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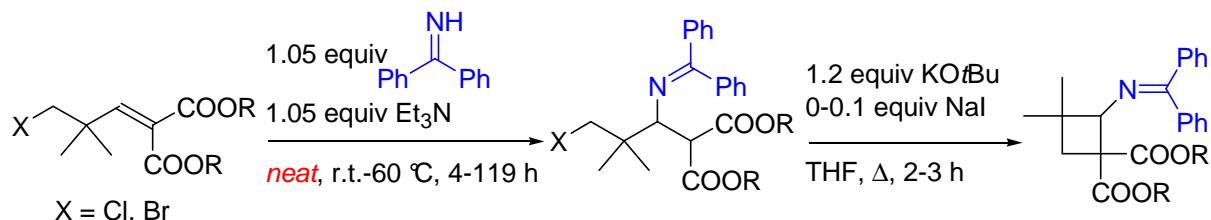
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Synthesis of novel β -aminocyclobutanecarboxylic acid derivatives by a solvent-free aza-Michael addition and subsequent ring closure

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Novel β -aminocyclobutanecarboxylic acid derivatives were prepared via a sequential solvent-free aza-Michael addition of benzophenone imine across 3-halopropylidenemalonates and base-induced ring closure. These highly substituted cyclobutanedicarboxylic acid derivatives were subjected to a reactivity study which demonstrated the tendency of these donor-acceptor substituted four-membered rings to be converted into their corresponding ring-opened products.

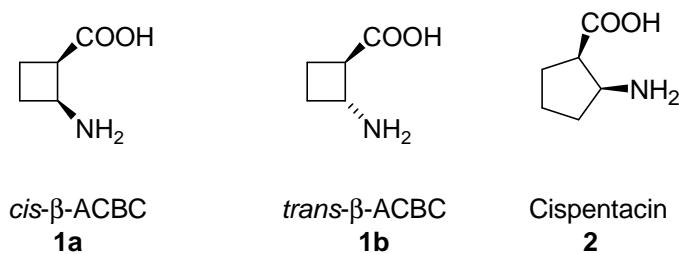
Introduction

The interest in cyclic β -amino acids has increased significantly in the past decades,^{1,2,3,4,5} which is due to the ability of β -amino acids to improve the metabolic stability of β -peptides in which they are incorporated.^{6,7} Moreover, β -peptides represent an important class of

foldamers,^{8,9} as they can adopt various secondary structures including helices, sheets and turns.^{7,10,11,12} More specifically, β -peptides that contain or consist of β -aminocyclobutanecarboxylic acid (β -ACBC **1**) monomers show secondary structures both in solution and in the solid state. The first cyclobutane-containing dipeptide, which was synthesised by the group of Ortuño starting from *cis*- β -ACBC **1a**, shows a hairpin-like conformation in the solid state, while a *cis*-cyclobutane-containing β -tetrapeptide and hexa- and octamers of *trans*- β -ACBC **1b** fold into 14- and 12-helical conformations resulting from the formation of inter- and intramolecular hydrogen bonds.^{13,14,15} Moreover, a β -peptide composed of four *cis*- β -ACBC **1a** residues has shown molecular self-assembly to form nanosized fibrils and gels,¹⁶ and *trans,trans*- and *trans,cis*-bis(cyclobutane)- β -dipeptides show a tendency to assemble into nanoscale fibres.^{17,18}

Another reason for the enhanced interest in carbocyclic β -amino acids is the biological activity of some of these constrained compounds, e.g. *cis*-2-aminocyclopentanecarboxylic acid **2** (cispentacin) which has shown antifungal activity against various *Candida* strains.^{19,20} The *in vitro* antifungal activity of β -aminocyclobutanecarboxylic acid **1** and 3- or 4-methylene-ACBC against *Candida* strains is dramatically lower.^{19,21}

Nevertheless, in recent years a lot of attention has been devoted to the synthesis of this four-membered β -amino acid **1** and its derivatives.



