of **23** (0.044 g, 0.095 mmol) in dry THF (4 mL) were added dropwise at 0 °C triethylamine (0.016 mL, 0.11 mmol) followed by phenyl chloroformate (0.015 mL, 0.12 mmol). The mixture was stirred at room temperature for 2 h, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1 to 8 : 2) to yield **24** as an oil (0.041 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.9 Hz, 3H), 1.20–1.34 (m, 10H), 1.52–1.55 (m, 2H), 2.50–2.57 (m, 2H), 3.82 (dd, J = 9.7 Hz and 6.0 Hz, 1H), 4.08 (dd, J = 9.7 Hz and 3.7 Hz, 1H), 4.48–4.58 (m, 1H), 4.74 (dd, J = 14.4 Hz and 5.9 Hz, 1H), 4.81–4.90 (m, 3H), 5.30 (dq, J = 10.5 Hz and 1.3 Hz, 1H), 5.43 (dq, J = 17.2 Hz and 1.6 Hz, 1H), 5.98–6.13 (m, 2H), 6.82 (d, J = 8.6 Hz, 2H), 7.04–7.11 (m, 4H), 7.21 (t, J = 7.5 Hz, 1H), 7.35 (dd, J = 8.1 Hz and 7.6 Hz, 2H), 7.56 (d, J = 9.0 Hz, 1H), 8.04 (dd, J = 8.9 Hz and 1.4 Hz, 1H), 8.15 (d, J = 0.7 Hz, 1H), 8.54 (d, J = 0.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.3, 22.8, 29.4, 29.6, 31.8, 32.0, 35.2, 48.6, 51.0, 65.7, 66.2, 109.2, 114.5, 118.3, 121.7, 123.5, 123.7, 124.9, 125.7, 127.9, 129.5, 129.6, 132.5, 135.9, 136.3, 142.3, 150.9, 154.4, 156.1, 166.4; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 584.3119, found: 584.3344.

1-{3-(4-Octylphenoxy)-2-[(phenoxycarbonyl)amino]propyl}-indazole-5-carboxylic acid (4). To a solution of **24** (0.038 g, 0.065 mmol) in dry THF (3 mL) was added under nitrogen tetrakis(triphenylphosphine)palladium(0) (0.008 g, 0.007 mmol). Then nitrogen was bubbled through the solution for 10 min. After addition of acetic acid (0.1 mL), the mixture was stirred at room temperature for 6 h, concentrated and chromatographed on silica gel (hexane–ethyl acetate–acetic acid, 8 : 2 : 0.1) to yield **4** as a solid (0.036 g, 98%). Mp: 189–190 °C; ^{1}H NMR (400 MHz, DMSO-D_6): δ 0.83 (t, J = 6.5 Hz, 3H), 1.16–1.30 (m, 10H), 1.44–1.55 (m, 2H), 2.49 (m, 2H), 4.02–4.12 (m, 2H), 4.23–4.34 (m, 1H), 4.61 (dd, J = 14.4 Hz and 8.0 Hz, 1H), 4.72 (dd, J = 14.5 Hz and 5.1 Hz, 1H), 6.76 (d, J = 7.8 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.26 (dd, J = 8.3 Hz and 7.3 Hz, 2H), 7.73 (d, J = 9.1 Hz, 1H), 7.92 (dd, J = 9.0 Hz and 1.2 Hz, 1H), 8.03 (d, J = 8.7 Hz, 1H), 8.27 (s, 1H), 8.43 (s, 1H), 12.76 (s_{broad}, 1H); ^{13}C NMR (101 MHz, DMSO-D_6): δ 14.0, 22.1, 28.6, 28.7, 28.9, 31.2, 31.3, 34.3, 49.2, 51.3, 67.1, 109.6, 114.4, 121.5, 123.3, 123.4, 124.0, 125.0, 126.6, 129.1, 129.2, 134.8, 135.2, 141.7, 153.9, 155.9, 156.2, 167.6; HRMS (ESI+) $[M + H]^+$ calculated: 544.2806, found: 544.2853.

