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Stereoselective synthesis of (3-aminodecahydro-1,4-methanonaphthalen-2-yl) methanols targeted to the C1 domain of protein kinase C

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ABSTRACT

Protein kinase C (PKC) is a widely studied molecular target for the treatment of cancer and other diseases. We have approached the issue of modifying PKC function by targeting the C1 domain in the regulatory region of the enzyme. By using the X-ray crystal structure of the PKCδ C1b domain combined with molecular modeling, we discovered (3-aminodecahydro-1,4-methanonaphthalen-2-yl)methanol as a novel C1 domain ligand. The stereoselective synthesis of this tricyclic γ-amino alcohol was based on two successive Diels–Alder reactions to construct the six continuous stereocenters of the key intermediate.

1. Introduction

The protein kinase C (PKC) family of serine/threonine protein kinases includes at least ten mammalian isoforms[1] that are involved in intracellular signal transduction cascades and in cellular events such as proliferation, differentiation and apoptosis.[2,3] The PKC family can be divided into three subgroups according to their structures and activation mechanisms.[4] Classical/conventional PKCs (cPKCs: α, βI, βII, and γ) require calcium and diacylglycerol (DAG, **1**) (Fig. 1) for activation, whereas novel PKCs (nPKCs: δ, ε, η, and θ) need only endogenous DAG for activation. In contrast to cPKCs and nPKCs, atypical PKCs (aPKCs: ζ and ι/λ) require neither calcium nor DAG for activation. Only the regulatory C1 domains of cPKCs and nPKCs are capable of binding DAG and tumor-promoting phorbol esters (**2a**, Fig. 1), leading to enzyme activation.[4]

Aberrant signaling through PKC isoforms and other C1 domain-containing proteins has been correlated to a number of conditions, including cancer,[5,6] neurological diseases;[7] especially Alzheimer's disease,[8–10] immunological diseases,[11,12] and cardiovascular diseases.[13–15] Therefore, PKC and other C1 domain-containing proteins have been subjects of intensive research and drug development.[16] Others[17] and we[18,19] have used the crystal structure of the C1b domain of PKCδ complexed with phorbol 13-*O*-acetate[20] (**2b**, Fig. 1) as the starting point in the design of new compounds as potent PKC C1 domain ligands. In addition to the above-mentioned crystal structure, the crystal structure of the full-length PKCβII complexed with adenosine 5′-(β,γ-imido)triphosphate was recently published.[21] Here we report the design and synthesis of (3-aminodecahydro-1,4-methanonaphthalen-2-yl)methanols (**3a**,**b**, Fig. 1) targeted to the C1b domain of PKCδ.

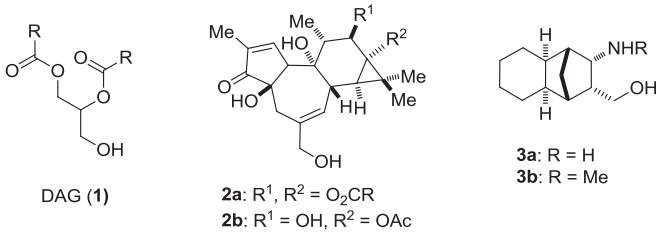

Fig. 1. Structures of DAG (**1**), phorbol esters (**2a**,**b**) and γ-amino alcohols (**3a**,**b**).

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2. Results and discussion

Docking simulations suggest that (**3a**) would be well accommodated in the PKCδ binding site (Fig. 2). In the X-ray structure of PKCδ, phorbol 13-*O*-acetate (**2b**) binds inside a groove on the PKCδ surface, forming a network of five hydrogen bonds.[20] This network involves two hydroxy and one carbonyl groups from phorbol 13-*O*-acetate that interact with the main chain amide and side chain hydroxy groups of Thr 242, the main chain amide and carbonyl groups of Gly 253, and the main chain carbonyl group of Leu 251 from the protein. Similar interactions are suggested by the docking simulations, whereby the hydroxy group of (**3a**) interacts with the main chain amide and side chain hydroxy groups of Thr 242, and the amino group of (**3a**) accepts hydrogen bonds from both the carbonyl group of Leu 251 and from that of Gly 253.

