

# Synthesis and reactions of silicon containing cyclic $\alpha$ -amino acid derivatives

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## Abstract

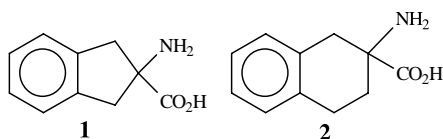
A simple synthesis of a new amino acid derivative 5,6-bis(trimethylsilyl)indanyl glycine via cobalt mediated [2 + 2 + 2] cycloaddition strategy is described. Co-trimerization of diyne building block containing amino acid moiety with bis(trimethylsilyl)acetylene in presence of  $\text{CpCo}(\text{CO})_2$  catalyst afforded the silylated indane-based  $\alpha$ -amino acid (AAA) derivative. Electrophilic aromatic substitution reaction, *ipso* to the trimethylsilyl group gave highly functionalised indane-based AAA derivatives.

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**Keywords:** Unusual amino acids; [2 + 2 + 2] cycloaddition; Silicon amino acids; Cyclopentadienyl cobalt dicarbonyl; *Ips*o substitution

## 1. Introduction

There has been a growing interest in the synthesis of unusual  $\alpha$ -amino acid (AAA) derivatives because of their utility as conformational directors in the design of highly structured peptides. Also, incorporation of various AAAs is now realised as a useful exercise in the synthesis of various proteins and this strategy enables better understanding of the dynamics of protein structure [1]. More specifically, cyclic  $\alpha,\alpha$ -disubstituted amino acids such as **1** and **2** have been used as critical residues to modulate the stability and activity of



various peptides as they were known to constrain the backbone of peptide through the formation of  $\alpha$ -helices and  $\beta$ -turns [2]. To address this problem in a comprehensive manner, our group has been engaged in developing new methodologies for the synthesis of

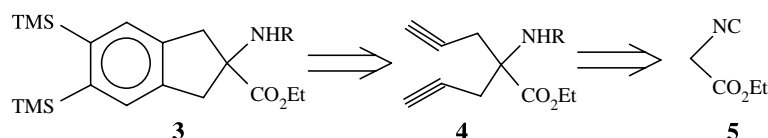
constrained AAAs. In this respect, our approach to unusual AAAs by “Building Block Strategy” has provided access to a variety of cyclic AAAs endowing with diverse functional groups [3].

As part of our ongoing program, we were interested in the synthesis of cyclic AAAs containing trialkylsilyl groups present in the side chains. Potential applications of silylated AAAs derivatives such as **3** (Fig. 1) are several folds. For example, amino acid derivatives containing TMS group in the aromatic system can undergo facile *ipso* substitution reaction and thus provide an easy access to various substituted derivatives in the aromatic ring [4]. Trialkylsilyl groups are also useful for attaining non-polar, hydrophobic properties desirable for the enhanced biological activity [5]. Thus, peptides containing such residues in place of natural amino acids might exhibit pronounced pharmacological properties and proteolytic stability of the modified peptide as indicated in the search for stable renin inhibitor [5b].

Despite the utility of TMS-based functional group transformations [6] very few silylated AAAs have appeared in the literature [7]. To our knowledge, there are no reports dealing with the synthesis of cyclic aromatic AAAs containing trimethylsilyl group of type **3**. Herein, we wish to report the full details for the synthesis of **3** along its electrophilic aromatic substitution reactions by *ipso* attack. It is well known that *ipso* substitution

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Fig. 1. Retrosynthetic analysis of compound **3**.

reaction allows a greater regio control with silylated aromatic substrates.

