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Galantamine derivatives: Synthesis, NMR study, DFT calculations and application in asymmetric catalysis

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ABSTRACT

In a search of effective ligands for asymmetric catalysis (−)-galantamine has been selected as a complex chiral framework for the synthesis of four novel diphenylphosphino-benzenecarboxamides. Their application in Pd-catalyzed asymmetric allylic alkylation proceeded with excellent conversion and moderate enantioselectivity due to the conformational flexibility of the galantamine derived compounds. To get insights into their molecular structure and conformational behaviour in solution a combination of experimental NMR methods and theoretical DFT calculations has been employed. The ligands exist as four conformers due to restricted rotation around the amide bond and due to flexibility of the 2,3,4,5-tetrahydro-1*H*-azepine ring. The experimentally measured barriers of C–N rotation (17.1 ÷ 17.7 kcal/mol) are higher than the barriers of observed exchange process in azepine ring (13.7 ÷ 14.0 kcal/mol). Their BOC precursors exist in solution as two conformers due to restricted rotation around the carbamate C–N bond. The experimentally measured barrier is lower than the amide barriers in ligands (16.1 ÷ 16.5 kcal/mol).

1. Introduction

(−)-Galantamine (Fig. 1) is an alkaloid, belonging to the *Amaryllidaceae* family and was initially isolated from the bulbs of Caucasian snowdrop (*Galanthus woronowii*), common snowdrop (*Galanthus nivalis*) and related genera [1]. Galantamine is a reversible, competitive acetylcholinesterase inhibitor and is widely prescribed as an anti-Alzheimer's disease drug [2]. Additionally, it is an allosteric modulator of nicotinic acetylcholine receptors, which enhances the cognitive brain function [3]. The multitarget action of galantamine and its comparatively low toxicity makes it a lead structure for the development of synthetic analogues with improved pharmacological properties [4–7]. Galantamine's structure allows modifications on the azepine tertiary nitrogen, the hydroxyl function of the cyclohexene ring, the cyclohexenol ring, and the methoxy function of the benzofurane ring [8]. Recently in our laboratories were designed, synthesized and tested several series of *N*-substituted galantamine derivatives, some of them displaying above 1000 times better activity than the parent structure [9–11].

Alkaloids and terpenes, due to their ready availability, inexpensiveness, complex chiral skeletons and functionalities allowing versatile structural modifications, serve as chiral sources and devices since the dawn of asymmetric synthesis [12–14]. In this context we have successfully developed and fine-tuned a number of (+)-camphor and (−)-β-pinene derived amido-phosphine ligands (Fig. 1). They were applied in the Pd-catalyzed asymmetric allylic alkylation (AAA) [15] affording excellent enantioselectivities [16,17]. The catalytic performance was greatly influenced by the type of the terpene core. Subsequently we expanded the approach towards modification of the alkaloid (−)-cytisine to chiral amido-phosphine ligands. The structures and the conformations of the ligands were elucidated on the basis of NMR, X-ray and DFT studies [18]. Their applications in Pd-catalyzed AAA proceeded with excellent conversions and enantioselectivities. The observed catalytic activity strongly correlated with the conformational behaviour.

Inspired by the complex galantamine architecture and its possible versatile modifications we focused on its transformation into chiral ligands. Herein we report the synthesis of norgalantamine and norlycoramine based diphenylphosphino-

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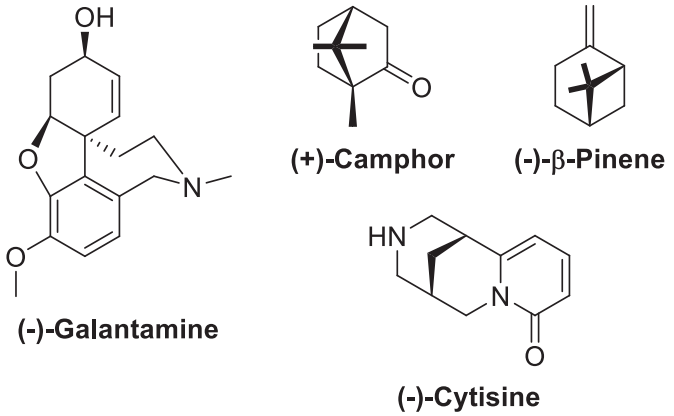


Fig. 1. Selected chiral scaffolds.

benzenecarboxamides, the elucidation of their structures and conformational behaviour in solution utilizing combination of experimental NMR methods and theoretical DFT calculations, and their application as ligands in Pd-catalyzed AAA.

2. Experimental

2.1. General

Reagents were commercial grade and used without further purification. CH_2Cl_2 was distilled from CaH_2. THF and Et_2O were distilled over sodium/benzophenone. Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with Merck Kieselgel 60 F_{254} 0.25 mm (Merck). Flash column chromatography was carried out using Silica Gel 60 230–400 mesh (Fluka). Melting points were determined in a capillary tube on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system (uncorrected). Optical rotation ($[\alpha]_D^{20}$) were measured on Perkin–Elmer 241 polarimeter. The NMR spectra were recorded on a Bruker Avance II+ 600 (600.13 for ^{1}H NMR, 150.92 MHz for ^{13}C NMR and 242.92 MHz for ^{31}P NMR) spectrometer with TMS (85% H_3PO_4 for ^{31}P) as internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants *J* (Hz), integration and identification. The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, COSY, HSQC, HMBC and NOESY experiments. Mass spectra (MS) were recorded on a Finnigan SSQ 7000 spectrometer QSTAR pulsar I (AB/MDS Sciex) (ESI). The high performance liquid chromatography (HPLC) separations were performed with an Agilent 1100 System fitted with diode array detector and manual injector with a 20 μl injection loop Chiralpak IC 250 × 4.6 mm, particle size 5 μm stainless-steel columns from Chiral Technologies Europe LTD were used. The analyses were performed at 25 °C with a flow rate of 1.0 ml/min. Elemental analyses were performed by Microanalytical Service Laboratory of Faculty of Chemistry, University of Sofia, using Vario EL*3* CHNS(O) and Microanalytical service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Science.

2.2. Synthesis

2.2.1. (4aS,6R,8aS)-11-(2-(Diphenylphosphino)benzoyl)-5,6,9,10,11,12-hexahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-6-ol ***1***

To a solution of 2-diphenylphosphinobenzoic acid (62 mg, 0.20 mmol) in dry CH_2Cl_2 (5 mL) under an argon atmosphere *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide (43 mg, 0.22 mmol), hydroxybenzotriazole (30 mg, 0.22 mmol), and norgalantamine (55 mg, 0.20 mmol) were added at rt. The mixture was stirred at rt for 24 h and then was directly subjected to flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 5:1) to give 66 mg (60% yield) of **1** as a white solid; m.p. 128–131 °C. $[\alpha]^{20}_D = -52.1$ (c 0.555, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 228 K): mixture of rotamers (64:21:15); signals for the major conformer: δ = 7.50–7.49 (m, 2H, H_{ar}), 7.46–7.45 (m, 3H, H_{ar}), 7.38–7.36 (m, 3H, H_{ar}), 7.35–7.34 (m, 1 H, H_{ar}), 7.32–7.31 (m, 2H, H_{ar}), 7.29–7.27 (m, 1H, H_{ar}), 7.13 (d, *J* = 7.7 Hz, 1H, H_{ar}), 6.83 (d, *J* = 7.4 Hz, 1H, H_{ar}), 6.61 (d, *J* = 8.3 Hz, 1H, H-2), 6.08 (d, *J* = 8.3 Hz, 1H, H-1), 6.06 (dd, *J* = 10.1, 4.7 Hz, 1H, H-7), 5.91 (d, *J* = 10.1 Hz, 1H, H-8), 4.89 (d, *J* = 14.2 Hz, 1H, H_{eq}-10), 4.68 (br, 1H, H-4a), 4.22–4.19 (m, 1H, H-6), 3.91 (d, *J* = 16.2 Hz, 1H, H_{eq}-12), 3.87 (s, 3H, OCH_3), 3.80 (d, *J* = 16.2 Hz, 1H, H_{ax}-12), 3.13 (d, *J* = 13.2 Hz, 1H, H_{ax}-10), 2.77–2.75 (m, 1H, H_{eq}-5), 2.52 (d, *J* = 11.6 Hz, 1H, OH), 2.11–2.08 (m, 1H, H_{ax}-5), 2.02–1.98 (m, 1H, H_{eq}-9), 1.92–1.89 (m, 1H, H_{ax}-9) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 228 K): signals for the major conformer: δ = 170.05 (d, $J_{P,C}$ = 2.6 Hz, C_q, C=O), 145.81 (C_q, C-3a), 143.92 (C_q, C-3), 141.18 (d, $J_{P,C}$ = 31.7 Hz, C_q, C_{ar}), 135.46 (d, $J_{P,C}$ = 8.6 Hz, C_q, C_{ar}), 135.34 (d, $J_{P,C}$ = 9.6 Hz, C_q, C_{ar}), 134.71 (d, $J_{P,C}$ = 21.2 Hz, 2CH, C_{ar}), 133.54 (CH, C_{ar}), 133.12 (d, $J_{P,C}$ = 18.7 Hz, 2CH, C_{ar}), 132.06 (C_q, C-12b), 129.35 (CH, C_{ar}), 129.10 (CH, C_{ar}), 128.59 (d, $J_{P,C}$ = 7.7 Hz, 2CH, C_{ar}), 128.50 (CH, C_{ar}), 128.40 (CH, C_{ar}), 128.38 (d, $J_{P,C}$ = 6.1 Hz, 2CH, C_{ar}), 127.78 (CH, C-7), 127.60 (C_q, C-12a), 126.45 (d, $J_{P,C}$ = 6.4 Hz, CH, C_{ar}), 126.01 (CH, C-8), 120.68 (CH, C-1), 109.99 (CH, C-2), 88.25 (CH, C-4a), 61.75 (CH, C-6), 55.63 (CH_3, OCH_3), 53.77 (CH_2, C-12), 48.01 (C_q, C-8a), 43.31 (CH_2, C-10), 35.72 (CH_2, C-9), 29.33 (CH_2, C-5) ppm. ^{31}P{^{1}H} NMR (242.92 MHz, $CDCl_3$, 228 K): signal for the major conformer: δ = -14.11 ppm. MS (ESI): *m*/z = 562 (100, $[M+1]^+$), 289 (67). $C_{35}H_{32}NO_4P$ (561.61): calcd. C 74.85, H 5.74, N 2.49, found C 75.09, H 5.81, N 2.57.