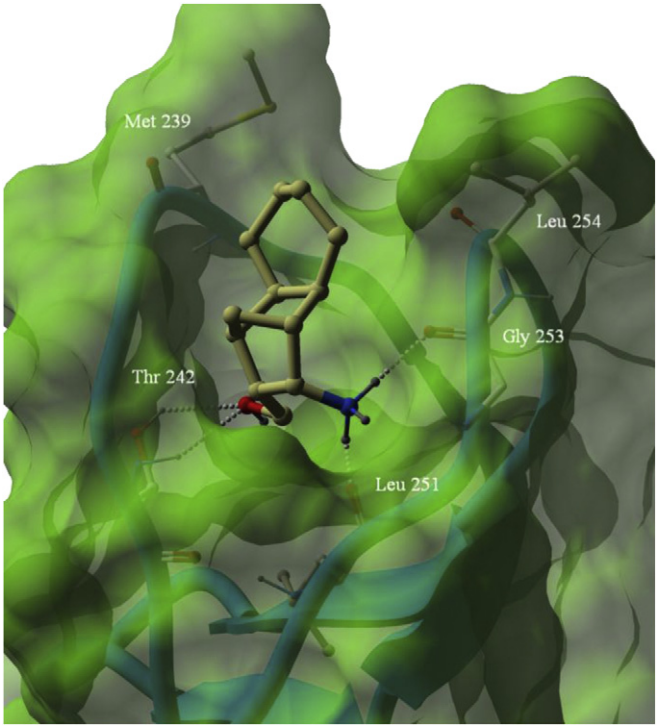
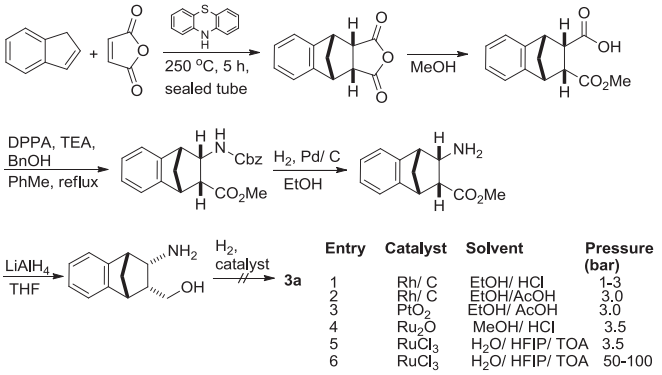


Fig. 2. The γ-amino alcohol (**3a**) docked in the crystal structure of the PKCδ C1b domain.[20] The C1b domain is represented as a transparent green surface and the secondary structure colored blue. The hit compound (**3a**) and the residues are presented in ball and stick representation and colored by atom type. Hydrogen bonds are shown as white spheres. The figure was created using ICM-Browser (version 3.7-2a, MolSoft L.L.C.).

The C1 domain-DAG/-phorbol ester complex is thought to be partly buried in the membrane bilayer.[20,22] To overcome an enthalpy penalty caused by interactions between the polar groove of the binding site and the bilayer, the ligands are thought to act as caps on the top part of the domain to produce a continuous hydrophobic surface and thus masking the polar groove. Also the docked hit compound (**3a**) seems to form a similar cap, since the polar amino and hydroxy groups of (**3a**) face toward the polar groove, and the hydrocarbon skeleton toward the supposed membrane direction.

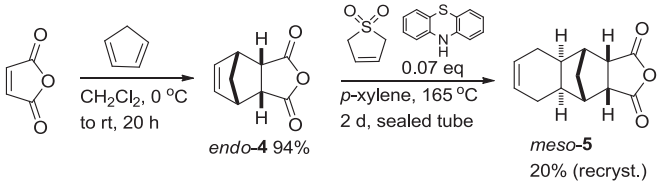
The initial synthetic endeavor of constructing the decahydronaphthalene core started from a thermal addition of 1*H*-indene to maleic anhydride giving the known *endo*-adduct[23] in moderate yield (30%) (Scheme 1). Ring-opening of the anhydride in refluxing methanol[24] gave the tricyclic carboxylic acid. It was used in the subsequent Curtius–Schmidt rearrangement reaction in the presence of benzyl alcohol to give the Cbz-protected amino ester followed by a catalytic hydrogenation (H_2, Pd/C) and a hydride reduction of the methyl ester. The subsequent key hydrogenation of the aromatic ring, under forcing conditions with various catalysts yielded the product as a mixture of intractable compounds, giving the desired decahydronaphthalene ring system of **3a** in poor yields (Scheme 1).



Entry	Catalyst	Solvent	Pressure (bar)
1	Rh/ C	EtOH/ HCl	1-3
2	Rh/ C	EtOH/AcOH	3.0
3	PtO_2	EtOH/ AcOH	3.0
4	Ru_2O	MeOH/ HCl	3.5
5	$RuCl_3$	H_2O/ HFIP/ TOA	3.5
6	$RuCl_3$	H_2O/ HFIP/ TOA	50-100

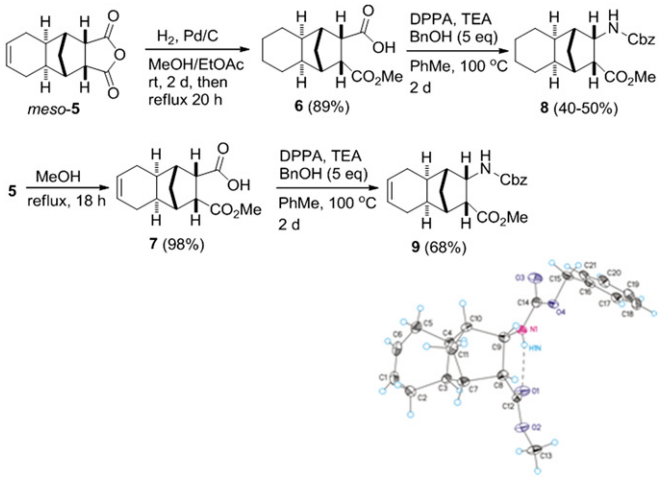
Scheme 1. The initial attempt to synthesize γ-amino alcohol (**3a**) from 1*H*-indene via the known *endo*-anhydride.[23]