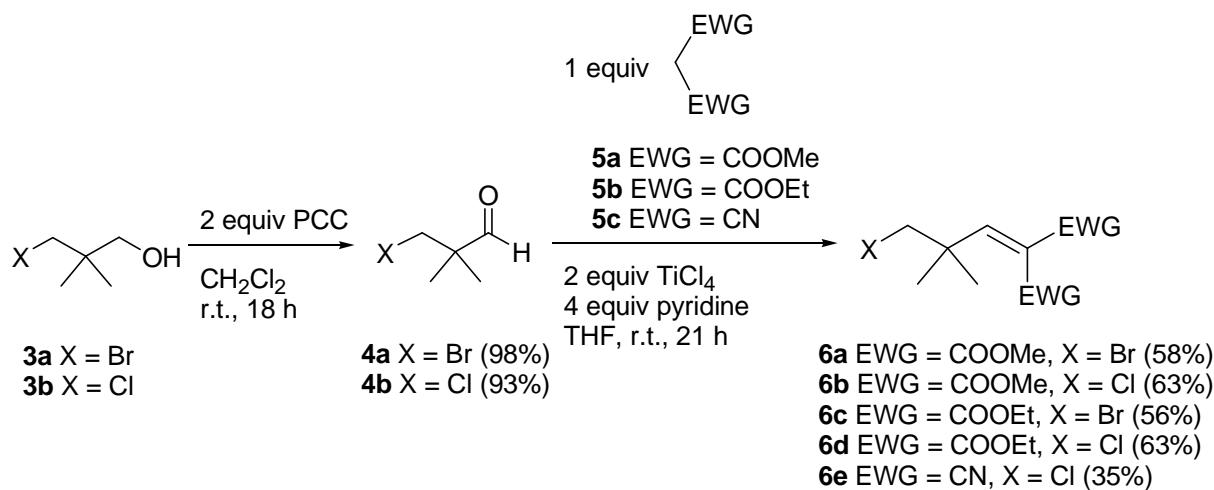
The most common way to synthesize β -ACBC derivatives used a [2+2] cycloaddition step.^{22,23,24,25,26} As such, the group of Aitken recently developed a route to synthesize the four enantiomers of β -aminocyclobutanecarboxylic acid **1**, each in enantiomerically pure form.^{27,28}

In previous research, dialkyl 2-bromoethylidenemalonates and dialkyl 3-chloropropylidenemalonates proved to be suitable substrates for the Michael Induced Ring Closure (MIRC) reaction towards a range of functionalised cyclopropanes and some cyclobutanes.^{29,30,31,32} β -Aminocyclobutanedicarboxylic acid derivatives are a poorly studied class of donor-acceptor (DA) substituted cyclobutanes which are prone to ring opening reactions.^{33,34} Therefore, in this work, the use of 3-halopropylidenemalonate derivatives as substrates for the synthesis of new β -aminocyclobutanedicarboxylic acid derivatives *via* an aza-MIRC reaction was investigated.

Results and discussion

Commercially available 3-halopropanols **3** were transformed into the corresponding aldehydes **4** using pyridinium chlorochromate (PCC) as oxidizing agent.³⁵ Subsequently, the Knoevenagel condensation of aldehydes **4** with malonates **5a-b** and malononitrile **5c** in the presence of titanium(IV) chloride and pyridine yielded 3-halopropylidenemalonates **6a-d** and -malononitrile **6e** in 35-63% yield.³⁶ (Scheme 1)

Scheme 1



Although the MIRC reaction of dimethyl (3-chloro-2,2-dimethylpropylidene)malonate **6b** with various nucleophiles (e.g. methoxide, cyanide and *tert*-butylthiolate) yielded new β -