2.2.2. t-Butyl ((4aS,6R,8aS)-5,6,9,10,11,12-hexahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-6-ol-11yl)carbamate ***2***

To a solution of norgalantamine (100 mg, 0.37 mmol) in dry CH_2Cl_2 (5 ml) NEt_3 (74 mg, 0.1 ml, 0.73 mmol) and $(BOC)_2O$ (88 mg, 0.40 mmol) were added at rt. The mixture was stirred at rt for 0.5 h then concentrated and purified by flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 4:1) to give 140 mg (79% yield) of **2** as a white solid; m.p. 73–76 °C. $[\alpha]^{20}_D = -36.4$ (c 0.668, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): mixture of rotamers (62:38); signals for major conformer δ = 6.77–6.66 (m, 2H, H-2, H-1), 6.04–5.97 (m, 2H, H-7, H-8), 4.69 (d, *J* = 15.7 Hz, 1H, H_{eq}-12), 4.60 (s, 1H, H-6), 4.29 (d, *J* = 14.6 Hz, 1H, H_{eq}-10), 4.15 (d, *J* = 15.7 Hz, 1H, H_{ax}-12), 4.16–4.13 (m, 1H, H-4a), 3.85 (s, 3H, OCH_3), 3.30 (t, *J* = 13.5 Hz, 1H, H_{ax}-10), 2.70 (d, *J* = 15.7 Hz, 1H, H_{eq}-5), 2.42 (t, *J* = 10.2 Hz, 1H, OH), 2.03 (dq, *J* = 15.7, 7.0 Hz, 1H, H_{ax}-5), 1.95 (dt, *J* = 13.1, 3.2 Hz, 1H, H_{eq}-9), 1.79–1.72 (m, 1H, H_{ax}-9), 1.37 (s, 9H, $C(CH_3)_3$) ppm; resolved signals for minor conformer δ = 6.80 (d, *J* = 8.2 Hz, 1H, H-1), 6.78 (d, *J* = 8.2 Hz, 1H, H-2), 6.04–5.97 (m, 2H, H-7, H-8), 4.88 (d, *J* = 15.5 Hz, 1H, H_{eq}-12), 4.60 (s, 1H, H-6), 4.18–4.16 (m, 1H, H_{eq}-10), 4.07 (d, *J* = 15.5 Hz, 1H, H_{ax}-12), 4.16–4.13 (m, 1H, H-4a), 3.83 (s, 3H, OCH_3), 3.40 (t, *J* = 13.4 Hz, 1H, H_{ax}-10), 2.70 (d, *J* = 15.7 Hz, 1H, H_{eq}-5), 2.42 (t, *J* = 10.2 Hz, 1H, OH), 2.03 (dq, *J* = 15.7, 7.0 Hz, 1H, H_{ax}-5), 1.86–1.76 (m, 2H, H-9), 1.42 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): signals for the major conformer: δ = 154.95 (C_q, C=O), 146.34 (C_q, C-3a), 144.20 (C_q, C-3), 132.38 (C_q, C-12b), 129.81 (C_q, C-12a), 127.99 (CH, C-8), 126.49 (CH, C-7), 120.89 (CH, C-1), 110.73 (CH, C-2), 88.39 (CH, C-6), 79.85 (C_q, $C(CH_3)_3$), 61.94 (CH, C-4a), 55.83 (CH_3, OCH_3), 51.93 (CH_2, C-12), 48.35 (C_q, C-8a), 45.38 (CH_2, C-10), 36.37 (CH_2, C-9), 29.81 (CH_2, C-5), 28.29 (CH_3, $C(CH_3)_3$) ppm; resolved signals for minor conformer δ = 154.59 (C_q, C=O), 146.27 (C_q, C-3a), 144.16 (C_q, C-3), 132.08 (C_q,

C-12b), 129.66 (C_q, C-12a), 127.87 (CH, C-8), 126.67 (CH, C-7), 121.51 (CH, C-1), 111.11 (CH, C-2), 88.24 (CH, C-6), 79.87 (C_q, $C(CH_3)_3$), 61.94 (CH, C-4a), 55.83 (CH_3, OCH_3), 51.35 (CH_2, C-12), 48.37 (C_q, C-8a), 45.65 (CH_2, C-10), 37.35 (CH_2, C-9), 29.77 (CH_2, C-5), 28.43 (CH_3, $C(CH_3)_3$) ppm.

2.2.3. t-Butyl ((4aS,6R,8aS)-6-ethoxy-5,6,9,10,11,12-hexahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-11yl) carbamate **3**

To a stirred solution of **2** (165 mg, 0.44 mmol) in DMF (5 ml) at 0 °C was added NaH (106 mg, 2.20 mmol). The mixture was stirred for 30 min at rt and then EtI (0.18 ml, 2.20 mmol) was added. The reaction was stirred at rt until the starting material was completely consumed (TLC). Next, it was cooled to 0 °C and treated with sat. aq. NH_4Cl. The organic phase was separated, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 8:1) to give 163 mg (92% yield) of **3** as a white solid; m.p. 42–45 °C. $[\alpha]^{20}_D = -110.0$ (c 0.324, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): mixture of rotamers (67:33); signals for major conformer δ = 6.61 (d, J = 8.1 Hz, 1H, H-2), 6.57 (d, J = 8.1 Hz, 1H, H-1), 6.11 (d, J = 10.4 Hz, 1H, H-8), 5.96 (d, J = 10.2 Hz, 1H, H-7), 4.64 (d, J = 15.5 Hz, 1H, H_{eq}-12), 4.53–4.45 (m, 1H, H-4a), 4.27 (d, J = 14.5 Hz, 1H, H_{eq}-10), 4.14 (d, J = 15.5 Hz, 1H, H_{ax}-12), 3.91 (s, 1H, H-6), 3.82 (s, 3H, OCH_3), 3.71–3.66 (m, 1H, OCH_2CH_3), 3.51–3.46 (m, 1H, OCH_2CH_3), 3.30 (t, J = 13.4 Hz, 1H, H_{ax}-10), 2.69–2.65 (m, 1H, H_{eq}-5), 2.00–1.94 (m, 1H, H_{ax}-5), 1.99–1.93 (m, 1H, H_{eq}-9), 1.73–1.70 (m, 1H, H_{ax}-9), 1.36 (s, 9H, $C(CH_3)_3$), 1.20 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm; resolved signals for minor conformer δ = 6.71 (d, J = 8.1 Hz, 1H, H-2), 6.62 (d, J = 8.1 Hz, 1H, H-1), 6.08 (d, J = 10.3 Hz, 1H, H-8), 5.96–5.94 (m, 1H, H-7), 4.84 (d, J = 15.5 Hz, 1H, H_{eq}-12), 4.53–4.45 (m, 1H, H-4a), 4.15–4.12 (m, 1H, H_{eq}-10), 4.07 (d, J = 15.5 Hz, 1H, H_{ax}-12), 3.91 (s, 1H, H-6), 3.81 (s, 3H, OCH_3), 3.71–3.66 (m, 1H, OCH_2CH_3), 3.51–3.46 (m, 1H, OCH_2CH_3), 3.39 (t, J = 13.2 Hz, 1H, H_{ax}-10), 2.69–2.65 (m, 1H, H_{eq}-5), 2.00–1.94 (m, 1H, H_{ax}-5), 1.87–1.82 (m, 1H, H_{eq}-9), 1.76–1.73 (m, 1H, H_{ax}-9), 1.41 (s, 9H, $C(CH_3)_3$), 1.20 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): signals for the major conformer: δ = 155.01 (C_q, C=O), 147.29 (C_q, C-3a), 144.12 (C_q, C-3), 131.66 (C_q, C-12b), 129.53 (C_q, C-12a), 128.42 (CH, C-8), 126.30 (CH, C-7), 120.01 (CH, C-1), 110.92 (CH, C-2), 86.57 (CH, C-4a), 79.72 (C_q, $C(CH_3)_3$), 68.12 (CH, C-6), 64.00 (CH_2, OCH_2CH_3), 55.87 (CH_3, OCH_3), 51.77 (CH_2, C-12), 48.28 (C_q, C-8a), 45.40 (CH_2, C-10), 37.67 (CH_2, C-9), 28.30 (CH_3, $C(CH_3)_3$), 27.59 (CH_2, C-5), 15.49 (CH_3, OCH_2CH_3) ppm; resolved signals for minor conformer δ = 154.58 (C_q, C=O), 146.16 (C_q, C-3a), 144.12 (C_q, C-3), 131.37 (C_q, C-12b), 129.33 (C_q, C-12a), 128.56 (CH, C-8), 126.09 (CH, C-7), 120.62 (CH, C-1), 111.18 (CH, C-2), 86.42 (CH, C-4a), 79.72 (C_q, $C(CH_3)_3$), 68.08 (CH, C-6), 63.98 (CH_2, OCH_2CH_3), 55.79 (CH_3, OCH_3), 51.24 (CH_2, C-12), 48.28 (C_q, C-8a), 45.70 (CH_2, C-10), 38.55 (CH_2, C-9), 28.43 (CH_3, $C(CH_3)_3$), 27.44 (CH_2, C-5), 15.49 (CH_3, OCH_2CH_3) ppm.

2.2.4. (4aS,6R,8aS)-6-Ethoxy-5,6,9,10,11,12-hexahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin **4**

To a solution of **3** (188 mg, 0.47 mmol) in CH_2Cl_2 (5 ml) was added dropwise CF_3CO_2H (2 ml) at 0 °C and the mixture was stirred at rt for 1 h. Next, it was cooled to 0 °C and treated with sat. aq. $NaHCO_3$. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/CH_3OH/NH_4OH = 5:1:0.1) to give 140 mg (99% yield) of **4** as an oil; $[\alpha]^{20}_D = -111.7$ (c 0.503, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): δ = 6.64 (d, J = 8.2 Hz, 1H, H-2), 6.62 (d, J = 8.2 Hz, 1H, H-1), 6.05 (dd, J = 10.4, 0.8 Hz, 1H, H-8), 6.01 (dd, J = 10.3, 4.4 Hz, 1H, H-7), 4.61 (br, 1H, H-4a), 4.07 (d, J = 15.4 Hz, 1H, H_{eq}-12), 4.01 (d, J = 15.5 Hz, 1H, H_{ax}-12), 3.91 (t, J = 4.7 Hz, 1H, H-6), 3.82 (s, 3H, OCH_3), 3.71–3.66 (m, 1H, OCH_2CH_3), 3.51–3.46 (m, 1H, OCH_2CH_3), 3.41 (dt, J = 14.4, 3.2 Hz, 1H, H_{eq}-10), 3.29–3.24 (m, 1H, H_{ax}-10), 2.66 (d, J = 15.7 Hz, 1H, H_{eq}-5), 1.96 (dq, J = 15.7, 9.3 Hz, 1H, H_{ax}-5), 1.89–1.81 (m, 2H, H-9), 1.20 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): δ = 147.16 (C_q, C-3a), 144.39 (C_q, C-3), 132.32 (C_q, C-12b), 129.94 (C_q, C-12a), 128.31 (CH, C-8), 126.44 (CH, C-7), 120.27 (CH, C-1), 111.34 (CH, C-2), 86.65 (CH, C-4a), 68.09 (CH, C-6), 64.00 (CH_2, OCH_2CH_3), 55.94 (CH_3, OCH_3), 52.85 (CH_2, C-12), 48.36 (C_q, C-8a), 46.66 (CH_2, C-10), 39.90 (CH_2, C-9), 27.52 (CH_2, C-5), 15.47 (CH_3, OCH_2CH_3) ppm.