This is why we decided to change the synthetic route to the decahydronaphthalene core. However, the Diels–Alder methodology was retained and we used the known *endo*-norbornen-5,6-*cis*-dicarboxylic anhydride (**4**)[25] as a dienophile for the [4+2] cycloaddition with 1,3-butadiene, generated in situ from the 3-sulfolene precursor. The *meso*-anhydride (**5**)[26] (Scheme 2) was produced in 20% yield (the crude product *exo*/*endo*-ratio ~4:1 by GC–MS) as a single diastereomer after recrystallization from acetone. It has the desired *exo*-stereochemistry in the fused cyclohexene ring as reported previously.[26]



Scheme 2. The tandem Diels–Alder sequence to construct the six continuous stereocenters of *meso*-anhydride (**5**)[26] via *endo*-(**4**).

A one-pot catalytic hydrogenation and methanolysis of **5** (H_2, Pd/C, EtOAc/MeOH, Δ, 3 days) gave the ester (**6**) with a completely reduced decahydronaphthalene core and it was isolated as a single diastereomer in high yield (89%, Scheme 3). When anhydride **5** was

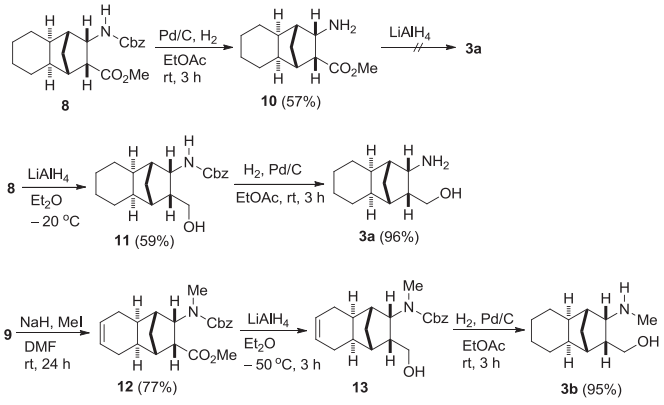


Scheme 3. Above: the synthesis of monomethyl hemiesters (**6**,**7**) from *meso*-anhydride (**5**)[26] followed by the one-pot Curtius–Schmidt rearrangement reaction of **6**, **7** to give the Cbz-protected amines (**8**, **9**). Below: ORTEP diagram (50% probability level) of the molecular structure of **9**.

subjected to methanolysis, alkene **7** was produced nearly quantitatively (98%, Scheme 3).

The key reaction in the preparation of the amino functionality in **3a** was the use of the modified Curtius–Schmidt rearrangement reaction.[27] Carboxylic acid **6** was first converted into the corresponding isocyanate via an acyl azide intermediate using diphenylphosphoryl azide (DPPA).[28] A one-pot reaction in the presence of triethylamine and benzyl alcohol gave carbamate **8** in moderate yield (40–50%) after chromatographic purification (Scheme 3). However, when **7** bearing a cyclohexene moiety was subjected to the same Curtius–Schmidt rearrangement conditions, the Cbz-amine **9** was isolated in higher yield (68%), and more importantly, as a solid reaction product. This, in turn, enabled us to carry out its single crystal X-ray structure analysis, which unambiguously confirmed the chemical structure of (**9**) in the solid state (Scheme 3).

The removal of the Cbz-protection group of compound (**8**) by catalytic hydrogenation (H_2, Pd/C, EtOAc, 2–3 h) gave the corresponding amine (**10**) (57%, Scheme 4). However, subsequent reduction with $LiAlH_4$ was not successful, since the incomplete reaction was followed by purification difficulties. Therefore, the synthetic sequence was reversed. The reduction of the methyl ester in (**8**) with $LiAlH_4$ was conducted at low temperature (−50 to −20 °C) since the nucleophilic intramolecular side reaction was found to take place at ambient temperature.[29] At this time the primary alcohol (**11**) was obtained in 59% yield after column chromatography on SiO_2 (Scheme 4). The final catalytic hydrogenation step reduced the fused cyclohexene ring and removed the carboxybenzyl group (H_2, Pd/C, EtOAc, rt, 3 h, Scheme 4) giving (±)-*cis*-(3-aminodecahydro-1,4-methanonaphthalen-2-yl)methanol (**3a**) as a pure compound.



Scheme 4. Synthesis of amine (**10**). *N*-Methylation of the Cbz-amine (**9**) and synthesis of the γ-amino alcohol (**3a**,**b**) by the successive hydride reduction and catalytic hydrogenation.