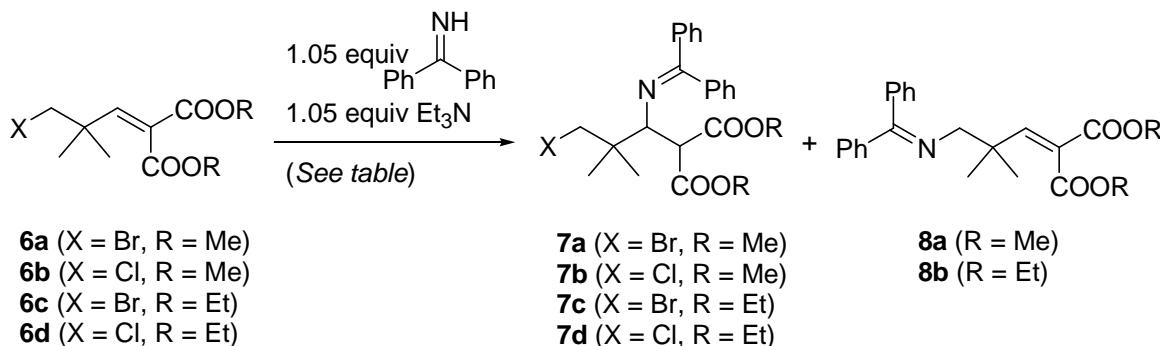
substituted cyclobutanedicarboxylates,³¹ treatment of malonate **6b** with different nitrogen nucleophiles in order to obtain novel β -ACBC derivatives was initially not successful. It appeared that primary and secondary amines could not be used as nucleophiles in this MIRC reaction. The Michael addition of benzylamine, analogous to isopropylamine,³¹ across dimethyl 2-(3-chloro-2,2-dimethylpropylidene)malonate **6b** was followed by a retro-Mannich type reaction that led to the formation of *N*-(3-chloro-2,2-dimethylpropylidene)benzylamine and dimethyl malonate **5a**. Also the attempt to use a secondary amine, *i.e.* pyrrolidine, as a nucleophile in the aza-MIRC reaction, was not successful. In this case, a substitution of the leaving group by the nucleophile was mainly observed, which was in analogy with the outcome of the reaction of dialkyl 2-bromoethylidenemalonates and secondary amines.³⁷ Subsequently, sodium azide was evaluated as nitrogen nucleophile. Sodium azide is a suitable nucleophile in the synthesis of β -aminocyclopropanecarboxylic acid (β -ACC) derivatives via the MIRC reaction starting from 2-bromoethylidenemalonates.^{30,38} However, when dimethyl 2-(3-chloro-2,2-dimethylpropylidene)malonate **6b** was treated with sodium azide under different reaction conditions in which the solvent (MeOH, DMF, DMSO, acetone, *t*BuOH), temperature (r.t.- Δ) and time were varied, no smooth conversion of the starting product to the target cyclobutane derivative or Michael adduct could be observed.

Benzophenone imine has proven to be a suitable nucleophile in the MIRC reaction starting from dialkyl 2-bromoalkylidenemalonates leading to dialkyl 2-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylates.²⁹ Therefore, the reactivity of this nitrogen nucleophile in the MIRC reaction towards dialkyl 2-(diphenylmethylideneamino)cyclobutane-1,1-dicarboxylates was investigated. To our satisfaction, when *tert*-butanol was used as solvent, instead of more nucleophilic MeOH which gave rise to side reactions, and in the presence of triethylamine as a base, the Michael addition of benzophenone imine across malonate **6b** was observed, but the intramolecular

substitution of the leaving group in δ -position which would lead to ring closure did not occur. Thus, acyclic β -amino ester **7b** was isolated in 57% yield after recrystallization from Et₂O (Table 1, Entry 1). The use of the solvent mixture *t*-BuOH/Et₂O in a ratio of 4/1 increased the yield of the Michael addition of benzophenone imine across alkylidenemalonate **6b** to 67% and shortened the reaction time (Table 1, Entry 2). The low solubility of adduct **7b** in Et₂O led to a better conversion of the starting product **6b**, disfavoring the reverse retro-Michael reaction. 3-Bromoalkylidenemalonate **6a** was treated with benzophenone imine under similar reaction conditions to obtain pure β -amino ester **7a** in 56% yield (Table 1, Entry 3). Unfortunately, the Michael addition of benzophenone imine leading to dimethyl malonates **7a** and **7b** proved to be poorly reproducible under these conditions. Furthermore, the addition of benzophenone imine across diethyl alkylidenemalonates **6c-d** appeared to be even more problematic, which is probably due to the steric hindrance caused by the presence of the two geminal ethyl esters on the double bond. When diethyl 2-(3-chloro-2,2-dimethylpropylidene)malonate **6d** was treated with 3 equiv of benzophenone imine, only 66% conversion of the starting product to the corresponding β -amino ester **7d** could be observed after six days of reaction (Table 1, Entry 4). In addition, the presence of an excess of benzophenone imine in the crude reaction mixture made isolation of the Michael adduct **7d** very difficult to virtually impossible.

Therefore, other conditions for the Michael addition of benzophenone imine across 3-halo alkylidenemalonates **6** had to be explored. Neither altering the solvent (*t*BuOH/THF 4/1, Et₂O, THF, CH₂Cl₂, CH₃CN) did lead to better results, nor did the use of other bases (NaH, KO*t*Bu) or addition of a Lewis acid (MgBr₂). The reaction was also conducted under microwave irradiation and in a pressure vial, but again no good conversion of substrates **6** to the corresponding acyclic β -amino esters **7** was observed.

