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One-pot synthesis of an indole-substituted 7,8-dicarba-*nido*-dodecahydroundecaborate(−1)†

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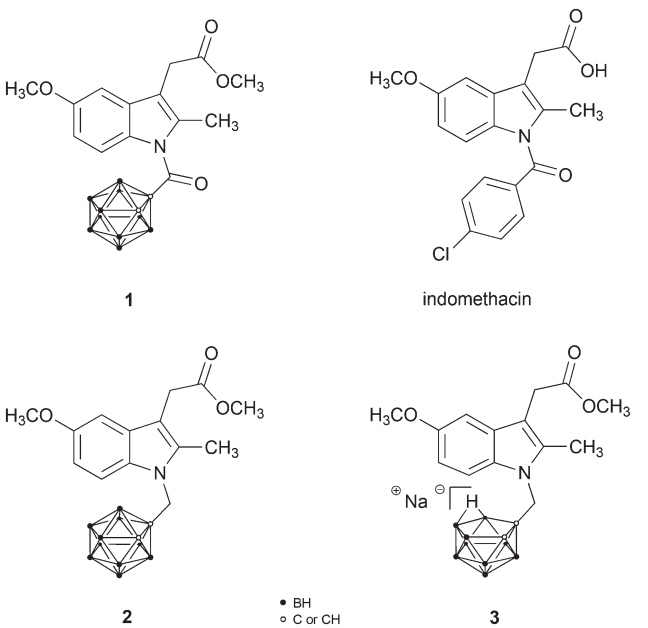
Carbaboranes are increasingly used as pharmacophores to replace phenyl substituents in established drug molecules. In contrast to traditional organic chemistry, elaborate procedures to introduce functionality frequently fail in the case of carbaboranes and their chemistry is often hampered by degradation of the cluster. Herein, the development of a one-pot synthesis of a water-soluble *N-nido*-dicarbaborato indole is presented, including a proposed mechanism for the reaction sequence. These studies provide useful synthetic tools for the conjugation of two important pharmacophores, indoles and carbaboranes.

Introduction

Indole is one of the most abundant heterocycles in nature (*e.g.*, in tryptophan, serotonin, melatonin) and is of great relevance as a pharmacophore in medical applications, which is reflected by the product scope of more than thirty indole-based pharmaceuticals with various applications including anti-cancer, anti-depressive, anti-hypertensive, anti-inflammatory and anti-HIV agents.[1] Besides their proposed applications as boron-delivery agents in boron neutron capture therapy,[2] carbaboranes have also received pronounced attention as pharmacophores in the last decade.[3] 1,2-, 1,7- and 1,12-dicarba-*closo*-dodecaboranes(12) (*i.e.*, *ortho*-, *meta*- and *para*-carboranes) are icosahedral boron clusters composed of ten BH and two CH vertices. These cluster compounds offer several advantages compared to other pharmacophores, including non-toxicity, remarkably high lipophilicity, and high metabolic stability, and their predominantly hydridic periphery facilitates unprecedented interactions with biomolecules (*e.g.*, enzymes and receptors).[3,4] Due to delocalisation of the cluster electrons and a volume similar to that of a rotating phenyl ring, carbaboranes are also considered as three-dimensional aromatic systems and are increasingly used as phenyl mimetics. We could recently demonstrate their unique pharmacophoric properties when introduced into established inhibitors of cyclooxygenase (COX), such as aspirin and indomethacin.[5] The replacement of the 4-chlorophenyl ring in indomethacin (an established anti-inflammatory drug to relieve pain, stiffness and swelling) by an *ortho*-carbaborane generates a highly potent and selective COX-2 inhibitor **1** (Scheme 1).[5c]

The amide bond in indomethacin and its analogues, however, is rather labile and can be easily hydrolysed, especially under basic conditions. Upon the introduction of an *ortho*-carbaborane, analogue **1** becomes even more prone to cleavage due to the high electron deficiency of the adjacent cluster. Thus, the replacement of the amide bond by a methylene group should generate a more stable analogue **2** (Scheme 1). The pronounced lipophilicity of carbaboranes is of advantage for biochemical interactions (*e.g.*, penetration of cell membranes), but insolubility in water may hamper the



Scheme 1

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† Electronic supplementary information (ESI) available: Experimental details of all reactions including synthetic procedures for starting materials. See DOI: 10.1039/c4dt03218g

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bioavailability of the compound. Directed deboronation (decapping) of the carbaborane cluster to yield the respective anionic *nido*-dicarbaborate analogue **3** (Scheme 1) thus would contribute to a better water solubility.