## 2. Strategy

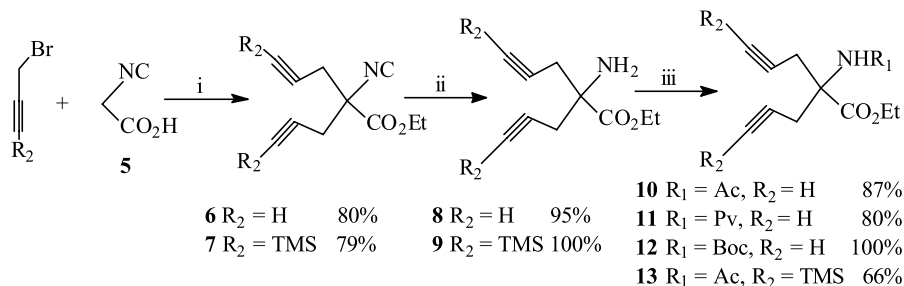
Our synthetic approach to bis(trimethylsilyl)indanyl glycines **3** is illustrated in Fig. 1. Although introduction of trimethylsilyl groups in the aromatic system can be achieved in different ways by adaptation of these methodologies to cyclic AAAs containing trimethylsilyl groups is generally a difficult task because most of the reaction conditions used for cyclic AAAs are not compatible with the silicon functionality. For example, trimethylsilyl groups are sensitive to acidic as well as basic conditions and neutral medium is considered to be appropriate in this regard. Therefore, we conceived a catalytic [2 + 2 + 2] cycloaddition strategy where the trialkylsilyl groups would be incorporated at the end of the synthetic sequence. Using various transition metal or organometallic catalysts [2 + 2 + 2] cyclotrimerization reaction can be achieved and this methodology has been proven to be a general and useful process. However, the yields of this process depend on the catalyst used for this purpose [8].

## 3. Results and discussion

The present strategy requires the synthesis of dialkyne building blocks **10–13** containing suitably protected amino acid moiety. In our previous study we have adopted a simple method using solid–liquid phase-transfer catalyst for the dialkylation of ethyl isocynoacetate **5**, an amenable AAA equivalent [9]. In this regard, the reaction of propargyl bromide or 3-bromo-1-

trimethylsilyl-1-propyne [10] with compound **5** in presence of  $K_2CO_3$  and tetrabutylammonium hydrogen sulphate (TBAHS) in acetonitrile gave the corresponding dialkynyl products **6** [11a] and **7** in good yields (Scheme 1). Since isocyanide group was found to be labile under the reaction conditions, it was necessary to convert **6** and **7** into more stable form. Therefore, isocyanide esters **6** and **7** were hydrolysed to amino esters **8** and **9**, respectively and were subjected to an appropriate protection sequence to afford the desired building blocks **10–13**.

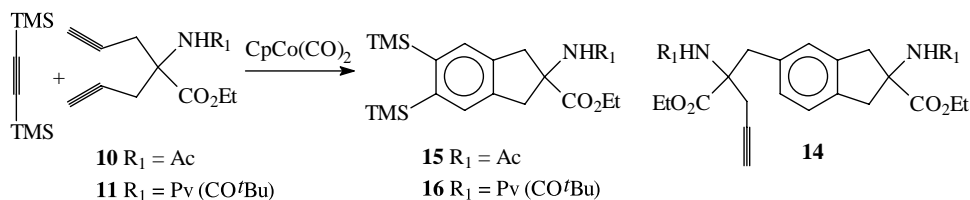
Having prepared the required building blocks, we next examined the cyclotrimerization reaction with silylated alkynes under different catalyst conditions. Wilkinson's catalyst is known to effect [2 + 2 + 2] cycloaddition reaction with a variety of monoalkynes and dialkynes [11]. However, substrates **10–13** failed to react with bis(trimethylsilyl)acetylene (BTMSA) under Wilkinson's catalyst condition to give co-trimerized products, instead, self-trimerization of dialkyne without involvement of monoalkyne (e.g., BTMSA) occurred in some cases, yielding the compounds of type **14** as the sole product. In a controlled experiment where the reaction was performed in absence of monoalkyne, self-trimerization of dialkyne was observed. Use of large excess of monoalkyne or catalyst however did not deliver the desired products. Unfavourable steric interaction of bulky monoalkyne with ligands on the rhodium atom during cyclization process may be the probable reason. Other electronic or conformational problems also may be detrimental for accomplishment of the reaction. In view of literature reports, we envisaged that the catalyst such as  $CpCo(CO)_2$  might facilitate the third alkyne participation to give co-trimerization products.  $CpCo(CO)_2$  catalyst has been used by several groups, particularly by Vollhardt [12], in the synthesis of several

Scheme 1. (i)  $K_2CO_3$ , TBAHS,  $CH_3CN$ , 80 °C, (ii) HCl, EtOH, RT and (iii)  $Ac_2O$  or  $(Boc)_2O$  or pivaloyl chloride,  $CH_2Cl_2$ .