After many attempts, it was found that the Michael addition of benzophenone imine across alkylidenemalonates **6**, using Et₃N as a base, could be achieved in the absence of a solvent (neat conditions). Treatment of alkylidenemalonates **6a,b,d** with 1.05 equiv benzophenone imine in the presence of triethylamine at 60 °C for 4-48 hours led to a full conversion to the corresponding Michael adducts **7a,b,d**, which were isolated in 67-79% yield after recrystallization from Et₂O (Table 1, Entry 5-7). The reaction of diethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate **6c** and benzophenone imine, however, gave rise to the formation of an alternative product, more specifically diethyl 2-[2,2-dimethyl-3-(diphenylmethylideneamino)propylidene]malonate **8b** (Table 1, Entry 8). The steric hindrance caused by the presence of the two geminal ethyl esters hampered the Michael addition of the nucleophile across the activated double bond, and in combination with the presence of a good leaving group (in this case bromide), a direct substitution of the leaving group by the nucleophile was more favorable. Detailed spectroscopic follow-up of the reactions showed that this substitution reaction did not occur when malonates **6a**, **6b** and **6d** were used as substrates. The reaction of malonate **6c** and benzophenone imine proceeded more selective towards the Michael adduct **7c** at room temperature but in this case, a longer reaction time was required (Table 1, Entry 9).

Table 1 Michael addition of benzophenone imine across alkylidenemalonates **6**

Entry	Substrate	Reaction conditions	Compound (Yield) ^a
1	6b	<i>t</i> BuOH, Δ , 72 h	7b (57%)
2	6b	<i>t</i> BuOH/Et ₂ O 4/1, Δ , 55 h	7b (67%)
3	6a	<i>t</i> BuOH/Et ₂ O 4/1, Δ , 24 h	7a (56%)
4	6d	<i>t</i> BuOH/Et ₂ O 4/1, Δ , 6 d ^b	7d (-) ^c
5	6a	neat, 60 °C, 4 h	7a (79%)
6	6b	neat, 60 °C, 24 h	7b (78%)
7	6d	neat, 60 °C, 48 h	7d (67%)
8	6c	neat, 60 °C, 20 h	8b (38%)
9	6c	neat, r.t., 119 h	7c (76%)

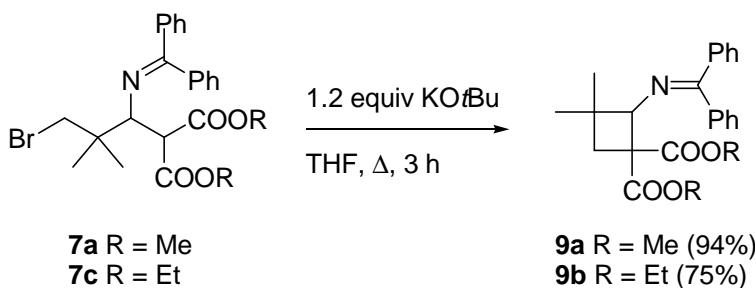
^a Isolated yield after recrystallization from Et₂O^b Reaction was carried out with 3 equiv benzophenone imine and 3 equiv Et₃N^c 66% conversion after 6 days, compound **7d** was not isolated

The use of 2-(3-chloro-2,2-dimethylpropylidene)malononitrile **6e** as substrate for the Michael addition of benzophenone imine under similar neat reaction conditions, resulted in an intractable mixture of reaction products in which the corresponding Michael adduct could not be detected.

Nevertheless, in this manner, a very simple, practical and more sustainable method for the Michael addition of benzophenone imine across alkylidenemalonates **6a-d**, without the use of hazardous and volatile solvents, was developed. In the very recent literature, other examples of solvent free aza-Michael additions across unsaturated substrates have been reported.^{39,40,41}

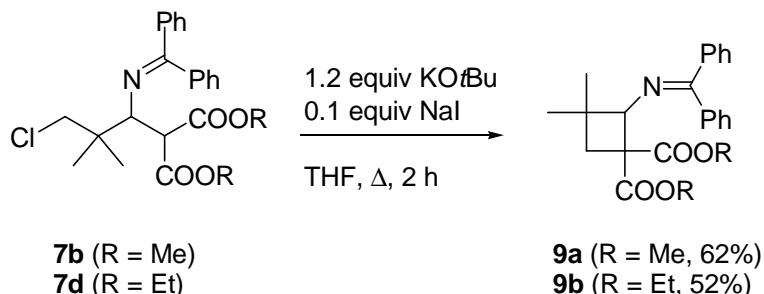
In order to synthesize the target β -aminocyclobutanecarboxylic acid derivatives **9a** and **9b**, the acyclic β -amino esters **7a-d** were treated with a base to enable ring closure. Treatment of 2-[3-bromo-2,2-dimethyl-1-(diphenylmethyleneamino)propyl]malonates **7a** and **7c** with 1.2 equiv of $\text{KO}t\text{Bu}$ in THF for three hours at reflux temperature afforded β -aminocyclobutanecarboxylic acid derivatives **9a** and **9b** in good to excellent yield (Scheme 2).