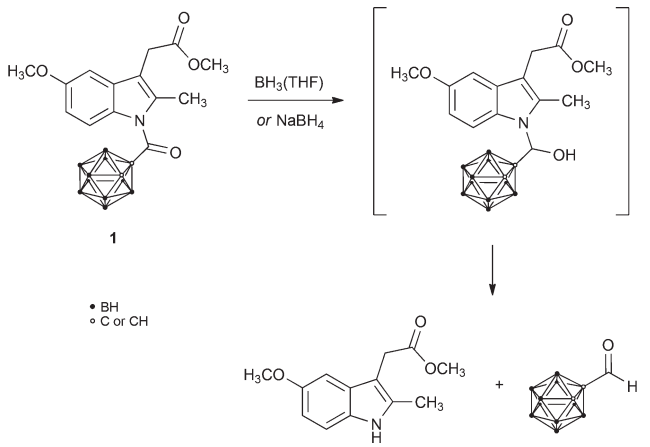
The preparation of indoles is well studied, and various synthetic procedures have been reported, although some involve numerous steps or apply rather harsh reaction conditions. However, when carbaboranes are present, the reaction conditions must be chosen carefully, as the cluster tends to undergo deboronation, especially in the presence of bases and nucleophiles, such as amines.[4b,6] Thus, mild or acidic conditions are preferred for the introduction of carbaboranes. In general, C-substituted carbaboranes can be prepared by a reaction of decaborane with substituted acetylenes.[4b,7] This method, however, is limited to the preparation of *ortho*-carbaboranes, preventing the application of a developed synthetic method for the other carbaborane isomers. Furthermore, reactive groups have to be protected during this reaction and bulky substituents at the carbon atoms of the acetylene derivative lead to only low yields.

A variety of aminoalkyl carbaboranes has been synthesised.[4b,8] However, to the best of our knowledge, carbaboranes bearing indolyl substituents at the carbon vertices of the cluster have not yet been reported, except from our own investigations.[5c,d] This might be due to complications associated with the synthesis of such compounds, as discussed below. But as both indoles and carbaboranes are important pharmacophores, the development of suitable synthetic routes is of increasing interest.

Results and discussion

Reduction of *N*-acylindole

A first synthetic approach towards **2** aimed at the reduction of the amide bond in **1** by using borane as a reducing agent (Scheme 2), which has been successfully applied to the reduction of other acylindoles.[9] However, only the respective semi-aminal was formed (monitored by TLC), which decomposed to the corresponding indole and carbaboranyl aldehyde upon isolation (characterised by NMR). The high electron deficiency of the carbaborane cluster may decrease the nucleophilicity of the carbonyl oxygen atom and thereby impede the attack of borane.[9b] Application of sodium borohydride also resulted in cleavage of the C–N bond.[8a] Due to the low basicity of the indole nitrogen atom [pK_a(indole-N*H*): 20.95 in DMSO],[10] acylindoles are generally prone to C–N cleavage, and this effect is enhanced by the electron-withdrawing carbaboranyl substituent.



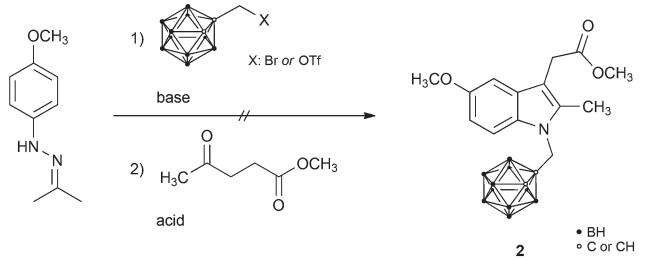
Scheme 2 Attempted reduction of **1**, which resulted in the C–N bond cleavage.