In order to convert the amino functionality of **3a** to a more hydrophobic one, its *N*-methyl derivative **3b** was synthesized since the C1 domain is thought to be partly buried in the bilayer during PKC activation.[20,22] The direct *N*-monomethylation of primary amines is known to be a difficult task in preparative synthetic chemistry. The harsh reaction conditions, poor yields, and low selectivity are the major limitations of direct N-methylation reactions of primary amines.[30] However, the use of Cbz-protection group in **9** allowed its N-monomethylation under mild conditions. Deprotonation of **9** with NaH in DMF followed by treatment with iodomethane gave the *N*-methyl derivative (**12**) (77%) without affecting the *cis*, *endo* relationship of the carboxymethyl and Cbz-amino groups (Scheme 4). The Cbz-protected γ-aminomethyl alcohol (**13**) was obtained conveniently from the parent alkene (**12**) under the same reaction conditions used for the preparation of the compound **11**, and it was subjected to the catalytic hydrogenation without further purification. (±)-[*cis*-3-(Methylamino)deca-1,4-methanonaphthalen-2-yl]methanol (**3b**) was isolated and converted to the hydrochloride salt (2 M HCl in Et_2O) in 90% yield (over two steps).

The synthesized (3-aminodecahydro-1,4-methanonaphthalen-2-yl)methanols (**3a**,**b**) were assayed for binding to the C1 domain of recombinant human PKCα and δ using a filtration method on 96-well plate format as described.[17] Crude cell lysates of *Baculovirus*-infected *Sf* 9 cells were used as the source for PKC in the assay; lysate from uninfected *Sf* 9 cells did not exhibit phorbol ester binding (data not shown). The compounds were tested at a concentration range of 0.3–20 μM. The results revealed that **3a** and **b** were unable to displace [20-^{3}H]phorbol-12,13-dibutyrate from PKCα and δ (data not shown). Further work is being conducted in an effort to modify the synthesized compounds.

3. Conclusions

We have developed a method for the synthesis of (3-aminodecahydro-1,4-methanonaphthalen-2-yl)methanols (**3a** and **b**) via a Curtius–Schmidt rearrangement of the hemiesters of the dicarboxylic acids **6** and **7**. The key steps in the synthesis of the carboxylic acids (**6** and **7**) were two sequential Diels–Alder reactions to construct the six continuous stereocenters of the anhydride (**5**). The synthesis of the target γ-amino alcohol (**3a**) proceeded in 32% yield over four steps from the known anhydride (**5**).

4. Experimental section

4.1. General experimental procedures

All reactions were carried out using commercially available starting materials (Aldrich, Schnelldorf, Germany and Fluka, Buchs, Switzerland) and solvents without further purification under an argon atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under argon with sodium/benzophenone ketyl and dichloromethane (CH_2Cl_2) with calcium hydride. Column chromatography was performed with Merck 230–400 mesh silica gel. The melting points were recorded with an Electrothermal capillary tube melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra in $CDCl_3$ or in DMSO-d_6 at ambient temperature were recorded on a Varian Mercury *Plus* 300 spectrometer. The chemical shifts were reported in parts per million (ppm) and on the δ scale from tetramethylsilane as an internal standard. The coupling constants *J* are quoted in hertz (Hz). The IR spectra for the novel compounds were recorded on a Bruker Vertex 70 FT-IR spectrometer, using attenuated total reflectance (ATR). GC–MS analyses were performed on a Hewlett–Packard 5890 series gas chromatograph equipped with an HP-5970 mass selective detector. LC–MS analyses were recorded on an Agilent 1100 HPLC instrument, an Agilent 1100 multiple wavelength UV detector (210 nm) and an MDS Sciex API 3000 triple quadrupole instrument with a turbo ion spray source. Analyses were carried out with positive polarity using Waters XTerraMS RP18 column (30×4.6 mm, 2.5 μm) and gradient elution. Elemental analyses (CHN) were obtained from Robertson Microlit Laboratories, Inc., Madison, New Jersey, USA.

4.1.1. Docking simulations. Docking simulations of γ-amino alcohol (**3a**) to the crystal structure of PKCδ C1b domain (pdb code: 1PTR) were carried out using Gold v4.1[31] at the SOMAv.2 interface of the Finnish Center for Scientific Computing.[32] A three-dimensional structure of (**3a**) was calculated using the molecular modeling platform Sybyl-X1.2 (Tripos Ltd)[33] and energy minimized using Gasteiger-Marsili charges, the Tripos forcefield, with 100 steps of the

Powel algorithm. Flexibility of the ligand was considered during docking simulations by Gold v4.1. The binding cavity was defined centered on oxygen atom 101 of threonine 242 with a radius of 10 Å. Ten docking runs were performed (100.000 runs of the genetic algorithm each), leading to the same binding pose for each run.

*4.1.2. endo-Norbornene-5,6-cis-dicarboxylic anhydride (**4**)[25].* Maleic anhydride (30.0 g, 306 mmol) briquettes were ground in mortar and dried 2–3 h in vacuo and then dissolved in anhydrous dichloromethane (60 mL). Cyclopentadiene (freshly distilled) (22.2 g, 337 mmol) in dichloromethane (10 mL) was added dropwise to the solution of maleic anhydride at 0 °C under argon. After 24 h the white precipitate was collected and washed with diethyl ether (2×20 mL) and dried in vacuo to give known **4**[25] as a white crystalline solid (47.0 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.30 (2H, m), 3.58–3.55 (2H, m), 3.52–3.47 (2H, m), 1.77 (1H, dd, J=1.8, 9.3 Hz); 1.57 (1H, dd, J=1.8, 9.3 Hz). GC–MS: $[M]^+$, m/z 164.