Scheme 2



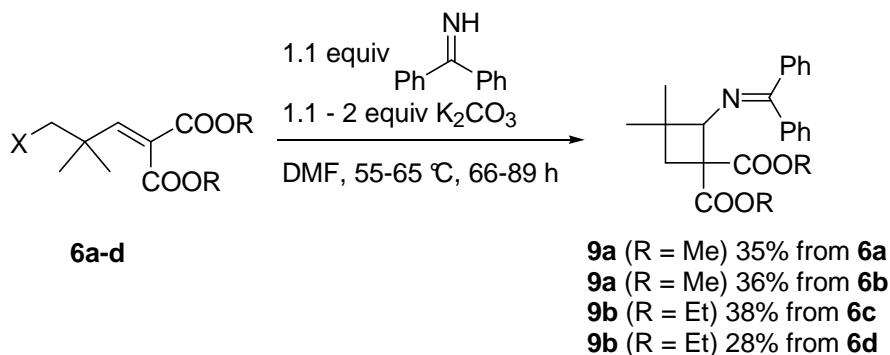
The cyclization of dimethyl 2-[3-chloro-2,2-dimethyl-1-(diphenylmethyleneamino)propyl]malonate **7b** to the corresponding cyclobutane **9a** was less straightforward. When $\text{KO}t\text{Bu}$ in *tert*-butanol under reflux or KHMDS or LiHMDS in THF at room temperature were used as basic conditions, the cyclization of malonate **7b** to cylobutane **9a** was sluggish (0-66% conversion) and suffered from competitive retro-Michael addition giving rise to alkylidenemalonate **6b** (up to 50%). The presence of chloride as leaving group and the sterically impeding geminal methyl groups prevent a smooth cyclobutanation of diester **7b**. Fortunately, the addition of a catalytical amount of NaI to achieve an *in situ* exchange of chloride by iodide, to the reaction of malonates **7b** and **7d** with $\text{KO}t\text{Bu}$ in THF under reflux conditions, led to the desired clean cyclization to β -ACBC derivatives **9a** and **9b** which were isolated in 52-62% yield (Scheme 3).

Scheme 3



In an attempt to synthesize the functionalized cyclobutanes **9a** and **9b** in one step via the Michael Induced Ring Closure (MIRC) reaction, malonates **6a-d** were treated with benzophenone imine in DMF at 55-65 °C in the presence of K_2CO_3 as a mild base (Scheme 4). Under these conditions, the addition of benzophenone imine to the activated substrates was followed by an intramolecular substitution of the leaving group and cyclobutanes **9a,b** could be isolated, albeit in rather low yields after recrystallization from MeOH.