Fischer indole synthesis

Fischer indole synthesis is one of the most studied procedures for generating indole systems from arylhydrazones and aldehydes or ketones in the presence of acid catalysts.[11] For the introduction of the carbaboranyl substituent, acetone phenylhydrazone was treated with bromomethyl carbaborane, followed by a reaction with levulinic acid methyl ester for indole formation (Scheme 3).[12] However, the substitution reaction was not successful. Although halomethyl carbaboranes in general show low reactivity in nucleophilic substitutions,[13] this is unusual, since dialkylamines were reported to readily replace the halogen, as they reduce the electron deficiency of the cluster by coordination at boron.[14] Furthermore, even the application of the usually more reactive triflate analogue did not result in a substitution.[15]

Nenitzescu indole synthesis

Therefore, in another approach the nitrogen atom was directly introduced at the carbaborane cluster as an aminomethyl group before synthetic steps towards the formation of the heterocycle by Nenitzescu indole synthesis were attempted. Aminoalkyl carbaboranes are highly reactive and versatile building blocks.[4b,8] Reaction of the carbaboranyl amine with methyl acetoacetate resulted in a tautomeric mixture of the enamine and the respective imine despite employing different acids [Brønstedt (*para*-TsOH)[12b,16] and Lewis acids (CF_3COOCa)[17]] as catalysts (Scheme 4). However, the following reaction with *para*-benzoquinone[12b,16] did not give the desired heterocycle. Although the Nenitzescu reaction is an important regioselective route to substituted indoles, its efficiency is highly dependent on substituent effects. The cyclisation proceeds *via* a Michael addition and nucleophilic attack by the



Scheme 3 Attempted Fischer indole synthesis towards compound **2**.

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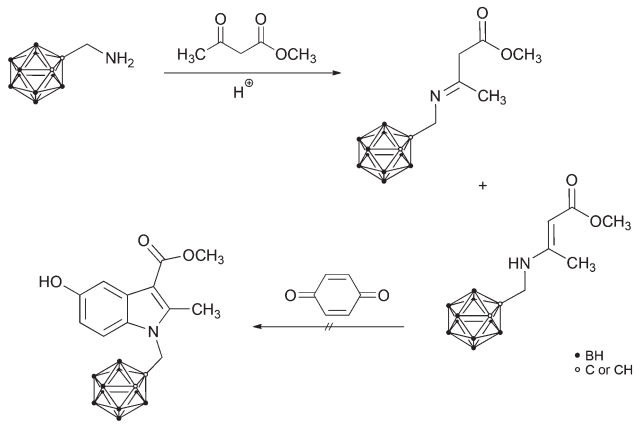


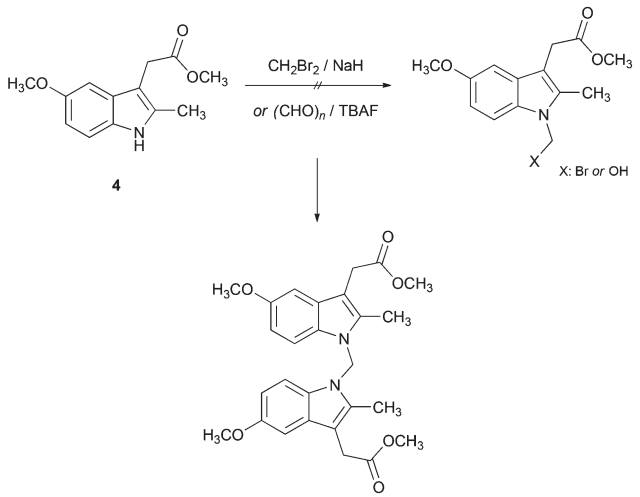
Scheme 4 Attempted Nenitzescu indole synthesis towards an analogue of compound **2**.

enamine at the quinone.[18] The highly electron-withdrawing carbaborane cluster probably reduces the electron density, especially at the nitrogen atom, and together with the bulkiness of the cluster may thus restrict the reactivity of the enamine.