(*S*)-*tert*-Butyl 2,2-dimethyl-4-[(4-octylphenoxy)methyl]oxazolidine-3-carboxylate ((S)-29). To a solution of 4-octylphenol (0.400 g, 1.94 mmol) in dry DMF (7 mL) was added sodium hydride (60% dispersion in mineral oil) (0.085 g, 2.13 mmol). The mixture was stirred at room temperature for about 30 min until no further development of hydrogen could be observed. A solution of (*R*)-*tert*-butyl 2,2-dimethyl-4-[(tosyloxy)methyl]oxazolidine-3-carboxylate ((***R***)-**27**)[19,20] (0.897 g, 2.33 mmol) in DMF (7 mL) was added dropwise and the mixture was heated at 70 °C for about 3 h. After addition of water (50 mL), the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 19 : 1) to yield (***S***)-**29** as an oil (0.661 g, 81%). ^{1}H NMR (400 MHz, DMSO-D_6): δ 0.84 (t, J = 6.7 Hz, 3H), 1.16–1.32 (m, 10H), 1.36–1.55 (m, 17H), 2.44–2.55 (m, 2H), 3.81 (t, J = 9.2 Hz, 1H), 3.91 (dd, J = 9.1 Hz and 1.5 Hz, 1H), 3.96–4.06 (m, 2H), 4.08–4.16 (m, 1H), 6.87 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-D_6): δ 13.9, 22.0, 22.9, 24.1, 26.4, 27.2, 28.0, 28.5, 28.6, 28.8, 31.2, 31.2, 34.2, 55.2, 55.6, 64.6, 64.9, 66.0, 66.7, 79.3, 79.7, 92.9, 93.2, 114.3, 114.3, 129.2, 134.6, 134.7, 151.0, 151.4, 156.2; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 420.3108, found: 420.3148.

(*R*)-*tert*-Butyl [1-hydroxy-3-(4-octylphenoxy)propan-2-yl]carbamate ((R)-30). To a solution of (***S***)-**29** (0.550 g, 1.31 mmol) in methanol (10 mL) was added *p*-toluenesulfonic acid monohydrate (0.113 g, 0.59 mmol). The mixture was stirred at room

temperature for about 4 h. After neutralization with saturated sodium bicarbonate solution (10 mL), methanol was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried with Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 8 : 2) to yield (***R***)-**30** as an oil (0.302 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J = 6.7 Hz, 3H), 1.15–1.37 (m, 10H), 1.46 (s, 9H), 1.53–1.57 (m, 2H), 2.33 (s, 1H), 2.46–2.62 (m, 2H), 3.74–3.85 (m, 1H), 3.86–3.95 (m, 1H), 3.96–4.16 (m, 3H), 5.20 (d, J = 6.8 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H); ^{13}C NMR; MS (EI 70 eV) m/z (%): 379 (2) M^+, 206 (75), 118 (100), 107 (64).

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(4-octylphenoxy)propyl 4-methylbenzenesulfonate ((S)-31). A solution of (***R***)-**30** (0.280 g, 0.74 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of tosyl chloride (0.282 g, 1.48 mmol) and 4-dimethylaminopyridine (0.045 g, 0.37 mmol) in CH_2Cl_2 (15 mL). The mixture was treated with triethylamine (204 μL, 1.46 mmol) and stirred for 12 h. The reaction mixture was washed three times with 1 M $KHSO_4$ and with brine, dried over Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1 to 8 : 2) to yield (***S***)-**31** as an oil (0.275 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.9 Hz, 3H), 1.21–1.34 (m, 10H), 1.43 (s, 9H), 1.53–1.57 (m, 2H), 2.37 (s, 3H), 2.50–2.57 (m, 2H), 3.84 (dd, J = 9.3 Hz and 5.4 Hz, 1H), 3.97 (dd, J = 9.3 Hz and 3.3 Hz, 1H), 4.14–4.27 (m, 3H), 4.94 (d, J = 7.1 Hz, 1H), 6.66 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2, 21.8, 22.8, 28.4, 29.4, 29.6, 31.9, 32.0, 35.2, 48.7, 65.5, 68.0, 80.3, 114.3, 128.0, 129.4, 130.0, 132.5, 135.9, 145.1, 155.1, 156.1; HRMS (ESI+) $[M + H]^+$ calculated: 534.2884, found: 534.2867.