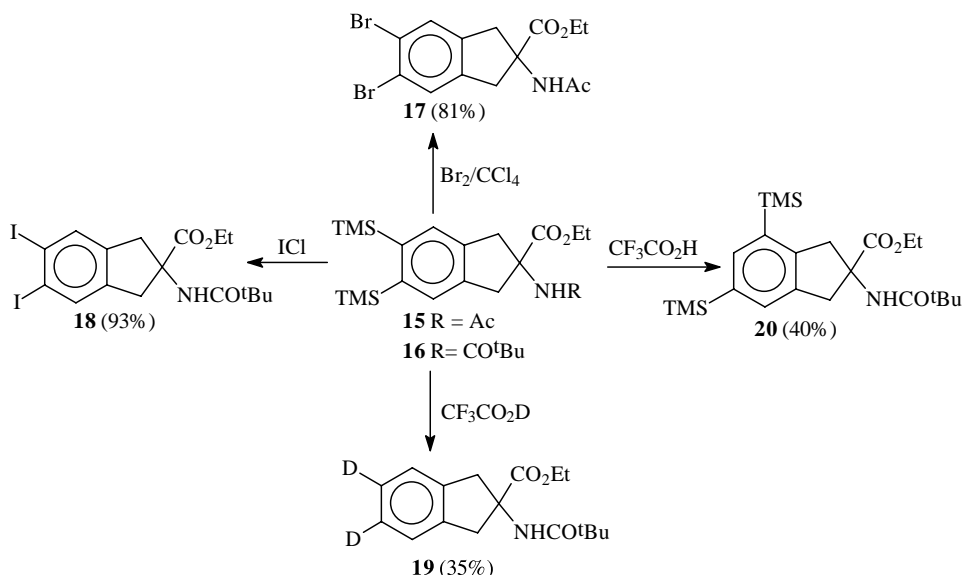
natural products and iterative synthesis of highly strained molecules. Thus, initial treatment of acetyl derivative **10** with BTMSA in presence of  $\text{CpCo}(\text{CO})_2$ , the desired product **15** was obtained in 12% yield (Scheme 2). It turns out that the order and nature of reagents added are critical for the outcome of this catalytic reaction. Vollhardt group reported that slow addition of a solution containing dialkyne and catalyst in BTMSA to a refluxing solution of catalyst in BTMSA is essential for the success of the reaction. However, in our case under the same condition no improved yields were obtained. Due to poor solubility of compound **10** in BTMSA, we prepared other derivatives such as pivaloyl (Pv) and Boc derivatives, and found that these derivatives had improved solubility in BTMSA. Indeed, use of pivaloyl derivative **11** gave improved yield (26%) of the product **16**. Although Boc protected compound **12** was fairly soluble in BTMSA, it was found to decompose under the reaction conditions. The excess BTMSA was recovered by distillation from the reaction mixture and can be recycled without any complications.

To investigate the reactivity of silylated AAA derivatives **15** and **16** in electrophilic substitution reactions, they were treated with bromine and iodine monochloride to

realise the formation of desired products **17** and **18**, respectively, in excellent yields (Scheme 3). Products could easily be identified as disappearance of distinct trimethylsilyl groups in NMR spectrum. By treatment of **16** with deuterium chloride in  $\text{CCl}_4$ , 35% deuterium exchanged product **19** was observed as determined by  $^1\text{H}$  NMR and mass spectral analysis. While reaction with trifluoroacetic acid, compound **16** rearranged to 4,6-bis(trimethylsilyl)indanylglycine derivative **20** in 40% yield. Compounds **19** and **20** were contaminated with the starting material and chromatographic methods were not suitable for separation. The yield of the reactions was determined by NMR spectral data. It may be worth noting that the halogen derivatives **17** and **18** can serve as useful substrates for metal mediated cross-coupling reactions [13] such as Suzuki or Stille coupling reactions to generate other substitutions at the amino acid or at peptide level. While the second building block, **13** bearing two bulky trimethylsilyl groups failed to undergo cyclotrimerization reaction under similar reaction conditions suggesting high steric constraints of this catalytic reaction. Attempted trimerization reactions of **13** with various alkynes in presence of Wilkinson's catalyst or  $\text{CpCo}(\text{CO})_2$  failed. Only starting material was recovered. Noticeably,



Scheme 2.



Scheme 3.

formation of self-trimerized product was not observed. This result suggests that the dialkyne **13** was found to be inert towards  $[2 + 2 + 2]$  cycloaddition reaction under the present reaction conditions.