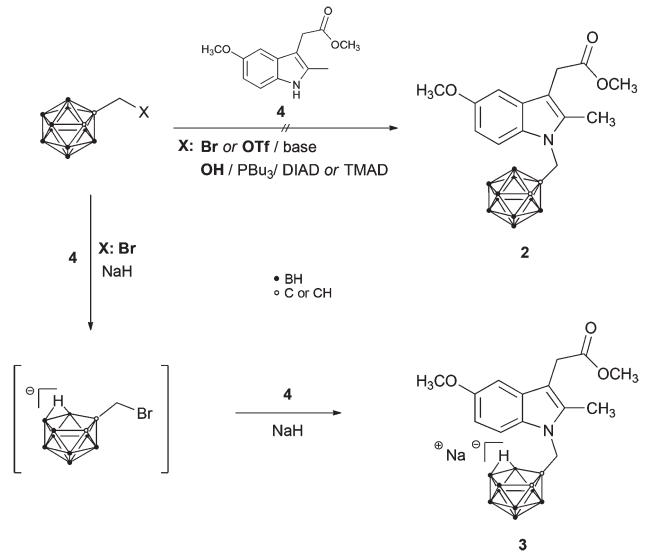
Nucleophilic substitution

Further approaches were carried out with the indole derivative **4** as the starting material for nucleophilic substitution reactions. First, the introduction of a methylene group with a terminal leaving group [Br, OH (to be further functionalised)] at the indole nitrogen atom was attempted (Scheme 5). Reaction of this indole derivative with a C-lithiated carbaborane could then readily generate the desired compound **2** in a salt elimination, often used for the substitution of carbaboranes.[4b] However, the reaction of **4** with dibromomethane or paraformaldehyde in the presence of a strong base almost exclusively afforded the methylene-bridged dimer of **4**,[19] even when the reaction was carried out under high-dilution conditions and in the presence of a large excess of the reactants [CH_2Br_2, $(CHO)_n$].

A general method for the synthesis of *N*-benzyl derivatives of indomethacin is benzylation of unsubstituted indoles with benzyl halides in the presence of a strong base.[12b] Therefore, 1-bromomethyl- or 1-trifluoromethanesulfonylmethyl-*ortho*-carbaborane was treated with indole **4** under various reaction conditions (Scheme 6).[15a] Furthermore, Mitsunobu conditions, which have also been reported for the alkylation of indoles,[20] were tested with the respective carbaboranyl methanol.[21] However, while none of these reactions gave the desired indomethacin analogue **2**, most of them resulted in prompt deboronation of the carbaborane cluster (monitored by TLC). Substitution reactions at the indole nitrogen atom usually require strong bases due to the very low acidity of the NH group.[10] The deprotonated indole in turn is a strong, nucleophilic base, which tends to attack the carbaborane cluster resulting in decapping. However, when **4** was used in excess in the reaction with bromomethyl-*ortho*-carbaborane, the respective *nido*-carbaborane derivative **3** was obtained (Scheme 6). This suggests a reaction mechanism in which the bromomethyl-*ortho*-carbaborane is first decapped by a deprotonated indole molecule, followed by a nucleophilic substitution with a second indolate anion yielding **3**. The increased electron density of the negatively charged *nido*-cluster enhances the reactivity compared to the charge-neutral halomethyl carbaborane and thereby enables a substitution reaction at the carbaborane cluster. Thus, this protocol presents a direct route towards indole-substituted *nido*-dicarbaborates. In contrast to compound **1**, indole derivative **3** is water-soluble and the bond linking both pharmacophores is stable under various conditions.