*4.1.3. meso-1,2,3,4,4a,5,8,8a-Octahydro-4,9-methanonaphtho[2,3-c]furan-1,3-dione (**5**)[26].* *endo*-Norbornene-5,6-*cis*-dicarboxylic anhydride (**4**) (6.00 g, 36.6 mmol) was dissolved in a solution of anhydrous degassed *p*-xylene (12 mL) and 3-sulfolene (14.0 g, 119 mmol, 3.2 equiv) and phenothiazine (0.500 g, 2.60 mmol, 0.07 equiv) were added. The reaction mixture was heated in a sealed tube at 165–170 °C for 48 h under argon. After 48 h, GC–MS analysis from the reaction mixture showed a formation of the Diels–Alder product together with some side products and starting material. Dichloromethane (20 mL) was added and the crude reaction mixture was hot filtrated and concentrated on a rotary evaporator. The crude product was recrystallized from acetone to yield the known *meso*-anhydride (**5**) as white thin needles (1.58 g, 20%). Mp 206–208 °C (lit. 208 °C).[26] ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.97–5.85 (2H, m), 3.43 (1H, d, J=2.1 Hz), 3.42 (1H, d, J=2.1 Hz), 2.58–2.55 (2H, m), 2.34–2.22 (2H, m), 2.12 (1H, 1H, d, J=10.8 Hz), 1.88–1.76 (2H, m), 1.62–1.54 (2H, m), 1.50 (1H, td, J=1.8, 10.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 129.2, 50.8, 47.3, 39.3, 38.6, 28.0. Anal. Calcd for $C_{13}H_{14}O_3$(218.09): C, 71.54; H, 6.47. Found: C, 70.94; H, 6.43. GC–MS: $[M]^+$, m/z 218.

*4.1.4. (±)-cis-3-(Methoxycarbonyl)decahydro-1,4-methanonaphthalene 2-carboxylic acid (**6**). meso*-Anhydride (**5**) (1.00 g, 4.59 mmol) was dissolved in an equimixture of methanol and EtOAc (35 mL) followed by addition of the palladium catalyst (Pd 10 wt % on activated carbon). The reaction mixture was stirred under hydrogen atmosphere (H_2 balloon) for 24 h at ambient temperature. Then hydrogenation was stopped and the reaction mixture was heated at 70 °C for another 24 h under argon. The catalyst was then removed by filtration through Celite and the resulting filtrate was concentrated on a rotary evaporator to yield carboxylic acid (**6**) as a white crystalline solid (1.03 g, 89%). Mp 111–113 °C. IR: ν 3300–2700 (br), 2964, 1734, 1697, 1178 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.29 (1H, br s), 3.64 (3H, s), 3.06 (1H, dd, J=3.6, 11.4 Hz), 3.01 (1H, dd, J=4.2, 11.7 Hz), 2.99 (1H, dd, J=3.6, 11.7 Hz), 2.26–2.18 (2H, m), 2.12–1.98 (2H, m), 1.85 (1H, d, J=10.2 Hz), 1.64–1.54 (2H, m), 1.42–1.28 (4H, m), 1.19 (1H, d, J=10.2 Hz), 1.18–1.06 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 173.8, 52.1, 48.1, 47.8, 47.1, 47.0, 37.0, 36.9, 35.3, 23.9, 23.8, 19.9, 19.8. Anal. Calcd for $C_{14}H_{20}O_4$(252.14): C, 66.65; H, 7.99. Found: C, 66.58; H, 7.99. GC–MS: The carboxylic acid (**6**) was *O*-methylated with diazomethane in Et_2O to give the corresponding diester: $[M]^+$, m/z 266.

*4.1.5. (±)-cis-3-(Methoxycarbonyl)-1,2,3,4,4a,5,8,8a-octahydro-1,4-methanonaphthalene-2-carboxylic acid (**7**). meso*-Anhydride (**5**) (2.26 g, 10.4 mmol) was dissolved in anhydrous methanol (90 mL) and refluxed for 18 h under argon. The reaction mixture was cooled to ambient temperature and filtered through a pad of charcoal followed by evaporation of the solvents by a rotary evaporator to yield carboxylic acid (**7**) as a white crystalline solid (2.39 g, 92%). Mp 110–111 °C. IR: ν 3200–2800 (br), 2969, 1742, 1694, 1195, 674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.57 (1H, br s), 5.90–5.80 (2H, m), 3.63 (3H, s), 3.09 (1H, dd, J=3.6, 11.4 Hz), 3.01 (1H, dd, J=4.1, 11.4 Hz), 2.34–2.25 (2H, m), 2.24–2.10 (4H, m), 1.95 (1H, d, J=10.8 Hz), 1.62–1.46 (2H, m), 1.23 (1H, d, J=10.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 173.4, 129.6, 129.5, 52.2, 48.1, 48.0, 47.9, 47.8, 37.3, 37.1, 35.8, 28.2, 28.1. Anal. Calcd for $C_{14}H_{18}O_4$(250.12): C, 67.18; H, 7.25. Found: C, 67.03; H, 7.22. GC–MS: The carboxylic acid (**7**) was *O*-methylated with diazomethane in Et_2O to give the corresponding diester: $[M]^+$, m/z 264.