2.2.5. (4aS,6R,8aS)-6-Ethoxy-11-(2-(diphenylphosphino)benzoyl)-5,6,9,10,11,12-hexahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin **5**

To a solution of 2-diphenylphosphinobenzoic acid (140 mg, 0.46 mmol) in dry CH_2Cl_2 (10 ml) under an argon atmosphere *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide (88 mg, 0.46 mmol), hydroxybenzotriazole (62 mg, 0.46 mmol), and **4** (138 mg, 0.46 mmol) were added at rt. The mixture was stirred at rt for 24 h and then was directly subjected to flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 10:1) to give 160 mg (60% yield) of **5** as a white solid; m.p. 99–103 °C. $[\alpha]^{20}_D = -57.7$ (c 1.227, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 228 K): mixture of rotamers (68:19:13); signals for the major conformer: δ = 7.47–7.44 (m, 5H, H_{ar}), 7.38–7.35 (m, 4H, H_{ar}), 7.32–7.31 (m, 2H, H_{ar}), 7.27–7.24 (m, 1 H, H_{ar}), 7.12 (d, J = 7.5 Hz, 1H, H_{ar}), 6.82 (d, J = 7.4 Hz, 1H, H_{ar}), 6.52 (d, J = 8.3 Hz, 1H, H-2), 6.01 (d, J = 10.7 Hz, 1H, H-8), 5.98 (dd, J = 10.3, 5.1 Hz, 1H, H-7), 5.96 (d, J = 8.5 Hz, 1H, H-1), 4.88 (d, J = 14.0 Hz, 1H, H_{eq}-10), 4.59 (br, 1H, H-4a), 3.93 (br, 1H, H-6), 3.92–3.85 (m, 2H, H-12), 3.82 (s, 3H, OCH_3), 3.84–3.80 (m, 1H, OCH_2CH_3), 3.46–3.43 (m, 1H, OCH_2CH_3), 3.14 (t, J = 13.3 Hz, 1H, H_{ax}-10), 2.82–2.79 (m, 1H, H_{eq}-5), 2.02–1.98 (m, 1H, H_{eq}-9), 1.95–1.92 (m, 1H, H_{ax}-9), 1.92–1.88 (m, 1H, H_{ax}-5), 1.23 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 228 K): signals for the major conformer: δ = 170.03 (d, $J_{P,C}$ = 3.8 Hz, C_q, C=O), 147.06 (C_q, C-3a), 144.16 (C_q, C-3), 141.69 (d, $J_{P,C}$ = 32.1 Hz, C_q, C_{ar}), 135.84 (d, $J_{P,C}$ = 9.3 Hz, C_q, C_{ar}), 135.80 (d, $J_{P,C}$ = 9.4 Hz, C_q, C_{ar}), 134.50 (d, $J_{P,C}$ = 21.3 Hz, 2CH, C_{ar}), 134.05 (d, $J_{P,C}$ = 15.7 Hz, C_q, C_{ar}), 133.62 (CH, C_{ar}), 133.26 (d, $J_{P,C}$ = 18.8 Hz, 2CH, C_{ar}), 131.54 (C_q, C-12b), 129.21 (CH, C_{ar}), 128.99 (CH, C_{ar}), 128.57 (d, $J_{P,C}$ = 7.4 Hz, 2CH, C_{ar}), 128.48 (CH, C_{ar}), 128.40 (CH, C_{ar}), 128.05 (d, $J_{P,C}$ = 6.4 Hz, 2CH, C_{ar}), 128.01 (CH, C-8), 127.50 (C_q, C-12a), 126.79 (d, $J_{P,C}$ = 6.8 Hz, CH, C_{ar}), 125.79 (CH, C-7), 119.75 (CH, C-1), 110.26 (CH, C-2), 86.40 (CH, C-4a), 67.91 (CH, C-6), 64.28 (CH_2, OCH_2CH_3), 55.52 (CH_3, OCH_3), 53.87 (CH_2, C-12), 47.95 (C_q, C-8a), 43.43 (CH_2, C-10), 37.03 (CH_2, C-9), 26.38 (CH_2, C-5), 15.44 (CH_3, OCH_2CH_3) ppm. ^{31}P{^{1}H} NMR (242.92 MHz, $CDCl_3$, 228 K): signal for the major conformer: δ = -14.04 ppm. MS (ESI): m/z = 590 (100, $[M+1]^+$), 289 (74). $C_{37}H_{36}NO_4P$ (589.24): calcd. C 75.38, H 6.15, N 2.38, found C 75.69, H 5.94, N 2.31.

2.2.6. (4aS,6R,8aS)-5,6,7,8,9,10,11,12-Octahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-6-ol **6**

To a solution of norgalantamine (250 mg, 0.92 mmol) in CH_3OH (5 ml) 10% Pd/C (85 mg) was added at 0 °C and the mixture was stirred at rt under a hydrogen atmosphere (balloon) for 24 h. The solids were removed by filtration through Celite and the filter cake was washed with CH_2Cl_2. The solvent was evaporated, and the resulting residue was purified by flash column chromatography (silica gel, CH_2Cl_2/CH_3OH/NH_4OH = 10:1:0.1) to give 240 mg (95% yield) of **6** as a white solid; m.p. 126–128 °C. $[\alpha]^{20}_D = -51.7$ (c 0.740, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): δ = 6.64 (d, J = 8.2 Hz, 1H, H-2), 6.61 (d, J = 8.2 Hz, 1H, H-1), 4.37 (t, J = 2.9 Hz, 1H, H-4a),

4.10–4.09 (m, 1H, H-6), 3.94 (d, J = 15.6 Hz, 1H, H_{eq}-12), 3.91 (d, J = 15.6 Hz, 1H, H_{ax}-12), 3.85 (s, 3H, OCH_3), 3.37 (dt, J = 14.4, 3.5 Hz, 1H, H_{eq}-10), 3.41 (ddd, J = 14.4, 11.1, 1.6 Hz, 1H, H_{ax}-10), 2.51 (dq, J = 16.0, 4.0 Hz, 1H, H_{eq}-5), 1.95 (dq, J = 13.9, 3.5 Hz, 1H, H_{eq}-9), 1.89 (dq, J = 16.0, 4.4 Hz, 1H, H_{ax}-5), 1.84–1.77 (m, 2H, H_{eq}-7, H_{eq}-8), 1.72–1.67 (m, H, H_{ax}-9), 1.67–1.62 (m, H, H_{ax}-8), 1.60–1.57 (m, H, H_{ax}-7) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): δ = 146.29 (C_q, C-3a), 144.05 (C_q, C-3), 136.47 (C_q, C-12b), 132.19 (C_q, C-12a), 120.51 (CH, C-1), 110.45 (CH, C-2), 89.85 (CH, C-6), 65.36 (CH, C-4a), 55.86 (CH_3, OCH_3), 53.62 (CH_2, C-12), 47.24 (CH_2, C-10), 47.18 (C_q, C-8a), 37.21 (CH_2, C-9), 31.44 (CH_2, C-5), 27.57 (CH, C-8), 23.91 (CH, C-7) ppm.

2.2.7. (4aS,6R,8aS)-11-(2-(Diphenylphosphino)benzoyl)-5,6,7,8,9,10,11,12-octahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-6-ol **7**

To a solution of 2-diphenylphosphinobenzoic acid (137 mg, 0.46 mmol) in dry CH_2Cl_2 (10 ml) under an argon atmosphere *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide (88 mg, 0.46 mmol), hydroxybenzotriazole (62 mg, 0.46 mmol), and **6** (125 mg, 0.46 mmol) were added at rt. The mixture was stirred at rt for 24 h and then was directly subjected to flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 3:1) to give 202 mg (79% yield) of **7** as a white solid; m.p. 130–135 °C. $[\alpha]^{20}_D$ = −37.5 (c 1.051, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 228 K): mixture of rotamers (65:20:15); signals for the major conformer: δ = 7.50–7.49 (m, 1H, H_{ar}), 7.46–7.44 (m, 4H, H_{ar}), 7.38–7.36 (m, 3H, H_{ar}), 7.32–7.31 (m, 3H, H_{ar}), 7.27–7.25 (m, 1 H, H_{ar}), 7.13–7.12 (m, 1H, H_{ar}), 6.79 (d, J = 7.5 Hz, 1H, H_{ar}), 6.59 (d, J = 8.3 Hz, 1H, H-2), 6.05 (d, J = 8.3 Hz, 1H, H-1), 4.86 (d, J = 13.9 Hz, 1H, H_{eq}-10), 4.38 (br, 1H, H-4a), 4.15 (br, 1H, H-6), 3.90 (s, 3H, OCH_3), 3.82 (d, J = 16.2 Hz, 1H, H_{eq}-12), 3.68 (d, J = 16.2 Hz, 1H, H_{ax}-12), 3.04 (t, J = 13.5 Hz, 1H, H_{ax}-10), 2.65–2.55 (m, 1H, H_{eq}-5), 2.02–1.99 (m, 1H, H_{eq}-9), 1.95–1.93 (m, 1H, H_{ax}-5), 1.89–1.84 (m, 1H, H_{ax}-9), 1.80–1.78 (m, 1H, H_{eq}-7), 1.73–1.68 (m, 3H, H_{ax}-7, H-8) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 228 K): signals for the major conformer: δ = 169.93 (d, $J_{P,C}$ = 2.7 Hz, C_q, C=O), 145.84 (C_q, C-3a), 143.93 (C_q, C-3), 141.24 (d, $J_{P,C}$ = 31.9 Hz, C_q, C_{ar}), 136.21 (C_q, C-12b), 135.54 (d, $J_{P,C}$ = 8.6 Hz, C_q, C_{ar}), 135.35 (d, $J_{P,C}$ = 9.7 Hz, C_q, C_{ar}), 134.71 (d, $J_{P,C}$ = 21.2 Hz, 2CH, C_{ar}), 134.02 (d, $J_{P,C}$ = 15.2 Hz, C_q, C_{ar}), 133.50 (CH, C_{ar}), 133.11 (d, $J_{P,C}$ = 18.7 Hz, 2CH, C_{ar}), 129.36 (CH, C_{ar}), 129.18 (CH, C_{ar}), 129.03 (CH, C_{ar}), 128.56 (d, $J_{P,C}$ = 7.5 Hz, 2CH, C_{ar}), 128.47 (CH, C_{ar}), 128.38 (d, $J_{P,C}$ = 6.7 Hz, 2CH, C_{ar}), 127.28 (C_q, C-12a), 126.46 (d, $J_{P,C}$ = 6.9 Hz, CH, C_{ar}), 120.37 (CH, C-1), 109.51 (CH, C-2), 89.54 (CH, C-4a), 65.15 (CH, C-6), 55.65 (CH_3, OCH_3), 53.88 (CH_2, C-12), 46.51 (C_q, C-8a), 43.66 (CH_2, C-10), 31.67 (CH_2, C-9), 30.75 (CH_2, C-5), 27.07 (CH, C-8), 22.74 (CH, C-7) ppm. ^{31}P{^{1}H} NMR (242.92 MHz, $CDCl_3$, 228 K): signal for the major conformer: δ = -14.16 ppm. MS (ESI): m/z = 564 (100, $[M+1]^+$), 289 (56). $C_{35}H_{24}NO_4P$ (563.22): calcd. C 74.58, H 6.08, N 2.49, found C 74.22, H 6.34, N 2.45.