Scheme 5 Attempted introduction of a bromo- or hydroxymethyl group at indole derivative **4**, which resulted in the formation of a methylene-bridged dimer (TBAF: tetrabutylammonium fluoride trihydrate).



Scheme 6 Nucleophilic substitution at indole **4** with functionalised carbaboranes under basic or Mitsunobu conditions (DIAD: diisopropyl azodicarboxylate; TMAD: tetramethyl azodicarboxamide) and the proposed mechanism of sequential decapping and nucleophilic substitution leading to the formation of derivative **3**.

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Conclusions

Different attempts to synthesise *N*-dicarbaboranyl indoles were described including discussions of probable interferences, which seem to result mainly from the high electron deficiency of the carbaborane cluster. A one-pot synthesis of *N-nido*-dicarbaborato indoles was presented and a possible reaction mechanism was proposed. This synthesis avoids the additional synthetic step of decapping the carbaborane cluster, which often involves rather harsh conditions (*e.g.*, alkoxides), and thus minimises interferences with other substituents at the indole systems. The procedure is generally applicable for *N*-substitution of indoles bearing moieties which are stable in the presence of strong bases. As indoles and carbaboranes are important pharmacophores, the development of further synthetic methods for linking them is of increasing interest. The presented synthetic procedure provides ready access to water-soluble and chiral *nido*-dicarbaborato indoles.

Experimental

General

Reactions were carried out under a nitrogen atmosphere using anhydrous solvents which were purified using an MBRAUN Solvent Purification System MB SPS-800. Chemicals were used as purchased. The synthesis of the starting materials is described in the ESI.† Thin-layer chromatography (TLC) was performed on pre-coated glass plates (0.25 mm, silica gel 60 F_{254}); visualisation of carbaborane compounds on TLC plates was achieved by treatment with a solution of $PdCl_2$ (1% in MeOH) and gentle heating. Column chromatography was carried out with silica gel (0.035–0.070 mm, 60 Å). ^{1}H, ^{11}B and ^{13}C NMR spectra were recorded on a Bruker AVANCE DRX 400 (400 MHz) with tetramethylsilane as an internal standard and referencing to the unified scale. FTIR spectra were recorded on a Perkin-Elmer System 2000 FTIR spectrometer, scanning between 400 and 4000 cm^{-1}. Mass spectra (HR-MS) were recorded on an ESI-FT-ICR Bruker-Daltonics spectrometer (APEX II, 7 T). Melting points were measured in sealed tubes.

Reduction of *N*-acylindole

General procedure. **1** was dissolved in THF before the addition of a reducing agent (BH_3(THF),[9b] $NaBH_4$, BH_3(THF)/$BF_3(OEt_2)$ or BH_3(THF)/$NaBH_4$) and the reaction mixture was stirred (at room temperature, heating at reflux or in a microwave reactor). The progress of the reactions was monitored by TLC. The reaction was quenched upon formation of the semi-aminal by addition of methanol, and the product was isolated by extraction. ^{1}H NMR spectra of the crude product showed a mixture of **4** and the carbaboranyl aldehyde (1-H(O)C-1,2-$C_2B_{10}H_{11}$).[22]

Fischer indole synthesis

General procedure. 1-Bromomethyl-1,2-dicarba-*closo*-dodecaborane(12) or 1-trifluoromethanesulfonylmethyl-1,2-dicarba-*closo*-dodecaborane(12) was added to a solution of acetone (4-methoxyphenyl)hydrazone and a base, and the reaction mixture was stirred for several hours. For the formation of the heterocycle, trifluoroacetic acid (TFA) and levulinic acid methyl ester were added and the mixture was heated at reflux.[12c,d] The progress of the reaction was monitored by TLC.

Substitution with 1-bromomethyl-1,2-dicarba-*closo*-dodecaborane(12). The reaction conditions tested (base/solvent/reaction temperature): NEt_3/CH_2Cl_2/room temperature; NaH/THF/reflux; NaH/CH_3CN/reflux.