Scheme 4

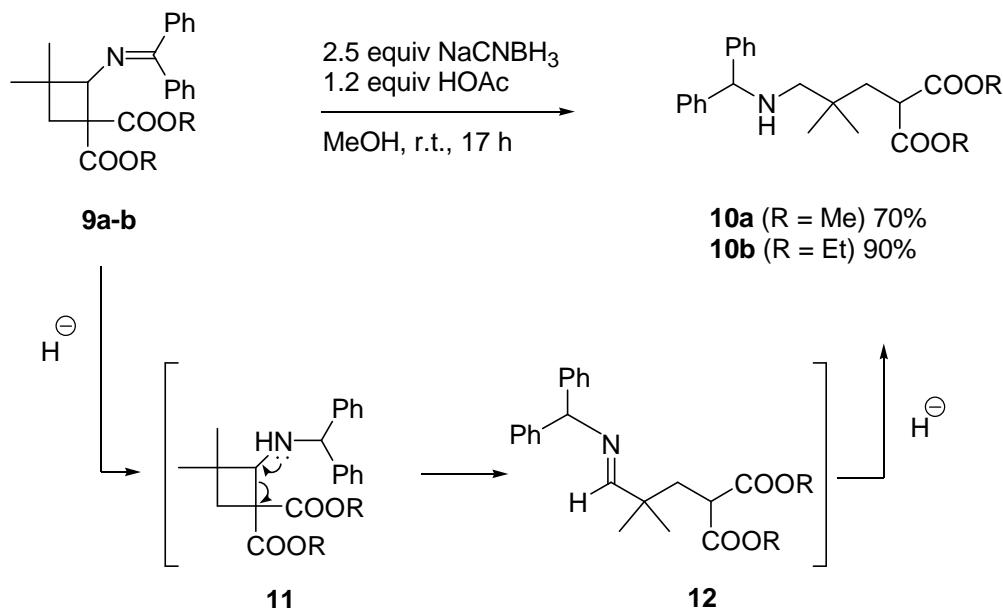


Upon reaction of malononitrile **6e** in DMF at different temperatures, a different reactivity towards benzophenone imine compared to malonates **6a-d** was observed and a tetrahydropyridine was isolated. Detailed information about this reaction and on the thermal stability of functionalised cyclobutanes **9a-b** in DMF can be found in the Supporting Information (Section 1 and 2).

As second part of the reactivity study of the novel β -aminocyclobutanecarboxylic acid derivatives **9**, the reduction of the imino function using NaCnBH_3 in the presence of acetic acid was carried out. Through this reduction, the donor-acceptor substituted β -ACBC

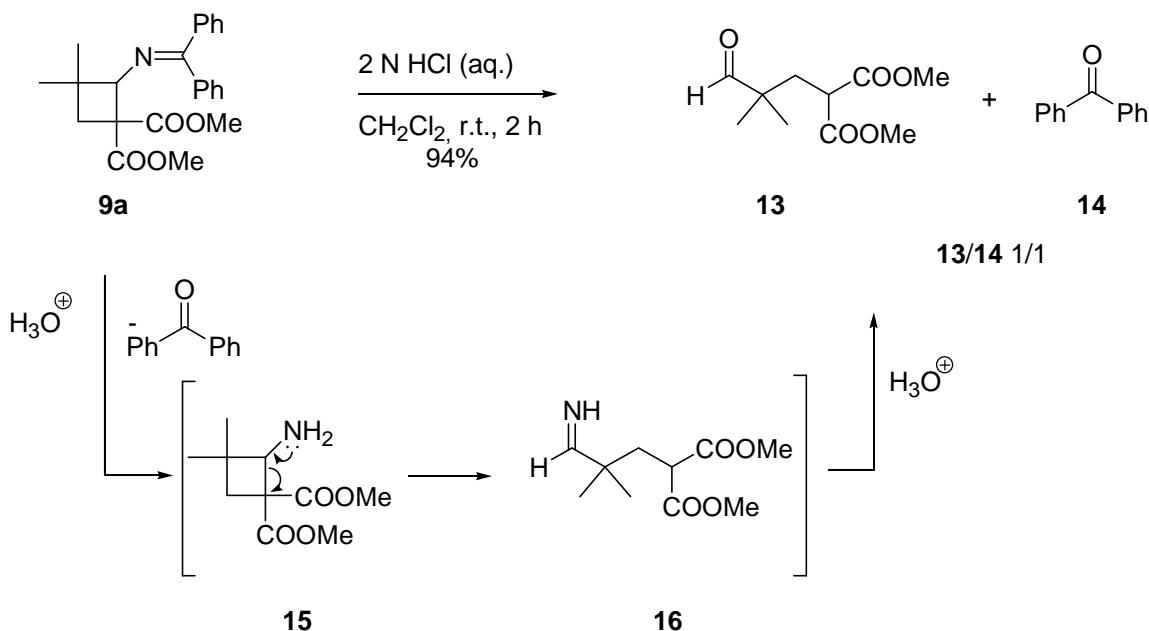
derivatives **11** are formed. The latter small-membered rings are, unlike β -ACBC **1**, not stable due to the presence of the two geminal esterfunctions which exhibit a strong electron-withdrawing effect. Accordingly, cyclobutanes **11** open *via* a push-pull mechanism towards imines **12**, which in turn are reduced to new δ -amino esters **10** (70-90% yield) (Scheme 5).⁴²

Scheme 5



The hydrolysis of the imino function of cyclobutane **9a**, in order to evaluate the possibility to form the corresponding β -amino acid eventually, led to the formation of an unstable β -ACBC derivative **15**, which was again prone to ring opening *via* a push-pull mechanism due to the presence of the donor-acceptor substituted cyclobutane ring. The crude reaction mixture, which was not purified, contained aldehyde **13** and benzophenone **14** in a 1:1 ratio (determined by analysis of the ^1H NMR spectrum of the crude reaction mixture) (Scheme 6).