#### 4. Conclusions

In summary, we have demonstrated a simple strategy for the synthesis of 5,6-bis(trimethylsilyl)indanyl glycine derivative via cobalt mediated  $[2 + 2 + 2]$  cycloaddition reaction. Though the yield of the key cycloaddition reaction with BTMSA is low, the simple and high yielding building blocks syntheses and electrophilic reactions of **15** and **16** should be an attractive feature in the generation of various indane-based AAA derivatives. In addition, facile introduction of various electrophiles *ipso* to the silyl groups in indane derived cyclic AAA is promising strategy for the creation of other functionalized unusual AAA and peptides, which are otherwise difficult to prepare.

#### 5. Experimental

##### 5.1. General

Melting points are uncorrected. Infrared spectra (FT-IR) were recorded as KBr pellets unless otherwise mentioned. UV spectra were taken in chloroform solvent. Acetonitrile and carbon tetrachloride were distilled over phosphorous pentoxide. Dry THF and diethyl ether were obtained by distillation over sodium-benzophenone ketyl. For all the reactions, anhydrous magnesium sulphate was used as drying agent after work up. Razel A-99 syringe pump was used in all the high dilution technique reactions. Ethyl isocyanoacetate, Wilkinson's catalyst, iodine monochloride, deuterium chloride were purchased from Aldrich Chemical Co (Milwaukee, WI, USA). CpCo(CO)<sub>2</sub> catalyst was purchased from Strem Chemicals Co (Newburyport, MA, USA). (Boc)<sub>2</sub>O, Bis(trimethylsilyl)acetylene (BTMSA) were obtained from Lancaster Synthesis (UK). 3-Bromo-1-trimethylsilyl-1-propyne was prepared according to the literature procedure [10].

##### 5.2. Building block synthesis

###### 5.2.1. Ethyl 2-isocyano-2-(1'-trimethylsilyl-1'-propyne)-5-trimethylsilyl-4-pentynoate (**7**)

A heterogeneous mixture of ethyl isocyanoacetate **5** (113 mg, 1 mmol), 3-trimethylsilyl-1-bromo-2-propyne (420 mg, 2.2 mmol), finely grounded potassium carbonate (829 mg, 6 mmol) and TBAHS (33.9 mg, 0.1 mmol) in dry acetonitrile (20 ml) was heated at 70 °C for 6 h. Then the solid material was filtered off and the filtrate was evaporated under reduced pressure. The

brown residue obtained was taken in ether (50 ml) and washed with water, brine and then dried. Evaporation of the solvent and purification of the crude product on a silica gel column using ethyl acetate–hexane (1:19) gave isonitrile derivative **7** (262 mg, 79%) as a light brown liquid which was hydrolysed immediately as described in the following experiment. IR (neat):  $\nu_{\max} = 2135, 1753 \text{ cm}^{-1}$ . 300 MHz; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.16$  (s, 18H), 1.52 (t, 3H,  $J = 7.1$  Hz), 2.91 (s, 4H), 4.30 (q, 2H,  $J = 7.1$  Hz) ppm. 75.43 MHz; <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 0.15, 14.1, 29.7, 63.2, 65.1, 90.4, 97.9, 161.1, 166.3$  ppm. Mass:  $m/e = 333$  (M<sup>+</sup>).

###### 5.2.2. Hydrolysis of compound **7**

To a solution of isonitrile derivative **7** (220 mg, 0.66 mmol) in absolute ethanol (5 ml) was added concentrated hydrochloric acid (five drops) at 0 °C and the mixture was stirred at RT for 4 h. Then, the solvent was evaporated under reduced pressure and the residue obtained was dissolved in water. The aqueous layer was basified with ammonia solution (pH = 10) and then extracted with ethyl acetate. The combined organic extract was washed with water, brine and dried. Evaporation of the solvent gave amino ester as a light brown liquid **9** (213 mg, 100%), which was used directly in subsequent reaction without further purification.