Substitution with 1-trifluoromethanesulfonylmethyl-1,2-dicarba-*closo*-dodecaborane(12). The reaction conditions tested (base/solvent/reaction temperature): NaOAc/CH_3CN/reflux;[15b] NEt_3/CH_2Cl_2/room temperature; NaH/THF/reflux.

Nenitzescu indole synthesis

Synthesis of carbaboranyl enamine. 1-Aminomethyl-1,2-dicarba-*closo*-dodecaborane(12) hydrochloride was deprotonated with NEt_3 in THF, filtered and the solvent was removed.[23] The free amine (1 eq.) was then refluxed with methyl acetoacetate (1 eq.) and a catalytic amount of *p*-TsOH in toluene,[12b,16] yielding a mixture of enamine and imine. ^{11}B {^{1}H} (128 MHz, $CDCl_3$): δ = −13.1 (4B), −11.7 (2B), −8.9 (2B), −5.1 (1B), 2.2 (1B); ESI-MS (positive mode, CH_3OH): *m*/*z*: 272.3 $[M + Na]^+$; the observed isotopic pattern was in agreement with the calculated one.

General procedure for indole synthesis. A solution of carbaboranyl enamine (in CH_2Cl_2, CH_3CN or CH_3NO_2) was added dropwise to a solution of *para*-benzoquinone and the reaction mixture was stirred (at room temperature or reflux).[12b,16] The reaction was monitored by TLC.

Nucleophilic substitution

General procedure for substitution at 4 with CH_2Br_2. **4** was dissolved in DMF and deprotonated with NaH at 0 °C. The deprotonated indole was then added dropwise to a solution of CH_2Br_2 (excess) and the reaction was stirred for several hours at room temperature. The solvent was removed and purification was carried out by column chromatography.

General procedure for substitution at 4 with $(CHO)_n$.[19,24] **4** and paraformaldehyde (excess) were dissolved in DMSO. TBAF (tetrabutylammonium fluoride) and some drops of water were added and the reaction was stirred for 2 h at room temperature. The product was extracted with EtOAc and purification was carried out by column chromatography.

General procedure for substitution at 4 with 1-TfO-CH_2-$C_2B_{10}H_{11}$ or 1-Br-CH_2-$C_2B_{10}H_{11}$. **4** was dissolved and deprotonated with a base; then 1-trifluoromethanesulfonylmethyl-1,2-dicarba-*closo*-dodecaborane(12) or 1-bromomethyl-1,2-dicarba-*closo*-dodecaborane(12) was added and the reaction mixture was either stirred at room temperature or refluxed for several hours. A variety of bases and solvents was tested: K_2CO_3: THF;[15a] Cs_2CO_3: DMF, CH_3CN; NaOAc: CH_3CN;[12c,d] Na{N($SiMe_3$)$_2$}: toluene, CH_3CN, THF; NaH: THF, DMF, CH_3CN, 1,4-dioxane; *n*-BuLi: THF.

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General procedure for a Mitsunobu reaction at 4 with 1-HO–CH_2–$C_2B_{10}H_{11}$.[20b] The reactions were carried out using either PBu_3/DIAD (diisopropyl azodicarboxylate) in THF or PBu_3/TMAD (tetramethyl azodicarboxamide) in toluene. 1-Hydroxymethyl-1,2-dicarba-*closo*-dodecaborane(12) (2 eq.) was added to a solution of **4** (1 eq.) and PBu_3 (2 eq.). At 0 °C, DIAD or TMAD (2 eq.) was added and the reaction mixture was stirred at 40 °C overnight. The reactions were monitored by TLC.