Scheme 6



The presence of the two ester functions, which activate the double bond of the starting compounds **6a-d**, in order to enable the Michael addition of benzophenone imine, leads to instability of the target cyclobutanes **9** under reducing and hydrolytic conditions. Therefore, it was attempted to eliminate one of the ester functions by a decarboxylation reaction under Krapcho conditions (utilizing NaCl or LiBr in DMSO/H₂O),⁴³ but this was not successful. As a final part of the reactivity study, several attempts were made to hydrolyze the ester functions of cyclobutanes **9** in order to obtain the corresponding *N*-protected cyclic β -amino acids. Unfortunately, none of the reaction conditions that were tested (the use of aq. NaOH, NaOH in MeOH or LiOH.H₂O) led to the formation of the envisioned acids. Other methods to transform these new β -amino esters **9** into the corresponding β -amino acids are currently under investigation in our lab.

In conclusion, a novel method to synthesize highly substituted β -ACBC derivatives starting from 3-halopropylidenemalonates was developed, using benzophenone imine in a solvent-free aza-Michael addition followed by a base-induced ring closure. A reactivity study of these

novel cyclobutanedicarboxylates demonstrated the necessity of a suitable protecting group on nitrogen to avoid ring opening of these small-membered rings.

General methods

¹H NMR spectra (300 MHz) and ¹³C NMR spectra (75 MHz) were recorded on a Jeol Eclipse+ 300 NMR spectrometer. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer. Mass spectra were recorded on an Agilent 1100 Series Mass spectrometer using a direct inlet system (ES, 4000V). Melting points were measured with a Büchi B-540 apparatus. Elemental analyses were measured with a Perkin-Elmer 2400 Elemental Analyzer.

Experimental section

Dialkyl 2-(3-halo-2,2-dimethylpropylidene)malonates **6** were prepared following a literature procedure.^{31,36}

Dimethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate 6a: Yield 58%. Clear oil. R_f = 0.28 (petroleum ether/EtOAc 6/1). ¹H NMR (CDCl₃, 300 MHz): δ 1.26 (6H, s); 3.37 (2H, s); 3.79 (3H, s); 3.84 (3H, s); 6.92 (1H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 25.2; 38.4; 44.0; 52.5; 52.7; 127.3; 151.1; 164.3; 166.8. IR (ATR, cm⁻¹): $\nu_{C=O}$ = 1730; $\nu_{C=C}$ = 1646. MS (ES, pos. mode): *m/z* (%): 279/81 (M+H⁺, 100). HRMS (ESI) calcd for C₁₀H₁₅BrO₄ 279.0232 (M+H⁺), found 279.0223.

Diethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate 6c: Yield 56%. Clear oil. R_f = 0.18 (petroleum ether/EtOAc 20/1). ¹H NMR (CDCl₃, 300 MHz): δ 1.27 (6H, s); 1.29 (3H, t, *J* = 7.2 Hz); 1.34 (3H, t, *J* = 7.2 Hz); 3.39 (2H, s); 4.24 (2H, q, *J* = 7.2 Hz); 4.31 (2H, q, *J* = 7.2 Hz); 6.88 (1H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 14.0; 14.1; 25.4; 38.4; 44.1; 61.6; 61.7; 128.1; 150.3; 163.9; 166.4. IR (ATR, cm⁻¹): $\nu_{C=O}$ = 1726; $\nu_{C=C}$ = 1647. MS (ES, pos. mode):

m/z (%): 307/09 (M+H⁺, 100). HRMS (ESI) calcd for C₁₂H₁₉BrO₄ 307.0545 (M+H⁺), found 307.0554.

Diethyl 2-(3-chloro-2,2-dimethylpropylidene)malonate 6d: Yield 63%. Clear oil. *R*_f = 0.20 (petroleum ether/EtOAc 10/1). ¹H NMR (CDCl₃, 300 MHz): δ 1.24 (6H, s); 1.29 (3H, t, *J* = 7.2 Hz); 1.35 (3H, t, *J* = 7.2 Hz); 3.48 (2H, s); 4.24 (2H, q, *J* = 7.2 Hz); 4.31 (2H, q, *J* = 7.2 Hz); 6.90 (1H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 14.0; 14.1; 24.5; 39.1; 54.4; 61.6; 61.7; 128.3; 150.1; 163.9; 166.5. IR (ATR, cm⁻¹): ν_{C=O} = 1726; ν_{C=C} = 1647. MS (ES, pos. mode): *m/z* (%): 263/65 (M+H⁺, 100). HRMS (ESI) calcd for C₁₂H₁₉ClO₄ 263.1050 (M+H⁺), found 263.1044.