###### 5.2.3. Ethyl 2-acetamido-2-(1'-trimethylsilyl-1'-propyne)-5-trimethylsilyl-4-pentynoate (**13**)

A solution of the amino ester **9** (213 mg, 0.66 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added acetic anhydride (134.5 mg, 1.31 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) at RT and stirred for 3 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and washed with water, brine and dried. Evaporation of the solvent and purification of the crude product on a silica gel column using ethyl acetate–hexane (1:11) gave acetyl derivative **13** (160 mg, 66%) as a white solid. M.p.: 90–92 °C. IR (KBr):  $\nu_{\max} = 3366, 2181, 1726, 1679 \text{ cm}^{-1}$ . 300 MHz; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta = 0.12$  (s, 18H), 1.32 (t, 3H,  $J = 7.1$  Hz), 2.04 (s, 3H), 2.76 (1/2 ABq, 2H,  $J = 16.8$  Hz), 3.30 (1/2 ABq, 2H,  $J = 16.8$  Hz), 4.27 (q, 2H,  $J = 7.1$  Hz), 6.48 (s, 1H) ppm. 75.43 MHz; <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta = 0.04, 14.2, 23.7, 26.5, 62.3$  (2C?), 88.1, 101.1, 169.7, 170.9 ppm. Mass:  $m/e = 365$  (M<sup>+</sup>). Anal. Calc. for C<sub>18</sub>H<sub>31</sub>Si<sub>2</sub>NO<sub>3</sub>: C: 59.13; H: 8.55; N: 3.83%. Found: C: 59.37, H: 8.73, N: 3.56%.

##### 5.3. $[2 + 2 + 2]$ cycloaddition reactions

###### 5.3.1. Ethyl 2-acetamido-5,6-bis(trimethylsilyl)indane-2-carboxylate (**15**)

In a two-necked round bottom flask (5 ml) attached with reflux condenser was charged with diyne building block **10** (29 mg, 0.13 mmol), CpCo(CO)<sub>2</sub> (0.2 μl) and BTMSA (0.2 ml). The flask was heated up to 140 °C under nitrogen. A solution of CpCo(CO)<sub>2</sub> (0.3 μl) in BTMSA

(0.2 ml) was added (syringe pump) over a period of 4 h. Then, the reaction mixture was stirred at 140 °C for an additional 1 h. The flask was cooled and connected to a vacuum line and distilled off the excess BTMSA, which can be recycled. The dark oily residue left was chromatographed on a silica gel column using ethyl acetate–hexane (1:1) as an eluent to give **15** as a white crystalline solid (6 mg, 12%). M.p.: 124–126 °C. IR (KBr):  $\nu_{\max}$  = 3360, 1728, 1665  $\text{cm}^{-1}$ . UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 235 nm,  $\epsilon$  = 3312  $\text{M}^{-1} \text{cm}^{-1}$ . 300 MHz;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 0.35 (s, 18H), 1.25 (t, 3H,  $J$  = 7.1 Hz), 1.94 (s, 3H) 3.21 (1/2 ABq, 2H,  $J$  = 16.6 Hz), 3.66 (1/2 ABq, 2H,  $J$  = 16.6 Hz), 4.22 (q, 2H,  $J$  = 7.1 Hz), 5.93 (s, 1H), 7.53 (s, 2H) ppm. 75.43 MHz;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 2.1, 14.2, 23.2, 43.9, 61.7, 65.6, 131.6, 139.6, 144.8, 170.1, 172.9 ppm. FAB-Mass:  $m/e$  = 391 ( $\text{M}^+$ ), 414 ( $\text{M} + \text{Na}$ ). Anal. Calc. for  $\text{C}_{20}\text{H}_{33}\text{Si}_2\text{NO}_3$ : C: 61.33, H: 8.50, N: 3.57%. Found: C: 61.25, H: 7.68, N: 3.34%.