(*R*)-Allyl 1-{2-[(*tert*-butoxycarbonyl)amino]-3-(4-octylphenoxy)-propyl}indazole-5-carboxylate ((R)-22). To a solution of allyl indazole-5-carboxylate (**15**) (0.114 g, 0.56 mmol) in dry DMF (5 mL) was added sodium hydride (60% dispersion in mineral oil) (0.024 g, 0.60 mmol). The mixture was stirred at room temperature for about 30 min until no further development of hydrogen could be observed. Then a solution of (***S***)-**31** (0.200 g, 0.37 mmol) in DMF (5 mL) was added dropwise and the mixture was heated at 80 °C for about 3 h. After addition of water (10 mL), the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1) to yield (***R***)-**22** as an oil (0.121 g, 57%). The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **22**. HRMS (APCI, direct probe) $[M + H]^+$ calculated: 564.3432, found: 564.3473.

(*R*)-Allyl 1-[2-amino-3-(4-octylphenoxy)propyl]indazole-5-carboxylate ((R)-23). (***R***)-**22** (0.080 g, 0.14 mmol) was reacted with trifluoroacetic acid in the same manner as described for the synthesis of **23** to yield (***R***)-**23** as an oil (0.065 g, 99%). The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **23**. MS (EI 70 eV) m/z (%): 463 (12) M^+, 258 (38), 248 (100), 107 (31).

(*R*)-Allyl 1-{3-(4-octylphenoxy)-2-[(phenoxycarbonyl)amino]-propyl}indazole-5-carboxylate ((R)-24). (***R***)-**23** (0.030 g, 0.064 mmol) was reacted with phenyl chloroformate (8 μL, 0.064 mmol) in the same manner as described for the synthesis of **24** to yield (***R***)-**24** as an oil (0.030 g, 79%). The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **24**. HRMS (APCI, direct probe) $[M + H]^+$ calculated: 584.3119, found: 584.3187.

(*R*)-1-{3-(4-Octylphenoxy)-2-[(phenoxycarbonyl)amino]propyl}-indazole-5-carboxylic acid ((R)-4). (***R***)-**4** was obtained from (***R***)-**24** (0.026 g, 0.045 mmol) in the same manner as described for the synthesis of **4**. Yield: 0.022 g, 91%. Mp: 173–174 °C. The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **24**. HRMS (APCI, direct probe) $[M + H]^+$ calculated: 544.2806, found: 544.2816. Enantiomeric excess determined by chiral HPLC: 93.1% ee. Specific rotation $[\alpha]_D^{20}$ = +5.4 (c = 0.20 g per 100 mL; ethyl acetate).

(*S*)-*tert*-Butyl 4-({5-[(allyloxy)carbonyl]indazole-1-yl}methyl)-2,2-dimethyloxazolidine-3-carboxylate ((S)-32). To a solution of allyl indazole-5-carboxylate (**15**) (0.913 g, 4.52 mmol) in dry DMF (15 mL) was added sodium hydride (60% dispersion in mineral oil) (0.199 g, 4.98 mmol). The mixture was stirred at room temperature for about 30 min until no further development of hydrogen could be observed. A solution of (*R*)-*tert*-butyl 2,2-dimethyl-4-[(tosyloxy)methyl]oxazolidine-3-carboxylate ((***R***)-**27**)[19,20] (2.09 g, 5.42 mmol) in DMF (15 mL) was added dropwise and the mixture was heated at 70 °C for about 3 h. After addition of water (50 mL), the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried with Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1 to 8 : 2) to yield (***S***)-**32** as an oil (1.20 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20–1.59 (m, 15H), 3.80–4.68 (m, 5H), 4.85 (dt, J = 5.6 Hz and 1.5 Hz, 2H), 5.30 (d, J = 10.6 Hz, 1H), 5.42 (dq, J = 17.2 Hz and 1.5 Hz, 1H), 5.98–6.14 (m, 1H), 7.48–7.67 (m, 1H), 8.03–8.15 (m, 2H), 8.50–8.55 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 23.1, 24.2, 27.0, 27.2, 28.5, 28.7, 49.6, 50.3, 56.8, 57.3, 65.3, 65.5, 65.6, 65.7, 80.7, 80.9, 93.9, 94.7, 108.7, 109.5, 118.2, 118.3, 123.2, 123.3, 123.8, 123.9, 124.7, 124.9, 127.4, 128.0, 132.5, 132.6, 135.1, 135.5, 141.8, 142.1, 151.7, 152.6, 166.4, 166.6; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 416.2180, found: 416.2174.