2.2.8. t-Butyl ((4aS,6R,8aS)-5,6,7,8,9,10,11,12-octahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-6-ol-11yl) carbamate ***8***

To a solution of **6** (176 mg, 0.64 mmol) in dry CH_2Cl_2 (10 ml) NEt_3 (129 mg, 0.2 ml, 1.28 mmol) and $(BOC)_2O$ (182 mg, 0.83 mmol) were added at rt. The mixture was stirred at rt for 1 h then concentrated and purified by flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 2:1) to give 204 mg (85% yield) of **8** as a white solid; m.p. 109–111 °C. $[\alpha]^{20}_D$ = −25.2 (c 1.060, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): mixture of rotamers (64:36); signals for major conformer δ = 6.65–6.63 (m, 2H, H-2, H-1), 4.61 (d, J = 15.5 Hz, 1H, H_{eq}-12), 4.33 (br, 1H, H-6), 4.27 (d, J = 14.3 Hz, 1H, H_{eq}-10), 4.10 (br, 1H, H-4a), 4.05 (d, J = 15.5 Hz, 1H, H_{ax}-12), 3.87 (s, 3H, OCH_3), 3.26–3.22 (m, 1H, H_{ax}-10), 2.59–2.51 (m, 2H, H_{eq}-5, OH), 1.91–1.89 (m, 1H, H_{ax}-5), 1.84–1.78 (m, 4H, H-9, H-8), 1.71–1.60 (m, 2H, H-7), 1.35 (s, 9H, $C(CH_3)_3$) ppm; resolved signals for minor conformer δ = 6.77 (d, J = 8.2 Hz, 1H, H-1), 6.67 (d, J = 8.2 Hz, 1H, H-2), 4.81 (d, J = 15.5 Hz, 1H, H_{eq}-12), 4.33 (br, 1H, H-6), 4.15 (d, J = 14.0 Hz, 1H, H_{eq}-10), 4.10 (br, 1H, H-4a), 3.98 (d, J = 15.3 Hz, 1H, H_{ax}-12), 3.85 (s, 3H, OCH_3), 3.33 (t, J = 13.4 Hz, 1H, H_{ax}-10), 2.59–2.51 (m, 2H, H_{eq}-5, OH), 1.91–1.89 (m, 2H, H_{ax}-5, H_{eq}-9), 1.84–1.79 (m, 2H, H-8), 1.71–1.60 (m, 3H, H-7, H_{ax}-9), 1.41 (s, 9H, $C(CH_3)_3$) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): signals for the major conformer: δ = 154.97 (C_q, C=O), 146.41 (C_q, C-3a), 144.15 (C_q, C-3), 136.00 (C_q, C-12b), 129.50 (C_q, C-12a), 120.64 (CH, C-1), 110.22 (CH, C-2), 89.63 (CH, C-6), 79.72 (C_q, $C(CH_3)_3$), 65.31 (CH, C-4a), 55.83 (CH_3, OCH_3), 51.87 (CH_2, C-12), 46.87 (C_q, C-8a), 45.61 (CH_2, C-10), 33.23 (CH_2, C-9), 31.36 (CH_2, C-5), 28.29 (CH_3, $C(CH_3)_3$), 27.57 (CH, C-8), 23.68 (CH, C-7) ppm; resolved signals for minor conformer δ = 154.56 (C_q, C=O), 146.30 (C_q, C-3a), 144.15 (C_q, C-3), 135.88 (C_q, C-12b), 129.32 (C_q, C-12a), 121.25 (CH, C-1), 110.61 (CH, C-2), 89.53 (CH, C-6), 79.72 (C_q, $C(CH_3)_3$), 65.31 (CH, C-4a), 55.83 (CH_3, OCH_3), 51.34 (CH_2, C-12), 46.87 (C_q, C-8a), 45.90 (CH_2, C-10), 33.97 (CH_2, C-9), 31.31 (CH_2, C-5), 28.43 (CH_3, $C(CH_3)_3$), 27.57 (CH, C-8), 23.84 (CH, C-7) ppm.

2.2.9. t-Butyl ((4aS,6R,8aS)-6-ethoxy-5,6,7,8,9,10,11,12-octahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin-11yl) carbamate ***9***

To a stirred solution of **8** (165 mg, 0.44 mmol) in DMF (5 ml) at 0 °C was added NaH (106 mg, 2.20 mmol). The mixture was stirred for 30 min at rt and then EtI (0.18 ml, 2.20 mmol) was added. The reaction was stirred at rt until the starting material was completely consumed (TLC). Next, it was cooled to 0 °C and treated with sat. aq. NH_4Cl. The organic phase was separated, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 10:1) to give 170 mg (96% yield) of **9** as a white solid; m.p. 80–82 °C. $[\alpha]^{20}_D$ = −62.5 (c 0.900, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): mixture of rotamers (66:34); signals for major conformer δ = 6.62 (d, J = 8.0 Hz, 1H, H-2), 6.57 (d, J = 8.0 Hz, 1H, H-1), 4.58 (d, J = 15.4 Hz, 1H, H_{eq}-12), 4.31 (br, 1H, H-4a), 4.25 (d, J = 14.5 Hz, 1H, H_{eq}-10), 4.05 (d, J = 15.4 Hz, 1H, H_{ax}-12), 3.85 (s, 3H, OCH_3), 3.70–3.67 (m, 1H, H-6), 3.62–3.57 (m, 1H, OCH_2CH_3), 3.45–3.40 (m, 1H, OCH_2CH_3), 3.23–3.19 (m, 1H, H_{ax}-10), 2.55–2.50 (m, 1H, H_{eq}-5), 1.92–1.98 (m, 1H, H_{eq}-7), 1.86–1.80 (m, 1H, H_{ax}-5), 1.83–1.79 (m, 2H, H-9), 1.72–1.61 (m, 3H, H_{ax}-7, H-8), 1.35 (s, 9H, $C(CH_3)_3$), 1.17 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm; resolved signals for minor conformer δ = 6.71 (d, J = 8.1 Hz, 1H, H-2), 6.63 (d, J = 8.1 Hz, 1H, H-1), 4.78 (d, J = 15.2 Hz, 1H, H_{eq}-12), 4.31 (br, 1H, H-4a), 4.13 (d, J = 14.4 Hz, 1H, H_{eq}-10), 3.98 (d, J = 15.2 Hz, 1H, H_{ax}-12), 3.84 (s, 3H, OCH_3), 3.70–3.67 (m, 1H, H-6), 3.62–3.57 (m, 1H, OCH_2CH_3), 3.45–3.40 (m, 1H, OCH_2CH_3), 3.30 (d, J = 13.4 Hz, 1H, H_{ax}-10), 2.55–2.50 (m, 1H, H_{eq}-5), 1.92–1.98 (m, 1H, H_{eq}-7), 1.88–1.85 (m, 1H, H_{eq}-9), 1.86–1.80 (m, 1H, H_{ax}-5), 1.72–1.68 (m, 1H, H_{ax}-9), 1.72–1.61 (m, 3H, H_{ax}-7, H-8), 1.40 (s, 9H, $C(CH_3)_3$), 1.17 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): signals for the major conformer: δ = 155.03 (C_q, C=O), 147.30 (C_q, C-3a), 144.00 (C_q, C-3), 134.91 (C_q, C-12b), 129.40 (C_q, C-12a), 119.86 (CH, C-1), 110.41 (CH, C-2), 88.62 (CH, C-4a), 79.61 (C_q, $C(CH_3)_3$), 71.34 (CH, C-6), 63.24 (CH_2, OCH_2CH_3), 55.92 (CH_3, OCH_3), 51.61 (CH_2, C-12), 47.16 (C_q, C-8a), 45.46 (CH_2, C-10), 34.72 (CH_2, C-9), 28.87 (CH_2, C-5), 28.30 (CH_3, $C(CH_3)_3$), 24.82 (CH, C-8), 24.73 (CH, C-7), 15.44 (CH_3, OCH_2CH_3) ppm; resolved signals for minor conformer δ = 154.57 (C_q, C=O), 147.19 (C_q, C-3a), 144.00 (C_q, C-3), 134.73 (C_q, C-12b), 129.21 (C_q, C-12a), 120.43 (CH, C-1), 110.71 (CH, C-2), 88.50 (CH, C-4a), 79.57 (C_q, $C(CH_3)_3$), 71.31 (CH, C-6), 63.22 (CH_2, OCH_2CH_3), 55.86 (CH_3, OCH_3), 51.10 (CH_2, C-12), 47.16 (C_q, C-8a), 45.78 (CH_2, C-10), 35.46 (CH_2, C-9), 28.75 (CH_2, C-5), 28.43 (CH_3,

C(CH_3)$_3$), 24.94 (CH, C-8), 24.82 (CH, C-7), 15.44 (CH_3, OCH_2CH_3) ppm.

2.2.10. (4aS,6R,8aS)-6-Ethoxy-5,6,7,8,9,10,11,12-octahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin **10**

To a solution of **9** (186 mg, 0.46 mmol) in CH_2Cl_2 (10 ml) was added dropwise CF_3CO_2H (2 ml) at 0 °C and the mixture was stirred at rt for 1 h. Next, it was cooled to 0 °C and treated with sat. aq. $NaHCO_3$. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/CH_3OH/NH_4OH = 10:1:0.2) to give 138 mg (99% yield) of **10** as a waxy solid; $[\alpha]^{20}_D = -82.7$ (c 0.814, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 293 K): δ = 6.62 (d, J = 8.1 Hz, 1H, H-2), 6.56 (d, J = 8.1 Hz, 1H, H-1), 4.35 (d, J = 3.8 Hz,1H, H-4a), 3.97 (d, J = 15.3 Hz, 1H, H_{eq}-12), 3.93 (d, J = 15.3 Hz, 1H, H_{ax}-12), 3.84 (s, 3H, OCH_3), 3.69–3.66 (m, 1H, H-6), 3.60–3.55 (m, 1H, OCH_2CH_3), 3.46–3.41 (m, 1H, OCH_2CH_3), 3.40–3.37 (m, 1H, H_{eq}-10), 3.17 (t, J = 13.1, 3.2 Hz, 1H, H_{ax}-10), 2.50 (dt, J = 15.7, 3.2 Hz, 1H, H_{eq}-5), 1.93–1.91 (m, 2H, H_{eq}-8, H_{eq}-9), 1.85 (dt, J = 15.7, 4.8 Hz, 1H, H_{ax}-5), 1.75–1.70 (m, 1H, H_{ax}-9), 1.71–1.64 (m, 2H, H_{eq}-7, H_{ax}-8), 1.62–1.60 (m, 1H, H_{ax}-7), 1.17 (t, J = 7.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 293 K): δ = 147.22 (C_q, C-3a), 144.24 (C_q, C-3), 135.38 (C_q, C-12b), 130.31 (C_q, C-12a), 120.03 (CH, C-1), 110.84 (CH, C-2), 88.75 (CH, C-4a), 71.36 (CH, C-6), 63.27 (CH_2, OCH_2CH_3), 55.99 (CH_3, OCH_3), 52.70 (CH_2, C-12), 47.35 (CH_2, C-10), 46.67 (C_q, C-8a), 37.64 (CH_2, C-9), 28.94 (CH_2, C-5), 24.89 (CH, C-8), 24.77 (CH, C-7), 15.45 (CH_3, OCH_2CH_3) ppm.