### 5.3.2. Ethyl 2-trimethylacetamido-5,6-bis(trimethylsilyl)indane-2-carboxylate (**16**)

A solution of **11** (58 mg, 0.22 mmol) in BTMSA (0.8 ml) containing  $\text{CpCo}(\text{CO})_2$  (3  $\mu\text{l}$ ) was added (syringe pump) to a refluxing BTMSA (0.3 ml) containing  $\text{CpCo}(\text{CO})_2$  (2  $\mu\text{l}$ ) under  $\text{N}_2$  over a period of 8 h. Then, the reaction mixture was stirred at 140 °C for an additional 1 h. The reaction mixture was cooled and excess solvent was distilled out under vacuum to give reusable BTMSA. The remaining dark residue was purified by column chromatography using ethyl acetate–hexane (1:4) mixture as an eluent to obtain compound **16** as a white crystalline solid (25 mg, 26%). M.p.: 160–162 °C. IR (KBr):  $\nu_{\max}$  = 3350, 1738, 1655  $\text{cm}^{-1}$ . UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 234 nm,  $\epsilon$  = 2854  $\text{M}^{-1} \text{cm}^{-1}$ . 300 MHz;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 0.35 (s, 18H), 1.17 (s, 9H), 1.23 (t, 3H,  $J$  = 7.1 Hz), 3.21 (1/2 ABq, 2H,  $J$  = 17.0 Hz), 3.69 (1/2 ABq, 2H,  $J$  = 17.0 Hz), 4.19 (q, 2H,  $J$  = 7.1 Hz), 6.16 (s, 1H), 7.51 (s, 2H) ppm. 75.43 MHz;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 2.1, 14.1, 27.4, 38.5, 44.3, 61.6, 64.8, 131.5, 139.6, 144.5, 173.4, 178.4 ppm. Mass:  $m/e$  = 433 ( $\text{M}^+$ ). Anal. Calc. for  $\text{C}_{23}\text{H}_{39}\text{Si}_2\text{NO}_3$ : C: 63.71, H: 9.07, N: 3.23%. Found: C: 63.55, H: 9.08, N: 3.34%.

### 5.3.3. Compound 14: dimerization of diyne **10** under Wilkinson's catalyst conditions

A solution of diyne building block **10** (50 mg, 0.22 mmol) and Wilkinson's catalyst (4 mg, 2 mmol%) in absolute ethanol (4 ml) was heated at 70 °C for 2 h. The solvent was evaporated and the purification of the crude product by a silica gel column using ethyl acetate–hexane (1:1) mixture as an eluent furnished self-trimerized product **14** ( $\text{R}_1 = \text{Ac}$ ) as a thick liquid (40 mg, 80%) which solidified on standing at RT. M.p.: 168–170 °C. IR (KBr):  $\nu_{\max}$  = 3372, 3290, 3265, 1743, 1656  $\text{cm}^{-1}$ . 300 MHz;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.24 (t, 3H,  $J$  = 7.1 Hz), 1.33 (t, 3H,  $J$  = 7.1 Hz), 1.95 (s, 3H), 1.99 (t, 1H,

$J$  = 2.5 Hz), 2.01 (s, 3H), 2.82 (d 1/2 ABq, 1H,  $J$  = 16.7, 2.5 Hz), 3.05 (d 1/2 ABq, 1H,  $J$  = 13.3, 3.4 Hz), 3.14–3.23 (m, 2H), 3.47 (dd, 2H,  $J$  = 16.7, 2.5 Hz), 3.56–3.68 (m, 2H), 4.17–4.30 (m, 4H), 5.97 (s, 1H), 6.27 (s, 1H), 6.87 (s, 1H), 6.89 (1/2 ABq, 1H,  $J$  = 7.7 Hz), 7.07 (1/2 ABq, 1H,  $J$  = 7.7 Hz) ppm. FAB-MS:  $m/e$  = 443 ( $\text{M} + \text{H}$ ), 465 ( $\text{M} + \text{Na}$ ).