(*S*)-Allyl 1-{2-[(*tert*-butoxycarbonyl)amino]-3-hydroxypropyl}-indazole-5-carboxylate ((S)-33). A solution of (***S***)-**32** (0.900 g, 2.17 mmol) in THF (10 mL) and 1 M HCl (10 mL) was heated at 70 °C for 3 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in methanol (20 mL) and triethylamine (1.04 mL, 7.46 mmol) and di-*tert*-butyl dicarbonate (0.543 g, 2.49 mmol) were added at 0 °C. The mixture was stirred for 12 h, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 8 : 2) to yield (***S***)-**33** as a solid (0.753 g, 93%). Mp: 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 3.11 (s_{broad}, 1H), 3.54 (dd, J = 11.7 Hz and 4.8 Hz, 1H), 3.69 (dd, J = 11.6 Hz and 3.6 Hz, 1H), 3.99–4.10 (m, 1H), 4.63 (dd, J = 14.4 Hz and 4.5 Hz, 1H), 4.71 (dd, J = 14.5 Hz and 6.5 Hz, 1H), 4.85 (dt, J = 5.7 Hz and 1.4 Hz, 2H), 5.13 (s, 1H), 5.30 (dq, J = 10.4 Hz and 1.3 Hz, 1H), 5.43 (dq, J = 17.2 Hz and 1.5 Hz, 1H), 6.06 (ddt, J = 17.2 Hz, 10.4 Hz and 5.6 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 8.10 (dd, J = 8.9 Hz and 1.5 Hz, 1H),

8.14 (d, J = 0.9 Hz, 1H), 8.54 (dd, J = 1.5 Hz and 0.8 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 28.5, 48.9, 51.9, 62.3, 65.8, 80.1, 109.4, 118.4, 123.4, 123.6, 124.9, 128.0, 132.5, 135.5, 142.4, 155.7, 166.4; HRMS (APCI, direct probe) $[M + H]^+$ calculated: 376.1867, found: 376.1870.

(*S*)-Allyl 1-{2-[(*tert*-butoxycarbonyl)amino]-3-(tosyloxy)propyl}-indazole-5-carboxylate ((S)-34). A solution of (*S*)-**33** (0.370 g, 0.99 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of tosyl chloride (0.376 g, 1.97 mmol) and 4-dimethylaminopyridine (0.060 g, 0.49 mmol) in CH_2Cl_2 (10 mL). The mixture was treated with triethylamine (273 μL, 1.96 mmol) and stirred at room temperature for 12 h. The reaction mixture was washed three times with 1 M $KHSO_4$ and with brine, dried over Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1 to 8 : 2) to yield (*S*)-**34** as an oil (0.490 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 2.41 (s, 3H), 3.93 (dd, J = 10.3 Hz and 5.5 Hz, 1H), 4.02 (dd, J = 10.2 Hz and 4.6 Hz, 1H), 4.28–4.38 (m, 1H), 4.49 (dd, J = 14.3 Hz and 5.8 Hz, 1H), 4.59 (dd, J = 14.0 Hz and 5.6 Hz, 1H), 4.86 (dt, J = 5.7 Hz and 1.4 Hz, 2H), 5.28–5.35 (m, 2H), 5.44 (dq, J = 17.2 Hz and 1.5 Hz, 1H), 6.07 (ddt, J = 17.2 Hz, 10.4 Hz and 5.7 Hz, 1H), 7.24–7.29 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 8.03–8.09 (m, 2H), 8.50 (dd, J = 1.6 Hz and 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.8, 28.3, 48.4, 49.8, 65.8, 68.4, 80.4, 109.1, 118.4, 123.5, 123.6, 124.8, 127.9, 128.1, 130.0, 132.2, 132.4, 135.7, 142.1, 145.3, 155.0, 166.4; HRMS (ESI+) $[M + H]^+$ calculated: 530.1955, found: 530.1994.