*4.1.6. (±)-cis-Methyl 3-[[(benzyloxy)carbonyl]amino]decahydro-1,4-methanonaphthalene-2-carboxylate (**8**).* Carboxylic acid (**6**) (1.57 g, 6.24 mmol), triethylamine (1.26 g, 12.5 mmol, 2.0 equiv), and diphenylphosphoryl azide (2.06 g, 7.56 mmol, 1.2 equiv) were dissolved in anhydrous toluene (40 mL) and heated at 100 °C for 2 h under argon. Then benzyl alcohol (3.26 g, 30.2 mmol, 5.0 equiv) was added and the resulting reaction mixture was heated at 110 °C for 3 d. The reaction mixture was cooled to ambient temperature and the solvents were evaporated by a rotary evaporator. The oily residue was purified by column chromatography on silica gel (eluent: EtOAc/*n*-Hex 1:3) to produce (**8**) as a colorless oil (1.24 g, 50%). IR (ATR): ν 3379, 2965, 1745, 1705, 1195 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.28 (5H, m), 6.86 (1H, br d, J=7.8 Hz), 5.12 (1H, d, J=12.3 Hz), 5.07 (1H, d, J=12.3 Hz), 4.16–4.08 (1H, m), 3.65 (3H, s), 2.97 (1H, dd, J=4.4, 11.0 Hz), 2.20–2.14 (2H, m), 1.94–1.84 (1H, m), 1.76 (1H, d, J=10.8 Hz) 1.70–1.54 (4H, m), 1.42–1.08 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 157.0, 137.6, 129.2, 128.9, 128.8, 67.3, 52.9, 52.4, 48.4, 48.1, 45.9, 37.3, 34.4, 33.2, 23.6, 23.5, 19.9,19.8. GC–MS: $[M]^+$, m/z 357.

*4.1.7. (±)-cis-Methyl 3-[[(benzyloxy)carbonyl]amino]-1,2,3,4,4a,5,8,8a-octahydro-1,4-methanonaphthalene-2-carboxylate (**9**).* Carboxylic acid (**7**) (1.12 g, 4.48 mmol), triethylamine (905 mg, 8.96 mmol, 2.0 equiv), and diphenylphosphoryl azide (1.48 g, 5.37 mmol, 1.2 equiv) were dissolved in anhydrous toluene (20 mL) and heated at 100 °C for 3 h under argon. Then benzyl alcohol (2.42 g, 22.4 mmol, 5.0 equiv) was added and the resulting reaction mixture was heated at 90 °C for 48 h. The reaction mixture was cooled to 20 °C and all volatiles were evaporated by a rotary evaporator. The oily residue was purified by column chromatography on silica gel (eluent: EtOAc/*n*-Hex 1:3) to yield (**9**) as a colorless oil (1.09 g, 68%), which crystallized on standing at −20 °C. Mp 96–97 °C. A sample of (**9**) for single crystal X-ray analysis was recrystallized from *n*-hexane. IR (ATR): ν 3365, 2933, 1741, 1708, 1264, 1049, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.22 (5H, m), 6.85 (1H, br d, J=7.5 Hz), 5.90–5.78 (2H, m), 5.12 (1H, d, J=12.3 Hz), 5.07 (1H, d, J=12.3 Hz), 4.13 (1H, m), 3.64 (3H, s), 3.00 (1H, dd, J=4.4, 11.0 Hz), 2.30–1.98 (5H, m), 1.87 (1H, d, J=10.8 Hz) 1.84–1.74 (1H, m), 1.60–1.48 (2H, m), 1.30 (1H, d, J=10.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 157.0, 137.6, 129.8, 129.3, 129.2, 128.9, 128.7, 67.3, 53.0, 52.5, 49.3, 48.8, 46.1, 37.9, 34.6, 33.6, 27.9, 27.8. Anal. Calcd for $C_{21}H_{25}NO_4$(355.18): C, 70.96; H, 7.09; N, 3.94. Found: C, 71.04; H, 7.15; N, 3.93. GC–MS: $[M]^+$, m/z 355. Crystallographic data of (**9**): $C_{21}H_{25}NO_4$, M=355.42, orthorhombic, *Pbca*, a=12.1273(3), b=15.3221(5), c=19.7539(6) Å, V=3670.59(19) Å^3, Z=8, D_c=1.286 g cm^{-3}, μ (Mo Kα)=0.089 mm^{-1}, F(000)=1520, block, colorless, size=0.40×0.20×0.20 mm, 11,378 reflections measured (R_{int}=0.0296), 3574 unique, wR_2=0.0876 for all data, conventional R=0.0362, [$(\Delta/\sigma)_{max}$=0.001] on F-values of 2439 reflections with $I>2\sigma(I)$, S=0.993 for all data and 239 parameters. CCDC 826130 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data