## 5.4. Electrophilic substitution reactions

### 5.4.1. Ethyl 2-acetamido-5,6-dibromoindane-2-carboxylate (**17**)

To a solution of **15** (10 mg, 0.02 mmol) and pyridine (2 mg, 0.02 mmol) in  $\text{CCl}_4$  (5 ml) was added bromine (8.18 mg, 0.05 mmol) in  $\text{CCl}_4$  (2 ml) at 0 °C and stirred for 2 h at RT. Reaction mixture was diluted with  $\text{CHCl}_3$  (10 ml) and washed with aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , water, brine and then dried. Evaporation of the solvent and purification of the crude product by a silica gel column using ethyl acetate–hexane (1:4) as an eluent gave dibromide **17** as a white crystalline solid (8.5 mg, 82%). M.p.: 196–197 °C. IR (KBr):  $\nu_{\max}$  = 3350, 1725, 1669  $\text{cm}^{-1}$ . UV ( $\text{CHCl}_3$ ):  $\lambda_{\max}$  = 290 nm,  $\epsilon$  = 3740  $\text{M}^{-1} \text{cm}^{-1}$ ;  $\lambda_{\max}$  = 242 nm,  $\epsilon$  = 4270  $\text{M}^{-1} \text{cm}^{-1}$ . 300 MHz;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 1.24 (t, 3H,  $J$  = 7.1 Hz), 1.97 (s, 3H), 3.25 (1/2 ABq, 2H,  $J$  = 16.6 Hz), 3.52 (1/2 ABq, 2H,  $J$  = 16.6 Hz), 4.21 (q, 2H,  $J$  = 7.1 Hz), 6.08 (s, 1H), 7.45 (s, 2H) ppm. 75.43 MHz;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  = 14.1, 23.2, 42.7, 62.0, 65.9, 122.6, 129.5, 141.4, 170.2, 172.5 ppm. Anal. Calc. for  $\text{C}_{14}\text{H}_{15}\text{NO}_3\text{Br}_2$ : C: 41.69, H: 3.75, N: 3.47%. Found: C: 41.38, H: 4.88, N: 3.38%.

### 5.4.2. Ethyl 2-trimethylacetamido-5,6-diiodoindane-2-carboxylate (**18**)

To a solution of bis-trimethylsilyl derivative **16** (22 mg, 0.05 mmol) in  $\text{CCl}_4$  (3 ml), iodine monochloride (16.5 mg, 0.1 mmol) in  $\text{CCl}_4$  (1 ml) was added at 0 °C. The violet coloured reaction mixture was stirred for 10 h at RT. Reaction mixture was then diluted with the  $\text{CHCl}_3$  and washed with aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , water, brine and dried. The solvent was evaporated and the crude product was crystallised from ethyl acetate–hexane mixture to furnish diiodo compound **18** as white needles (25 mg, 91%). The spectral data of the compound is identical with the compound synthesised by a different route [11c].

### 5.4.3. Ethyl 2-trimethylacetamido-5,6-dideuteroindane-2-carboxylate (**19**)

To ortho silyl derivative **16** (9 mg, 0.02 mmol) in  $\text{CCl}_4$  (2 ml) was added deuterium chloride (4 mg, 0.1 mmol) at 0 °C and the reaction mixture was stirred at RT for 2 h. The mixture was diluted with  $\text{CCl}_4$  and washed with water and then dried. Evaporation of the solvent gave white solid (8 mg) whose  $^1\text{H}$  NMR spectrum indicated

35% product formation. 300 MHz;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (for product **19** only):  $\delta = 1.22$  (s, 9H), 1.26 (t, 3H,  $J = 7.3$  Hz), 3.23 (1/2 ABq, 2H,  $J = 16.8$  Hz), 3.72 (1/2 ABq, 2H,  $J = 16.8$  Hz), 4.27 (q, 2H,  $J = 7.3$  Hz), 6.16 (s, 1H), 7.51 (s, 2H) ppm. Mass:  $m/e = 291$  ( $\text{M}^+$ ).

#### 5.4.4. Ethyl 2-trimethylacetamido-4,6-bis(trimethylsilyl)indane-2-carboxylate (**20**)

To ortho silyl derivative **16** (9 mg, 0.02 mmol) in a mixture of dry  $\text{CCl}_4$  and MeOH (4 ml, 1:1) and was added trifluoroacetic acid (2.5 ml) at 0 °C. The mixture was stirred at RT for 24 h and then it was diluted with  $\text{CCl}_4$  and washed with water and dried. Evaporation of the solvent and purification of the product by a silica gel column chromatography using ethyl acetate–hexane mixture (1:3) as an eluent gave white solid whose  $^1\text{H}$  NMR spectrum indicated 40% of product (**19**) formation. 300 MHz;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (for product **20** only):  $\delta = 0.25$  (s, 9H), 0.35 (s, 9H), 1.16 (s, 9H), 1.26 (t, 3H,  $J = 6.9$  Hz), 3.21 (1/2 ABq, 2H,  $J = 16.8$  Hz), 3.69 (1/2 ABq, 2H,  $J = 16.8$  Hz), 4.27 (q, 2H,  $J = 6.9$  Hz), 6.15 (s, 1H), 7.19 (1/2 ABq, 1H,  $J = 7.6$  Hz), 7.35 (1/2 ABq, 1H,  $J = 7.6$  Hz) ppm.

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