2.2.11. (4aS,6R,8aS)-6-Ethoxy-11-(2-(diphenylphosphino)benzoyl)-5,6,7,8,9,10,11,12-octahydro-3-methoxy-4aH-[1]benzofuro[3a,3,2-ef][2]benzazepin **11**

To a solution of 2-diphenylphosphinobenzoic acid (126 mg, 0.41 mmol) in dry CH_2Cl_2 (10 ml) under an argon atmosphere *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide (79 mg, 0.41 mmol), hydroxybenzotriazole (56 mg, 0.41 mmol), and **10** (125 mg, 0.41 mmol) were added at rt. The mixture was stirred at rt for 24 h and then was directly subjected to flash column chromatography (silica gel, CH_2Cl_2/EtOAc = 5:1) to give 170 mg (70% yield) of **11** as a white solid; m.p. 93–96 °C. $[\alpha]^{20}_D = -62.7$ (c 1.065, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 228 K): mixture of rotamers (66:24:10); signals for the major conformer: δ = 7.50–7.48 (m, 2H, H_{ar}), 7.45–7.44 (m, 4H, H_{ar}), 7.38–7.36 (m, 3H, H_{ar}), 7.34–7.32 (m, 1H, H_{ar}), 7.31–7.30 (m, 1H, H_{ar}), 7.28–7.25 (m, 1 H, H_{ar}), 7.12 (d, J = 7.9 Hz, 1H, H_{ar}), 6.81 (d, J = 7.4 Hz, 1H, H_{ar}), 6.53 (d, J = 8.3 Hz, 1H, H-2), 5.94 (d, J = 8.3 Hz, 1H, H-1), 4.87 (d, J = 13.9 Hz, 1H, H_{eq}-10), 4.40 (br, 1H, H-4a), 3.86 (s, 3H, OCH_3), 3.78 (d, J = 16.2 Hz, 1H, H_{eq}-12), 3.74 (br, 1H, H-6), 3.70 (d, J = 16.2 Hz, 1H, H_{ax}-12), 3.67–3.64 (m, 1H, OCH_2CH_3), 3.43–3.39 (m, 1H, OCH_2CH_3), 3.04 (t, J = 13.2 Hz, 1H, H_{ax}-10), 2.61–2.59 (m, 1H, H_{eq}-5), 1.97–1.95 (m, 1H, H_{eq}-9), 1.95–1.90 (m, 1H, H_{ax}-9), 1.86–1.84 (m, 1H, H_{ax}-5), 1.80–1.78 (m, 1H, H_{eq}-7), 1.73–1.71 (m, 1H, H_{eq}-8), 1.61–1.58 (m, 2H, H_{ax}-7, H_{ax}-8), 1.20 (t, J = 6.9 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$, 228 K): signals for the major conformer: δ = 169.91 (d, $J_{P,C}$ = 2.6 Hz, C_q, C=O), 146.69 (C_q, C-3a), 143.75 (C_q, C-3), 141.42 (d, $J_{P,C}$ = 32.4 Hz, C_q, C_{ar}), 135.55 (d, $J_{P,C}$ = 8.7 Hz, C_q, C_{ar}), 135.28 (d, $J_{P,C}$ = 9.6 Hz, C_q, C_{ar}), 134.59 (d, $J_{P,C}$ = 21.2 Hz, 2CH, C_{ar}), 134.37 (C_q, C-12b), 133.71 (d, $J_{P,C}$ = 15.4 Hz, C_q, C_{ar}), 133.41 (CH, C_{ar}), 133.03 (d, $J_{P,C}$ = 18.6 Hz, 2CH, C_{ar}), 129.25 (CH, C_{ar}), 129.08 (CH, C_{ar}), 128.91 (CH, C_{ar}), 128.50 (d, $J_{P,C}$ = 7.4 Hz, 2CH, C_{ar}), 128.33 (d, $J_{P,C}$ = 8.4 Hz, 2CH, C_{ar}), 128.26 (CH, C_{ar}), 126.98 (C_q, C-12a), 126.57 (d, $J_{P,C}$ = 7.0 Hz, CH, C_{ar}), 119.52 (CH, C-1), 109.25 (CH, C-2), 88.46 (CH, C-4a), 71.28 (CH, C-6), 63.18 (CH_2, OCH_2CH_3), 55.40 (CH_3, OCH_3), 53.40 (CH_2, C-12), 46.81 (C_q, C-8a), 43.26 (CH_2, C-10), 34.37 (CH_2, C-9), 27.73 (CH_2, C-5), 24.88 (CH, C-7), 24.45 (CH, C-8), 15.33 (CH_3, OCH_2CH_3) ppm. ^{31}P{^{1}H} NMR (242.92 MHz, $CDCl_3$, 228 K):signal for the major conformer: δ = -14.41 ppm. MS (ESI): m/z = 592 (100, $[M+1]^+$), 289 (62). $C_{37}H_{38}NO_4P$ (591.25): calcd. C 75.11, H 6.47, N 2.37, found C 74.82, H 6.81, N 2.43.

2.3. Computational details

All calculations were performed with Gaussian09 program package [19] at the DFT level of theory.

The geometries of all four conformations of the ligands have been fully optimized and the corresponding transition states were localized using B3LYP [20] functional with 6-31+G(d,p) basis set [21] with Grimme's D3 empirical correction [22]. Solvent was included implicitly to the optimizations via the SMD [23] model with the built in parameters for solvent $CHCl_3$. The nature of all critical points was confirmed by means of the vibrational analysis, and ZPV energies were evaluated. The thermal corrections to Gibbs free energy to 298.15 K have been calculated for all minima from unscaled vibrational frequencies obtained at the same level.

The ΔH, ΔS and ΔG values were calculated for T = 298.15 K at the same level of theory including zero-point energy in the particular solvent environment (represented by relative permittivity) and vibrational, rotational and translational thermal energy corrections.

The GIAO ^{1}H and ^{13}C NMR chemical shifts in $CHCl_3$ were calculated using MPW1K functional [24] with 6–311++G(2d,2p) basis set [25–28] using B3LYP/6–31+(d,p) geometries.

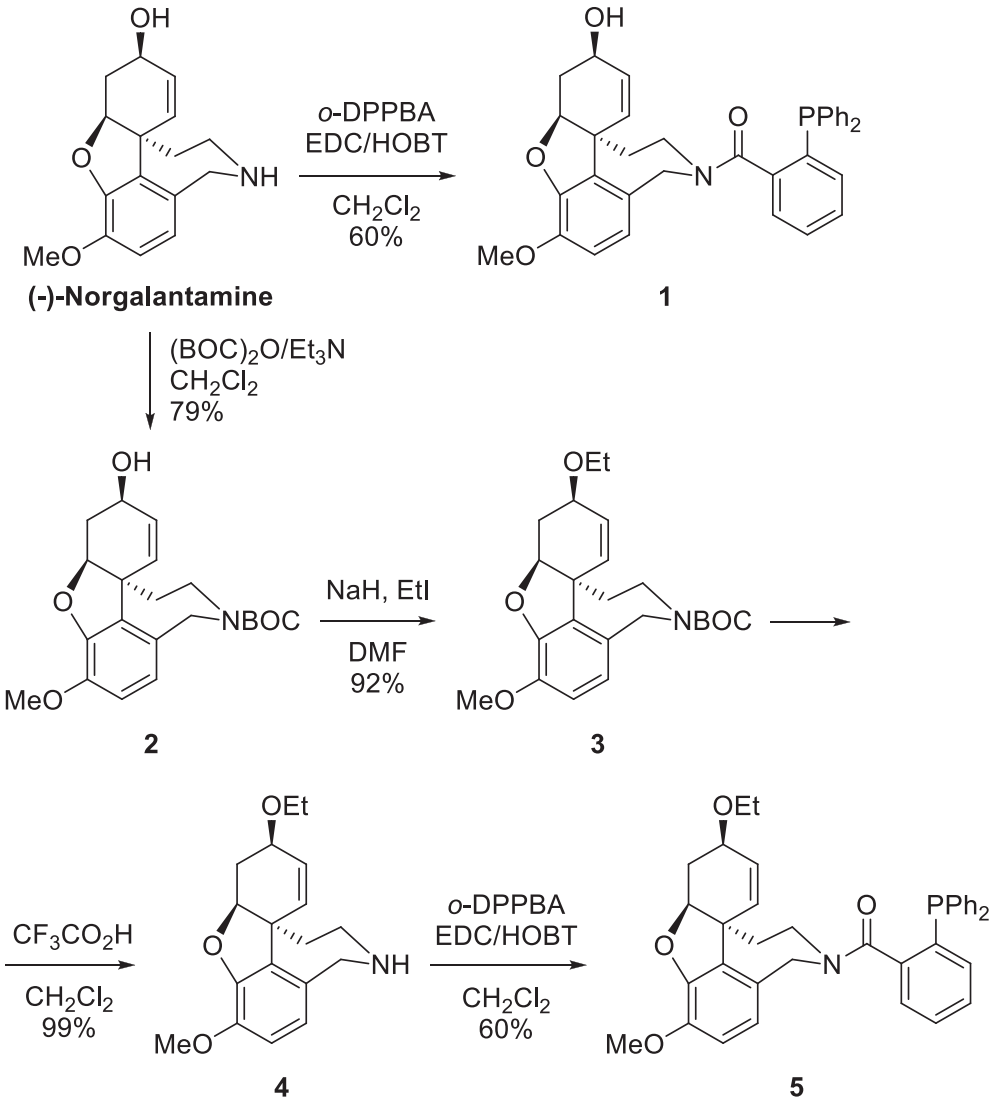
2.4. Dynamic NMR studies

^{1}H, ^{13}C and ^{31}P spectra were recorded on a Bruker II+ 600 spectrometer (BBO probe) at 600.13 for ^{1}H NMR, 150.92 MHz for ^{13}C NMR and 242.92 MHz for ^{31}P NMR with TMS (85% H_3PO_4 for ^{31}P) as internal standard for chemical shifts (δ, ppm). The spectra were recorded in steps of 5 K between 228 and 323 K (0.05M in 600 μL $CDCl_3$). Temperature calibration was done with B-VT 3000 unit (it was checked and calibrated with methanol and ethylene glycol reference samples). ^{1}H NMR spectra were acquired using a spectral width of 10 kHz, an acquisition time of 3.4 s and 32 scans, zerofilled to 64k datapoints (0.15 Hz per point) and processed without apodization.