Sodium 7-{[5-methoxy-2-methyl-3-(methoxycarbonyl-methyl)-1*H*-indolyl] methyl}-7,8-dicarba-*nido*-dodecahydro-undecaborate(−1) (3). NaH (60% suspension in mineral oil; 0.09 g, 2.2 mmol, 2.6 eq.) was added to a solution of **4** (0.49 g, 2.1 mmol, 2.5 eq.) in CH_3CN (25 mL) at 0 °C. After stirring for 20 min at 0 °C the suspension was added dropwise to a solution of 1-bromomethyl-1,2-dicarba-*closo*-dodecaborane(12) (0.20 g, 0.8 mmol, 1.0 eq.) in CH_3CN (15 mL) at 0 °C. After stirring at room temperature overnight the reaction was quenched by addition of water (10 mL). The product was extracted with EtOAc and purified by column chromatography (*n*-hexane–EtOAc 6 : 1 → 1 : 10) yielding an orange oil from which colourless crystals crystallised over several weeks at room temperature. The crystals were washed with CH_2Cl_2, dissolved in CH_3OH and filtered to remove any methyl borates and the product was precipitated with CH_2Cl_2 to yield **3** as a pale beige solid with moderate water solubility (0.11 g, 34%): mp: 190 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = −3.2 to −2.6 (br, 1H, *endo*-H), 0.3–2.5 (br, 9H, B_9H_9), 1.61 (br s, 1H, $C_{cluster}H$), 2.36 (s, 3H, CH_3), 3.64 (s, 3H, $COOCH_3$), 3.69 (s, 2H, OOC-CH_2), 3.81 (s, 3H, OCH_3), 4.06 (d, $^2J_{H,H}$ = 16 Hz, 1H, N-CH_2), 4.36 (d, $^2J_{H,H}$ = 16 Hz, 1H, N-CH_2), 6.72 (dd, $^3J_{H,H}$ = 8 Hz, $^4J_{H,H}$ = 2 Hz, 1H, CH_{ind}), 6.92 (d, $^4J_{H,H}$ = 2 Hz, 1H, CH_{ind}), 7.22 (d, $^3J_{H,H}$ = 8 Hz, 1H, CH_{ind}) ppm; ^{11}B (128 MHz, CD_3OD): δ = −36.7 (d, $^1J_{B,H}$ = 141 Hz, 1B), −33.3 (dd, $^1J_{B,H}$ = 129 Hz, 38 Hz, 1B), −22.8 (d, $^1J_{B,H}$ = 145 Hz, 1B), −19.2 (d, $^1J_{B,H}$ = 137 Hz, 1B), −18.7 (d, $^1J_{B,H}$ = 159 Hz, 1B), −17.6 (d, $^1J_{B,H}$ = 138 Hz, 1B), −15.0 (d, $^1J_{B,H}$ = 148 Hz, 1B), −11.1 (d, $^1J_{B,H}$ = 133 Hz, 1B), −10.5 (d, $^1J_{B,H}$ = 126 Hz, 1B) ppm; ^{13}C{^{1}H} (100 MHz, CD_3OD): δ = 11.0 (CH_3), 31.3 (CH_2), 48.7 ($C_{cluster}H$), 48.9 ($C_{cluster}$), 51.8 (N-CH_2), 52.3 ((CO)OCH_3), 56.4 (OCH_3), 101.2 (CH_{ind}), 104.1 (C_{ind}), 110.9 (CH_{ind}), 111.6 (CH_{ind}), 129.1 (C_{ind}), 133.5 (C_{ind}), 136.7 (C_{ind}), 155.1 (C_{ind}), 174.9 (CO) ppm; IR (KBr): $\tilde{\nu}$ = 3450 (s), 2963 (m), 2532 (s), 1718 (s), 1620 (m), 1583 (m), 1485 (s), 1460 (m), 1439 (m), 1342 (m), 1262 (m), 1221 (s), 1179 (m), 1156 (m), 1095 (m), 1030 (s), 893 (w), 845 (w), 798 (m), 705 (w), 574 (w), 491 (w), 436 (w) cm^{-1}; HR-ESI-MS (negative mode, DMSO–CH_3OH) *m*/*z* [M−Na]$^-$: calcd for $C_{16}H_{27}B_9NO_3$: 379.2862, found: 379.2870; the observed isotopic pattern was in agreement with the calculated one.

Acknowledgements

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