Center, 12 Union Road, Cambridge, CB2 1EZ, U. K; fax: (internet) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

*4.1.8. (±)-cis-Methyl 3-aminodecahydro-1,4-methanonaphthalene-2-carboxylate (**10**).* Cbz-amine (**8**) (282 mg, 0.79 mmol) was dissolved in EtOAc (6 mL) and the palladium catalyst (Pd 10 wt % on activated carbon) was added. The reaction mixture was stirred under hydrogen atmosphere (H_2 balloon) for 22 h at ambient temperature. The catalyst was then removed by filtration through Celite, and the filtrate was concentrated on a rotary evaporator. The crude product was purified by column chromatography on silica gel (eluent: EtOAc/MeOH/TEA 90:10:3) to yield amine (**10**) as a colorless oil (100 mg, 57%). An analytical sample of (**10**) was made by formation of the corresponding hydrochloride salt with 4 M HCl in 1,4-dioxane. Mp (**10**) hydrochloride 212 °C (dec). IR (ATR): ν 2926, 1736, 1218, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.67 (3H, s), 3.49 (1H, dd, J=4.2, 10.5 Hz), 2.81 (1H, dd, J=4.2, 10.5 Hz), 2.12 (1H, d, J=4.2 Hz), 2.09–1.96 (2H, m), 1.95 (1H, m), 1.89 (2H, br s), 1.75 (1H, td, J=1.5, 10.8 Hz) 1.68–1.54 (2H, m), 1.44–1.24 (5H, m), 1.18 (1H, td, J=0.9, 10.8 Hz) 1.15–1.10 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 53.9, 52.0, 50.5, 49.1, 47.8, 36.5, 33.8, 33.4, 23.9, 23.8, 20.1, 20.0. Anal. Calcd for $C_{13}H_{21}NO_2 \cdot HCl$ (259.13): C, 60.11; H, 8.54; N, 5.39; Cl, 13.65. Found: C, 57.85; H, 8.21; N, 5.19. GC–MS: $[M]^+$, m/z 223.

*4.1.9. (±)-cis-[Benzyl-3-(hydroxymethyl)decahydro-1,4-methanonaphthalen 2-yl] carbamate (**11**).* To a suspension of lithium aluminum hydride (560 mg, 1.48 mmol, 1.5 equiv) in anhydrous diethyl ether (5 mL) at 0 °C was added the methyl ester (**8**) (355 mg, 1.00 mmol) (Et_2O, 3 mL) under argon. The progress of the reduction was monitored by TLC, which showed no starting material present after 40 min. The reaction mixture was quenched by addition of satd aqueous solution of NH_4Cl (5 mL) followed by addition of EtOAc (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatography on silica gel (eluent: EtOAc/*n*-Hex 2:3) to yield (**11**) as a white solid (332 mg, 59%). Mp 99–100 °C. IR (ATR): ν 3284, 2940, 1678, 1541, 1250, 1045, 744, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (5H, m), 5.18 (1H, br d, J=6.3 Hz), 5.11 (2H, s), 4.04 (1H, m), 3.71 (1H, dd, J=8.4, 11.0 Hz), 3.55 (1H, dd, J=5.2, 11.0 Hz), 2.28–2.16 (1H, m), 2.08 (1H, d, J=3.3 Hz), 1.99 (1H, d, J=3.3 Hz), 1.98–1.88 (1H, m), 1.74 (1H, td, J=1.5, 10.5 Hz), 1.70–1.56 (4H, m), 1.40–1.08 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 137.1, 129.4, 129.1, 67.9, 61.7, 53.3, 48.5, 47.0, 45.6, 35.6, 35.2, 33.7, 23.8, 20.0, 19.9. Anal. Calcd for $C_{20}H_{27}NO_3$(329.20): C, 72.92; H, 8.26; N, 4.25. Found: C, 72.65; H, 8.20; N, 4.38. GC–MS: $[M]^+$, m/z 221, refers to the intramolecular cyclization, where the reduced primary alcohol has reacted with the carbonyl carbon of the Cbz group and formed the corresponding cyclic carbamate (m/z 221) by elimination of benzyl alcohol.

*4.1.10. (±)-cis-(3-Aminodecahydro-1,4-methanonaphthalen-2-yl)-methanol (**3a**).* Cbz-amine (**11**) (289 mg, 0.88 mmol) was dissolved in EtOAc (8 mL) and the palladium catalyst (Pd 10 wt % on activated carbon) was added. The reaction mixture was stirred under hydrogen atmosphere (H_2 balloon) for 3 h at ambient temperature. After addition of MeOH (15 mL), the catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated on a rotary evaporator to give the γ-amino alcohol (**3a**) as a colorless oil (165 mg, 96%) without a need for further purification. Compound (**3a**) crystallized on standing at −20 °C. An analytical sample of (**3a**) was made by formation of the corresponding hydrochloride salt with 4 M HCl in 1,4-dioxane. Mp (**3a**) hydrochloride 254 °C (dec). IR (ATR): ν 3210, 2937, 1527, 1015, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (1H, t, J=11.1 Hz), 3.57 (1H, dd, J=4.8, 11.4 Hz), 3.36 (1H, dd, J=4.1, 11.1 Hz), 2.29 (2H, br s), 2.11 (1H, m), 1.90–1.56 (7H, m), 1.42–1.08 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.2, 53.9, 51.3, 46.7, 44.3, 36.2, 34.5, 33.6, 24.2, 23.9, 20.2, 20.0. Anal. Calcd for $C_{12}H_{21}NO$ (195.16): C, 73.80; H, 10.84; N, 7.17. Found: C, 74.05; H, 10.81; N, 7.01. GC–MS: $[M]^+$, m/z 195. LC–MS: $[M+1]^+$, m/z 196.