^{31}P EXSY spectra (noesygpphzs) were recorded on a BBO probe in steps of 5 K between 228 and 253 K and between 263 K and 273 K. The spectra were acquired using a spectral width of 1.2 kHz, 2048 x 256 complex time domain datapoints, mixing times in the range of 0.1–2.5 s and 2 scans in about 45 min. The spectra were zerofilled to 4096 x 4096 datapoints and processed with a shifted square sine bell apodization in both dimensions. Populations and exchange rates were obtained from diagonal- and crosspeak integrals using EXSYCalc (MestreLab Research S.L.).

^{1}H EXSY spectra (noesygpphzs) were recorded on a BBO probe in steps of 10 K between 273 and 323 K. The spectra were acquired using a spectral width of 4.2 kHz, 2048 x 256 complex time domain datapoints, mixing times in the range of 0.02–1.5 s and 2 scans in about 45 min. The spectra were zerofilled to 4096 x 4096 datapoints and processed with a shifted square sine bell apodization in both dimensions. Populations and exchange rates were obtained from diagonal- and crosspeak integrals using EXSYCalc (MestreLab Research S.L.).

Errors analysis: Usually the presented errors in activation parameters are the statistical errors based on scattering of the data points around the Eyring straight line only. The errors in this analysis are due to inaccuracies in both the calculated rate constants, ***k***, and the measured temperatures, ***T*** and are computed according to the error propagation equations of Binsch [29] and Heinzer and Oth [30]. The absolute error in temperature is assumed



Scheme 1. Synthesis of diphenylphosphino-benzenecarboxamide ligands **1** and **5**.

to be not more than ±0.5 K. The relative errors in ***k*** are estimated to be not more than ±10% at all temperatures according the precision of the volume integration of peaks. The errors analysis was performed using self-made computer program using the cited equations.

2.5. General procedure for the palladium-catalized allylic alkylation

A: A mixture of chiral ligand (0.03 mmol), $[Pd(\eta_3\text{-}C_3H_5)Cl]_2$ (6.0 mg, 0.016 mmol), and LiOAc (0.05 mmol) in a dry solvent (3 mL) was stirred at rt in a Schlenk tube for 30 min. Then, rac- 1,3-diphenylprop-2-en-1-yl acetate (126 mg, 0.5 mmol) was introduced followed, after stirring for another 5 min, by *N*,O-bis- (trimethylsilyl)acetamide (BSA; 0.37 mL, 1.5 mmol) and dimethyl malonate (0.17 mL, 1.5 mmol). The mixture was stirred at rt for 24 h, then the reaction mixture was diluted with diethyl ether (10 mL) and washed consecutively with sat. aq. NH_4Cl and water. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate, 9:1).

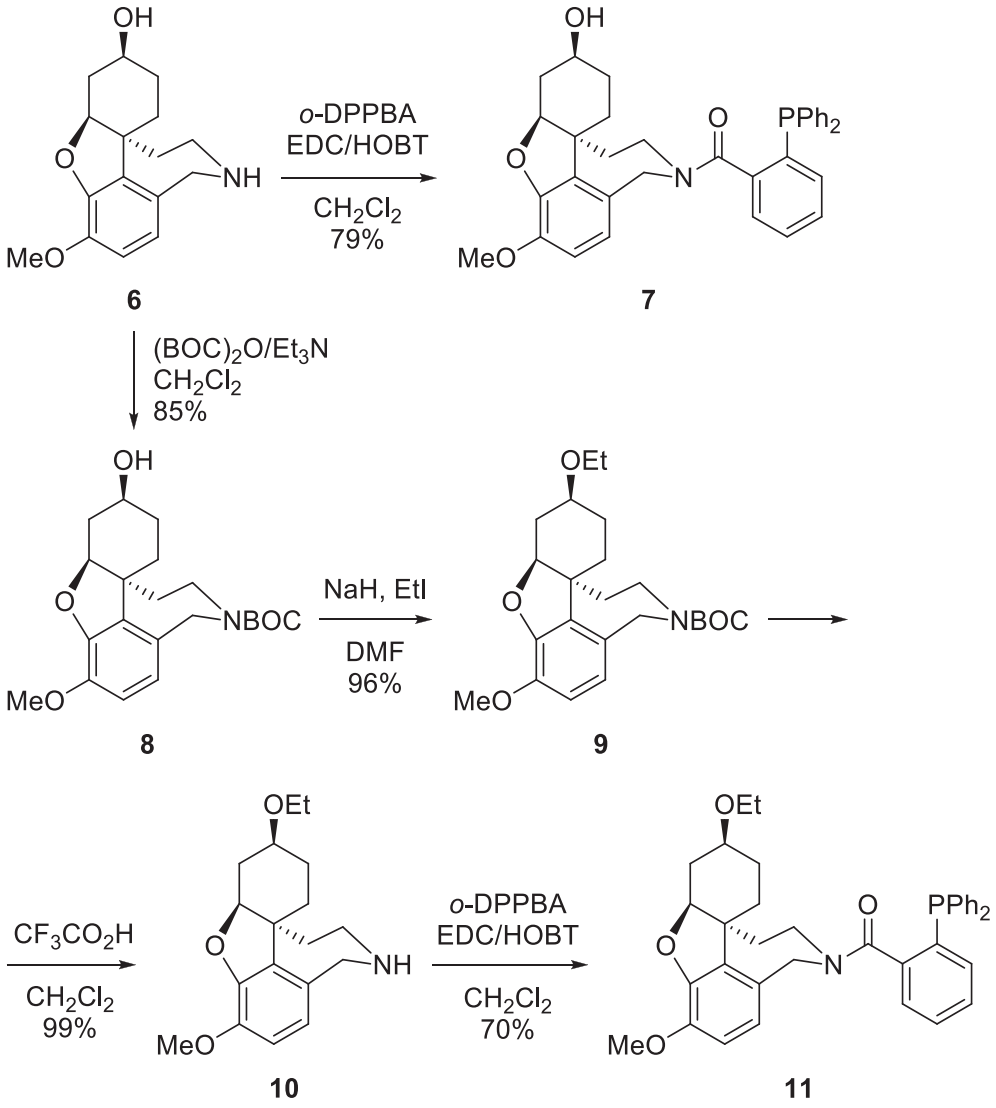
B: A mixture of chiral ligand (0.03 mmol), $[Pd(\eta_3\text{-}C_3H_5)Cl]_2$ (6.0 mg, 0.016 mmol), in a dry solvent (3 mL) was stirred at rt in a Schlenk tube for 30 min. Then, rac- 1,3-diphenylprop-2-en-1-yl acetate (126 mg, 0.5 mmol) was introduced followed, after stirring for another 5 min, by Cs_2CO_3 (0.326 g, 1.0 mmol) and dimethyl malonate (0.11 mL, 1.0 mmol). The mixture was stirred at rt for 24 h. The reaction was quenched with sat. aq. NH_4Cl, extracted with EtOAc (3 × 20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane:ethyl acetate, 9:1).

The enantioselectivity was determined by HPLC analysis with a chiral column (Chiralpak IC; hexane/i-PrOH, 96:4; flow rate, 1 mL/min; t_R, 8.2; t_S, 9.1 min). The absolute configurations of the enantiomers were determined by comparison of the retention times with that of an authentic sample and by measurement of the optical rotation of the product.

3. Results and discussion

3.1. Synthesis of galantamine derivatives

(−)-Norgalantamine and (−)-norlycoramine are readily available from naturally occurring galantamine and being secondary



Scheme 2. Synthesis of diphenylphosphino-benzenecarboxamide ligands **7** and **11**.

amines provide the possibility for nitrogen derivatization. Norgalantamine was synthesized by selective *N*-demethylation of galantamine *via* a non-classical Polonovski reaction [31]. Norlycoramine was obtained quantitatively from norgalantamine by catalytic hydrogenation of its cyclohexene ring applying a known procedure [32].

Condensation of norgalantamine with *ortho*-diphenylphosphinobenzoic acid (*o*-DPPBA) in the presence of *N*-[-3-(dimethylamino)propyl]-*N*-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) resulted in diphenylphosphino-benzenecarboxamide **1** which was isolated in 60% yield after flash column chromatography (Scheme 1). Our next goal was to obtain an analogue after alkylation of the hydroxyl function of the cyclohexene ring. Protection of the nitrogen was necessary in order to avoid formation of quaternary ammonium salts [33]. Thus, reaction with di-*tert*-butyl dicarbonate in the presence of trimethylamine afforded the *N*-Boc derivative **2**. The latter was subsequently alkylated with ethyl iodide after deprotonation with NaH to give **3**. Deprotection to **4** proceeded quantitatively with trifluoroacetic acid. Diphenylphosphino-benzenecarboxamide **5** was obtained in 60% yield by application of the coupling reaction with *o*-DPPBA (Scheme 1).

The same sequence of reactions was applied for norlycoramine **6** (Scheme 2). Its direct condensation with *o*-DPPBA furnished diphenylphosphino-benzenecarboxamide with free hydroxyl function **7**. Initial protection of norlycoramine **6** gave its *N*-Boc derivative **8**, which was subsequently ethylated to **9**. Deprotection of the latter resulted in **10**, which was condensed with *o*-DPPBA to give diphenylphosphino-benzenecarboxamide ligand with ethoxy group **11**. Oxidation of the phosphines to the corresponding phosphine oxides was minimized by using a non-aqueous work-up procedure, subjecting the reaction mixtures directly to flash column chromatography on silica gel.