(*S*)-Allyl 1-{2-[(*tert*-butoxycarbonyl)amino]-3-(4-octylphenoxy)-propyl}indazole-5-carboxylate ((S)-22). To a solution of 4-octylphenol (0.210 g, 1.02 mmol) in dry DMF (5 mL) was added sodium hydride (60% dispersion in mineral oil) (0.041 g, 1.03 mmol). The mixture was stirred at room temperature for about 30 min until no further development of hydrogen could be observed. Then a solution of (*S*)-**34** (0.450 g, 0.85 mmol) in DMF (5 mL) was added dropwise and the mixture was heated at 80 °C for about 3 h. After addition of water (10 mL), the reaction mixture was exhaustively extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4, concentrated and chromatographed on silica gel (hexane–ethyl acetate, 9 : 1) to yield (*S*)-**22** as a solid (0.311 g, 65%). Mp: 70–71 °C. The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **22**. HRMS (APCI, direct probe) $[M + H]^+$ calculated: 564.3432, found: 564.3470.

(*S*)-Allyl 1-[2-amino-3-(4-octylphenoxy)propyl]indazole-5-carboxylate ((S)-23). (*S*)-**22** (0.200 g, 0.35 mmol) was treated with trifluoroacetic acid in a similar manner as described for the synthesis of **23** to yield (*S*)-**23** as an oil (0.160 g, 97%). The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **23**. HRMS (APCI, direct probe) $[M + H]^+$ calculated: 464.2908, found: 464.2906.

(*S*)-Allyl 1-{3-(4-octylphenoxy)-2-[(phenoxycarbonyl)amino]-propyl}indazole-5-carboxylate ((S)-24). Following the procedure described for the synthesis of **24**, (*S*)-**23** (0.140 g, 0.30 mmol) was reacted with phenyl chloroformate (42 μL, 0.33 mmol) to yield (*S*)-**24** as a solid (0.144 g, 82%); mp: 115–116 °C. The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **24**. HRMS (ESI+) $[M + H]^+$ calculated: 584.3119, found: 584.3125.

(*S*)-1-{3-(4-Octylphenoxy)-2-[(phenoxycarbonyl)amino]propyl}-indazole-5-carboxylic acid ((S)-4). Following the procedure described for the synthesis of **4**, (*S*)-**24** (0.120 g, 0.21 mmol) was converted to (*S*)-**4** (0.104 g, 93%); mp: 184–185 °C. The ^{1}H NMR and ^{13}C NMR spectral data were identical with those of **4**. HRMS (ESI+) $[M + H]^+$ calculated: 544.2806, found: 544.2796. Enantiomeric excess determined by chiral HPLC: 100% ee. Specific rotation $[\alpha]_D^{20} = -5.4$ (c = 0.20 g per 100 mL; ethyl acetate).

Biological evaluation

Inhibition of cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$). Inhibition of $cPLA_2\alpha$ was measured according to a recently published procedure.[21] Briefly, $cPLA_2\alpha$ isolated from porcine platelets was incubated with co-vesicles consisting of the substrate 1-stearoyl-2-arachidonoyl-*sn*-glycero-3-phosphocholine (200 μM) and 1,2-dioleoyl-*sn*-glycerol (100 μM). Enzyme reactions were terminated after 60 min and $cPLA_2\alpha$ activity was determined by measuring the arachidonic acid released by the enzyme in absence and presence of a test compound with reversed phase HPLC and UV-detection at 200 nm after on-line solid phase extraction. Because under the published conditions (RP18 column with mobile phase acetonitrile–water–phosphoric acid (85%), 77 : 23 : 0.1, v/v/v) the test compounds **2** and **4** co-eluted with the analyte arachidonic acid, the separation conditions had to be modified. Separation could be achieved using an Phenomenex Aqua 3 μ C18 column (4.6 mm (I.D.) × 150 mm) protected with a Phenomenex C18 guard column (3 mm (I.D.) × 4 mm) using acetonitrile–10 mM aqueous $Na_2HPO_3 \times 12\ H_2O$, pH 7.4 (60 : 40, v/v) as mobile phase at a flow rate of 0.7 mL.

Metabolic stability in rat liver S9 fractions. The metabolic stability was tested using S9 fractions of rat liver homogenate.[22] Briefly, test compounds were incubated under aerobic conditions in absence and presence of the co-factor NADPH. The metabolic reactions were terminated after 30 min. The extent of metabolism was evaluated with reversed phase HPLC and UV-detection at 240 nm.

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