*4.1.11. (±)-cis-Methyl 3-[[(benzyloxy)carbonyl]methylamino)]-1,2,3,4 4a,5,8,8a-octahydro-1,4-methanonaphthalene-2-carboxylate (**12**).* Carbamate (**9**) (0.400 g, 1.13 mmol) in anhydrous DMF (5 mL) was added to a cooled solution of NaH (108 mg, 2.49 mmol, 2.2 equiv, 65% disp. in mineral oil) in DMF (5 mL) at 0 °C under argon. After 60 min, iodomethane (280 μL, 4.52 mmol) was added and the reaction mixture was stirred for 24 h at ambient temperature under argon. The solvents were evaporated off by a rotary evaporator, and the crude reaction mixture was purified by column chromatography on silica gel (eluent: EtOAc/*n*-Hex 1:4) to yield (**12**) as a colorless oil (320 mg, 77%). IR (ATR): ν 3383, 2945, 1732, 1696, 1143, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.28 (5H, m), 5.90–5.84 (2H, m), 5.15 (1H, d, J=12.6 Hz), 5.09 (1H, d, J=12.6 Hz), 4.28 (1H, dd, J=3.9, 5.7 Hz), 3.66 (3H, s), 2.95 (3H, s), 2.64 (1H, dd, J=1.7, 5.7 Hz), 2.32–2.12 (5H, m), 2.02–1.90 (2H, m), 1.82–1.66 (3H, m), 1.62–1.46 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 157.6, 136.9, 129.0, 128.8, 128.6, 128.1, 128.0, 67.3, 62.2, 52.1, 50.9, 48.3, 48.2, 43.5, 34.9, 33.9, 31.3, 27.4, 27.3. Anal. Calcd for $C_{22}H_{27}NO_4$(369.19): C, 71.52; H, 7.37; N, 3.79. Found: C, 71.41; H, 7.23; N, 4.04. GC–MS: $[M]^+$, m/z 369.

*4.1.12. (±)-cis-[Benzyl-3-(hydroxymethyl)-1,2,3,4,4a,5,8,8a-octahydro-1,4-methanonaphthalen-2-yl] (methyl)carbamate (**13**).* To a suspension of lithium aluminum hydride (20 mg, 0.53 mmol, 1.5 equiv) in anhydrous diethyl ether (5 mL) at −30 °C was added the methyl ester (**12**) (130 mg, 0.35 mmol) in Et_2O (8 mL) under argon. The reduction was monitored by TLC, which showed no starting material present after 2 h. The reaction mixture was quenched by addition of a satd aqueous solution of NH_4Cl (2 mL) followed by addition of EtOAc (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to give **13** as a crude product. The crude product was used for the next step without further purification.

*4.1.13. (±)-cis-3-[(Methylamino)decahydro-1,4-methanonaphthalen-2-yl]methanol (**3b**).* The crude Cbz-amine (**13**) (59 mg, 0.17 mmol) was dissolved in EtOAc (3 mL) and the palladium catalyst (Pd 10 wt % on activated carbon) was added. The reaction mixture was stirred under hydrogen atmosphere (H_2 balloon) for 2 h at ambient temperature. After addition of MeOH (5 mL), the catalyst was removed by filtration through Celite and the filtrate was concentrated on a rotary evaporator to give γ-amino alcohol (**3b**) as a colorless oil (32 mg, 90%) Analytical sample of (**3b**) was made by formation of the corresponding hydrochloride salt with 4 M HCl in 1,4-dioxane. Mp (**3b**) hydrochloride 254 °C (dec). IR (ATR): ν 3393, 2933, 1508, 1041, 668 cm^{-1}; ^1H NMR (300 MHz, D_2O): δ 3.58–3.46 (2H, m), 3.05 (1H, t, J=4.5 Hz), 2.71 (3H, s), 2.28 (1H, d, J=2.4 Hz), 1.92 (1H, s), 1.80 (1H, dd, J=1.5, 11.4 Hz), 1.78–1.56 (5H, m), 1.46–1.12 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.2, 65.7, 54.1, 45.1, 45.0, 43.6, 35.0, 33.2, 30.9, 23.4, 23.2, 19.6, 19.4. Anal. Calcd for $C_{13}H_{23}NO$ (209.18): C, 74.59; H, 11.07; N, 6.69. Found: C, 74.45; H, 10.92; N, 6.40. GC–MS: $[M]^+$, m/z 209.

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