3.2. Conformational analysis and molecular geometry

The structures of the newly synthesized compounds were confirmed by 1D and 2D NMR spectra. Conformational exchanges occurred in solution at rates that were intermediate on the NMR time scale. The signals of phosphino-carboxamide ligands **1, 5, 7** and **11** were broad at room temperature and therefore, it was necessary to measure NMR spectra at lower temperatures. The spectra of compounds **2, 3, 4, 8, 9** and **10** were recorded at room temperature. In the case of secondary amines **4** and **10** only one

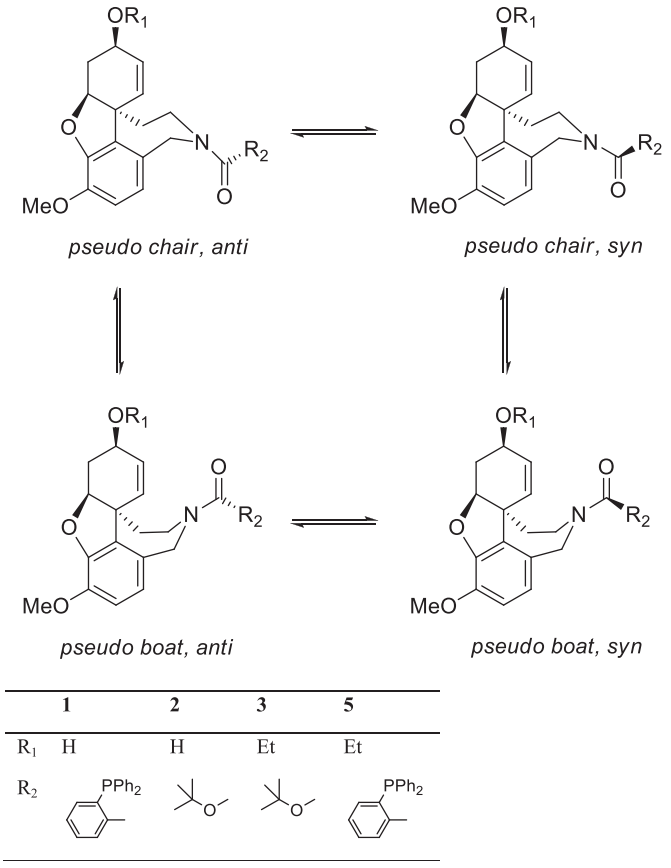


Fig. 2. Possible conformers for norgalantamine derivatives (**1**, **2**, **3** and **5**). Analogous conformation exchanges are valid for norlycoramine derivatives (**7**, **8**, **9** and **11**).

Table 1
Population (%) of conformers obtained by integration of ^{1}H and ^{31}P NMR spectra and by DFT calculations at 25 °C.

No	Configuration	NMR[a]	B3LYP/6-31+G(d,p)
1	*pseudo chair, anti*	61.8	98.2
	pseudo chair, syn	21.5	1.3
	pseudo boat, anti	15.6	0.4
	pseudo boat, syn	1.1	0.0
5	*pseudo chair, anti*	63.4	79.8
	pseudo chair, syn	21.0	17.9
	pseudo boat, anti	14.8	2.2
	pseudo boat, syn	0.9	0.1
7	*pseudo chair, anti*	62.7	95.2
	pseudo chair, syn	20.3	3.2
	pseudo boat, anti	15.8	1.4
	pseudo boat, syn	1.2	0.2
11	*pseudo chair, anti*	64.7	86.9
	pseudo chair, syn	23.8	12.0
	pseudo boat, anti	10.3	0.4
	pseudo boat, syn	1.2	0.8
2	*pseudo chair, anti*	62.2	42.4
	pseudo chair, syn	37.8	56.2
	pseudo boat, anti	n.o.	1.1
	pseudo boat, syn	n.o.	0.3
3	*pseudo chair, anti*	65.2	64.2
	pseudo chair, syn	34.8	34.0
	pseudo boat, anti	n.o.	0.4
	pseudo boat, syn	n.o.	1.5
8	*pseudo chair, anti*	63.3	61.5
	pseudo chair, syn	36.7	37.8
	pseudo boat, anti	n.o.	0.4
	pseudo boat, syn	n.o.	0.4
9	*pseudo chair, anti*	65.8	85.4
	pseudo chair, syn	34.2	14.1
	pseudo boat, anti	n.o.	0.3
	pseudo boat, syn	n.o.	0.2

[a] ratio of isomers determined by integration of peaks in ^{31}P NMR spectra at 228 K (**1**, **5**, **7** and **11**) and by integration of peaks in ^{1}H NMR spectra at 273 K (**2**, **3**, **8**, and **9**).

Table 2
Experimental and calculated ^{13}C chemical shifts using B3LYP/6−31+(d,p) geometries.[a]

Conformers	C-10 Exp./calc.	C-12 Exp./calc.	Exp. observed population
1-*pseudo chair, syn*	n.o./52.23	n.o./53.85	
1 *pseudo chair, anti*	43.31/49.15	53.77/58.64	Major
5-*pseudo chair, syn*	n.o./52.38	n.o./53.70	
5 *pseudo chair, anti*	43.43/49.37	53.87/58.45	Major
7-*pseudo chair, syn*	n.o./52.45	n.o./54.08	
7 *pseudo chair, anti*	43.66/49.52	53.88/58.90	Major
11-*pseudo chair, syn*	n.o./52.62	n.o./53.97	
11 *pseudo chair, anti*	43.26/49.80	53.40/58.78	Major
2-*pseudo chair, syn*	45.65/50.35	51.35/55.94	
2 *pseudo chair, anti*	45.38/50.27	51.93/56.19	Major
3-*pseudo chair, syn*	45.70/50.51	51.24/56.09	
3 *pseudo chair, anti*	45.40/50.14	51.77/56.03	Major
8-*pseudo chair, syn*	45.90/50.61	51.34/56.28	
8 *pseudo chair, anti*	45.61/50.50	51.87/56.44	Major
9-*pseudo chair, syn*	45.78/50.78	51.10/56.29	
9 *pseudo chair, anti*	45.46/50.40	51.61/56.17	Major

[a] Experimental ^{13}C NMR chemical shifts are measured at 228 K for **1**, **5**, **7** and **11** while for **2**, **3**, **8** and **9** the reported values are at room temperature. The PCM//MPW1K/6−311++G(2d,2p) calculated ^{13}C NMR chemical shifts use TMS as a reference system. n.o.: not observed.

preferred conformer was registered at room temperature.

The possible conformers for each ligand are two as a result of rotation around the amide bond (*syn* and *anti*), and at least two conformers due to flexibility of the 2,3,4,5-tetrahydro-1*H*-azepine ring (*pseudo chair* and *pseudo boat*) (Fig. 2). The restricted rotation around C−N bond in amides and carbamates is experimentally and theoretically thoroughly studied and well documented [34−37]. The conformational properties of a seven-membered ring is considerably altered by the presence of a double bond: cycloheptane displays pseudorotation [38] within both the *boat* and the *chair* conformational families, while in cycloheptene the *chair* is relatively rigid without pseudorotation [39]. Previous investigations of various heterocyclic analogues of benzocycloheptene [40−47] have demonstrated the frequent existence of three distinct seven-membered ring geometries: *chair*, *boat* and *twist−boat* conformations. During the conformational NMR studies of tetrahydro-1,4-benzothiazepines [48] and *N*-substituted-1,3,4,5-tetrahydro-1*H*-2-benzazepines [49] a single *chair*-to-*chair* interconversion of the benzazepine ring was detected. The configuration of nitrogen atom in seven-membered ring of our compounds is not anymore sp3, but sp2 and this further alters the conformational properties of a seven-membered ring. Therefore we observe exchange between *pseudo chair* and *pseudo boat* conformers, which was proved by DFT calculations. The ^{1}H, ^{13}C and ^{31}P NMR spectra of ligands **1, 5, 7** and **11** showed signals for four conformers, while for *N*-BOC derivatives **2, 3, 8** and **9** two conformers were detected at room temperature. The assignment of conformers in VT NMR spectra of studied compounds is a challenging task that requires combination of dynamic NMR study and DFT calculation. In order to assign the signals of conformers in NMR spectra we performed DFT and NMR shift calculations for all 4 conformers of the ligands and their BOC precursors. The study of exchange processes between the conformers was performed experimentally by ^{31}P EXSY spectra of **1, 5, 7** and **11,** ^{31}H EXSY spectra of **2, 3, 8** and **9** and by DFT calculations of the amide or carbamate C−N rotation. The ratio of isomers was

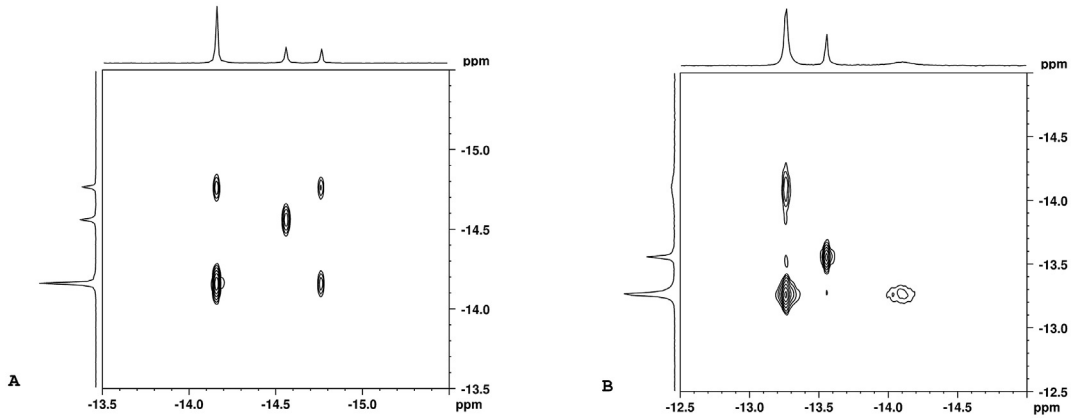


Fig. 3. A: ^{31}P EXSY NMR spectrum of compound **7** in $CDCl_3$ at 228 K using mixing time of 1.5 s (*pseudo chair* to *pseudo boat* exchange), **B:** ^{31}P EXSY NMR spectrum of compound **7** in $CDCl_3$ at 263 K using mixing time of 3.0 s (*anti* to *syn* exchange).

Table 3
Experimental and Theoretical thermodynamic parameters of studied amide and carbamate C–N rotation.

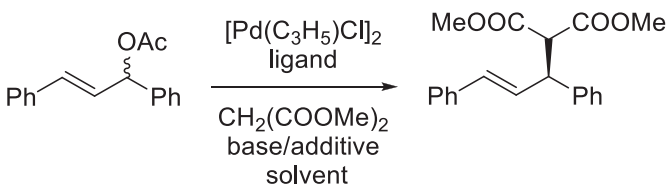
Comp.	Process	$\Delta H^{\neq}$ (298 K)[a] kcal mol^{-1}	$\Delta S^{\neq}$ (298 K)[a] cal K^{-1} mol^{-1}	$\Delta G^{\neq}$ (298 K)[a] kcal mol^{-1}	$\Delta G^{\neq}$ (298 K)[b] kcal mol^{-1}
1	*pseudo chair* (*anti* to *syn*)	11.5 ± 2.2	−20.8 ± 8.3	17.68 ± 0.07	17.1
1	*pseudo chair* (*syn* to *anti*)	14.7 ± 2.3	−9.6 ± 8.8	17.59 ± 0.07	19.7
5	*pseudo chair* (*anti* to *syn*)	18.9 ± 1.7	−5.2 ± 6.5	17.35 ± 0.07	16.9
5	*pseudo chair* (*syn* to *anti*)	16.6 ± 1.8	−4.2 ± 6.5	17.82 ± 0.07	17.8
7	*pseudo chair* (*anti* to *syn*)	18.0 ± 4.1	3.0 ± 14.5	17.12 ± 0.12	18.2
7	*pseudo chair* (*syn* to *anti*)	20.6 ± 2.5	11.4 ± 9.4	17.23 ± 0.07	20.2
11	*pseudo chair* (*anti* to *syn*)	n.m.	n.m.	n.m.	18.1
11	*pseudo chair* (*syn* to *anti*)	n.m.	n.m.	n.m.	19.3
2	*pseudo chair* (*anti* to *syn*)	15.4 ± 0.6	−2.4 ± 1.8	16.12 ± 0.07	17.2
2	*pseudo chair* (*syn* to *anti*)	15.2 ± 0.6	−4.2 ± 1.8	16.44 ± 0.07	17.1
3	*pseudo chair* (*anti* to *syn*)	15.8 ± 0.6	−1.1 ± 1.5	16.13 ± 0.07	15.9
3	*pseudo chair* (*syn* to *anti*)	15.3 ± 0.6	−4.1 ± 1.8	16.54 ± 0.07	16.3
8	*pseudo chair* (*anti* to *syn*)	15.8 ± 0.6	−1.0 ± 1.9	16.12 ± 0.07	16.4
8	*pseudo chair* (*syn* to *anti*)	15.3 ± 0.6	−4.1 ± 1.7	16.49 ± 0.07	16.6
9	*pseudo chair* (*anti* to *syn*)	15.9 ± 0.6	−0.7 ± 2.5	16.11 ± 0.07	15.9
9	*pseudo chair* (*syn* to *anti*)	15.4 ± 0.6	−3.6 ± 1.8	16.53 ± 0.07	17.0

[a] NMR experiment (n.m.: not measured).
[b] PCM//B3LYP/6-31+G(d,p).

Table 4
Experimental thermodynamic parameters of studied conformational exchange process in azepine ring.

Comp.	Process	$\Delta H^{\neq}$ (298 K)[a] kcal mol^{-1}	$\Delta S^{\neq}$ (298 K)[a] cal K^{-1} mol^{-1}	$\Delta G^{\neq}$ (298 K)[a] kcal mol^{-1}
1	*pseudo chair* to *pseudo boat*	11.5 ± 0.8	−8.5 ± 3.4	14.01 ± 0.07
1	*pseudo boat* to *pseudo chair*	12.6 ± 0.8	−6.5 ± 3.4	14.48 ± 0.07
5	*pseudo chair* to *pseudo boat*	11.9 ± 0.8	−6.3 ± 3.4	13.82 ± 0.08
5	*pseudo boat* to *pseudo chair*	13.3 ± 0.8	−3.2 ± 2.8	14.27 ± 0.07
7	*pseudo chair* to *pseudo boat*	12.1 ± 0.8	−5.7 ± 3.6	13.76 ± 0.07
7	*pseudo boat* to *pseudo chair*	13.6 ± 0.8	−1.6 ± 3.0	14.11 ± 0.07
11	*pseudo chair* to *pseudo boat*	12.5 ± 0.9	−4.1 ± 2.9	13.72 ± 0.08
11	*pseudo boat* to *pseudo chair*	14.6 ± 0.8	−2.0 ± 4.2	14.07 ± 0.07

[a] NMR experiment.



Scheme 3. Pd-catalyzed asymmetric allylic alkylation of (*E*)-1,3-diphenyl-2-propen-1-yl acetate.

determined by integration of peaks in ^{31}P VT or ^{1}H VT NMR spectra (Table 1). DFT calculations envisaged in good agreement the populations of the conformers and thus the individual conformers are identified in ^{31}P VT and ^{1}H VT NMR spectra.

The assignment of the signals in ^{1}H and ^{13}C NMR spectra to particular conformer was based on NMR shift calculations. The experimental and calculated ^{13}C chemical shifts for methylene carbons C-10 and C-12 of *pseudo chair* conformers, which are most sensitive to amide rotation, are presented in Table 2. The experimental ^{13}C NMR chemical shifts of compounds **1**, **5**, **7** and **11** were measured at 228 K, while the reported values of **2**, **3**, **8** and **9** were

Table 5
Palladium-catalyzed AAA of racemic (*E*)-1,3-diphenyl-2-propen-1-yl acetate with dimethyl malonate.[a]

Entry	L*	Solvent	Base/Additives	Yield (%)[b]	ee(%)[c]
1	**1**	CH_2Cl_2	Cs_2CO_3	99	37, *R*
2	**7**	CH_2Cl_2	Cs_2CO_3	99	37, *R*
3	**5**	CH_2Cl_2	BSA/CsOAc	99	32, *R*
4	**5**[d]	CH_2Cl_2	BSA/CsOAc	99	37, *R*
5	**11**	CH_2Cl_2	BSA/CsOAc	99	29, *R*
6	**11**	THF	BSA/CsOAc	99	27, *R*
7	**11**	THF	BSA/LiOAc	17	40, *R*
8	**11**	CH_2Cl_2	BSA/LiOAc	64	25, *R*
9	**11**	CH_2Cl_2	BSA/NaOAc	99	29, *R*
10	**11**	CH_2Cl_2	BSA/KOAc	99	26, *R*
11	**11**	CH_2Cl_2	Cs_2CO_3	99	20, *R*

[a] Reaction conditions: **A** 1 equiv. substrate, 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 0.06 equiv. ligand, 3 equiv. N,O-bis(trimethylsilyl)acetamide (BSA), 3 equiv. dimethylmalonate, catalytic amount of additive salts, 24 h. **B** 1 equiv. substrate, 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 0.06 equiv. ligand, 2 equiv. Cs_2CO_3 2 equiv. dimethylmalonate, 24 h.
[b] Isolated pure products after column chromatography.
[c] Enantiomeric excess determined by HPLC analysis (Chiralpak IC chiral column). The absolute configuration was determined by comparison of the specific rotation to the literature value [53].
[d] The reaction was carried out by using 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 0.12 equiv. ligand.

at room temperature. The carbons C-12 from *anti* conformers were shifted to lower field (53.40–53.88 ppm) due to deshielding effect of the magnetically anisotropic amide carbonyl group compared to that of C-10 (43.26–43.66). The same has to be expected for C-10 and C-12 carbons from *syn* conformers. It was noted that predicted difference in chemical shifts between C-10 and C-12 carbons in *anti* conformers is higher than in *syn* conformers, especially in compounds **1**, **5**, **7** and **11**. A good agreement between calculated and observed ^{13}C chemical shifts was found.

Further refinements of the assignment were based on the observed exchange peaks in the ^{31}P EXSY spectra of **1**, **5**, **7** and **11**. The ^{31}P EXSY spectrum of ligand **7** at 228 K and mixing time of 1.5 s (Fig. 3A) showed exchange between *pseudo chair* to *pseudo boat* (pair of *anti* conformers), while the exchange between *pseudo chair* to *pseudo boat* (pair of *syn* conformers) is difficult to see due to very low population of *pseudo boat* conformer. At 263 K using mixing time of 2.5 s the ^{31}P EXSY spectrum of ligand **7** (Fig. 3B) showed *anti* to *syn* exchange. Similar ^{31}P EXSY spectra were measured for ligands **1**, **5** and **11**. In case of ligand **11** it was impossible to measure several ^{31}P EXSY spectra optimized for *anti* to *syn* exchange and estimate the exchange barrier due to very small difference in ^{31}P chemical shifts of conformers at temperatures close to 263 K.

The experimental and theoretical thermodynamic parameters of the studied exchange processes in ligands **1**, **5**, **7** and **11** are presented in Tables 3 and 4. There is a good agreement between the experimental and DFT calculated values. The barriers of amide exchange have typical values [34], while the barriers of carbamate C–N rotation (compounds **2**, **3**, **8** and **9**) are in some extent lower than amide barriers, but the barriers of about 16 kcal/mol are also typical values [37].

The experimental thermodynamic parameters of the studied exchange process of azepine ring in ligands **1**, **5**, **7** and **11** are in the range between 13.7 and 14.0 kcal/mol. These barriers are higher than the calculated barrier for interconversion in cycloheptane (8.5 kcal/mol using CCSD/6–311++G** [50] and 7.9 kcal/mol using MM4 [51]). These barriers are also higher than estimated barrier of *chair*/*boat* exchange in *N*-Benzoyl-5-substituted-1-benzazepines (9.7 kcal/mol) [52]. However in our case the azepine ring is somewhat different in structure (2,3,4,7-tetrahydro-1*H*-azepine versus 2,3,4,5-tetrahydro-1*H*-azepine). DFT calculations of the studied exchange process of azepine ring in ligands **1**, **5**, **7** and **11** were not performed because of the need of huge computational resources for these relatively big molecules. On the other hand on the basis of collected experimental and theoretical data the structure elucidation of studied compounds was performed and conformational processes that interconvert the individual conformers were revealed at the possible reasonable computational cost. Better agreement between the experimental and DFT calculated parameters might be achieved by increasing the basis sets and/or using other DFT functional, but this is out of the scope of the current study.

In conclusion the combination of experimental VT ^{31}P and ^{1}H EXSY spectra, theoretical DFT calculation of possible conformers, DFT NMR shifts calculations and DFT calculations of C–N bond rotation in amides and carbamates enabled us to clarify the conformational processes in the studied compounds.

3.3. Pd-catalyzed asymmetric allylic alkylation

The chiral phosphine-amide ligands were evaluated in the Pd-catalyzed AAA of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a palladium source (Scheme 3). Several parameters were investigated: the system used to generate the dimethyl malonate anion, the salt additive, the solvent effect and the ratio of the ligand to the palladium precursor (Table 5). Two procedures were explored for generation of the dimethyl malonate anion: either in situ by Trost's procedure using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of alkali metal acetates, or by using 2 equivalents of anhydrous caesium carbonate as a base. The solvent effect was examined by replacement of CH_2Cl_2 with THF. Additionally the effect of the base additive was also evaluated. The reactions proceeded with excellent conversion but with moderate enantioselectivity. In all cases the substitution products have predominantly (*R*)-configurations. Probably the conformational flexibility of the galantamine derived ligands leads to more than one active catalytic species and as a result to low asymmetric inductions [18].

4. Conclusion

(−)-Galantamine has been used as a scaffold for the synthesis of four novel diphenylphosphino-benzenecarboxamides. They were obtained from norgalantamine and norlycoramine readily available from galantamine. The combination of experimental VT ^{31}P and ^{1}H EXSY spectra, theoretical DFT calculation of possible conformers, DFT NMR shifts calculations and DFT calculations of C–N bond rotation in amides and carbamates has been used to clarify the conformational processes in the studied compounds. The ligands exist as four conformers due to restricted rotation around the amide bond and due to flexibility of the 2,3,4,5-tetrahydro-1*H*-azepine ring. The application of the chiral phosphine-amides as ligands in Pd-catalyzed AAA proceeded with excellent conversion and moderate enantioselectivity as a result of the conformational flexibility of the galantamine derived ligands.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Irena Philipova: Conceptualization, Investigation, Writing - review & editing. **Georgi Stavrakov:** Conceptualization,

Investigation, Writing - review & editing. **Vladimir Dimitrov:** Conceptualization, Writing - review & editing. **Nikolay Vassilev:** Conceptualization, Investigation, Writing - review & editing.

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Appendix A. Supplementary data

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