2-(3-Chloro-2,2-dimethylpropylidene)malononitrile 6e: Yield 35%. Clear oil. *R*_f = 0.19 (petroleum ether/EtOAc 9/1). ¹H NMR (CDCl₃, 300 MHz): δ 1.46 (6H, s); 3.54 (2H, s); 7.29 (1H, s). ¹³C NMR (CDCl₃, 75 MHz): δ 24.6; 41.8; 53.0; 89.6; 110.8; 112.6; 172.7. IR (ATR, cm⁻¹): ν_{CN} = 2236; ν_{C=C} = 1607. MS (ES, neg. mode): *m/z* (%): 194/96 (39), 185/87 (33), 149 (100).

Synthesis of dialkyl 2-[3-halo-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonates 7. As a representative example, the synthesis of dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate **7a** is described here. In a flame-dried flask, triethylamine (2 mmol, 1.05 equiv) was added to a mixture of dimethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate **6a** (1.9 mmol, 1 equiv) and benzophenone imine (2 mmol, 1.05 equiv). This mixture was stirred at 60 °C under solvent-free conditions for four hours. Subsequently, dry diethyl ether was added, the solution was filtered and the filtrate was concentrated *in vacuo*. Pure dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate **7a** was obtained after recrystallization from diethyl ether in 79% yield.

Dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate 7a:

Yield 79%. White crystals. Mp = 140.6-142.1 °C. ^1H NMR (CDCl₃, 300 MHz): δ 0.94 (3H, s); 1.05 (3H, s); 3.30 (1H, d, J = 9.9 Hz); 3.42 (1H, d, J = 9.9 Hz); 3.52 (3H, s); 3.70 (3H, s); 4.02 (1H, d, J = 6.1 Hz); 4.36 (1H, d, J = 6.1 Hz); 7.27-7.60 (10H, m). ^{13}C NMR (CDCl₃, 75 MHz): δ 22.1; 23.4; 40.7; 44.2; 52.4; 52.7; 53.9; 66.0; 128.0; 128.1; 128.6; 128.7; 130.3; 135.5; 139.6; 168.4; 168.6; 169.5. IR (ATR, cm⁻¹): $\nu_{\text{C=O}}$ = 1732; $\nu_{\text{C=N}}$ = 1626. MS (ES, pos. mode): m/z (%): 460/62 (M+H⁺, 100). Anal. Calcd for C₂₃H₂₆BrNO₄: C 60.01, H 5.69, N 3.04. Found: C 59.83, H 5.58, N 3.27.

Dimethyl 2-[3-chloro-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate 7b:

Yield 78%. White crystals. Mp = 127.3-128.4 °C. ^1H NMR (CDCl₃, 300 MHz): δ 0.92 (3H, s); 1.04 (3H, s); 3.35 (1H, d, J = 11.0 Hz); 3.47 (1H, d, J = 11.0 Hz); 3.53 (3H, s); 3.70 (3H, s); 4.04 (1H, d, J = 6.1 Hz); 4.34 (1H, d, J = 6.1 Hz); 7.28-7.60 (10H, m). ^{13}C NMR (CDCl₃, 75 MHz): δ 21.0; 22.3; 41.3; 52.4; 52.7; 53.3; 53.7; 65.9; 128.0; 128.1; 128.6; 128.7; 130.3; 135.6; 139.7; 168.4; 168.6; 169.4. IR (ATR, cm⁻¹): $\nu_{\text{C=O}}$ = 1733; $\nu_{\text{C=N}}$ = 1657. MS (ES, pos. mode): m/z (%): 416/18 (M+H⁺, 100). Anal. Calcd for C₂₃H₂₆ClNO₄: C 66.42, H 6.30, N 3.37. Found: C 66.43, H 6.60, N 3.32.

Diethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate 7c:

Prepared at room temperature instead of 60 °C. Yield 76%. White crystals. Mp = 96.9-97.4 °C. ^1H NMR (CDCl₃, 300 MHz): δ 0.93 (3H, s); 1.04 (3H, t, J = 7.2 Hz); 1.05 (3H, s); 1.23 (3H, t, J = 7.2 Hz); 3.31 (1H, d, J = 9.9 Hz); 3.43 (1H, d, J = 10.5 Hz); 3.88-4.04 (2H, m); 3.98 (1H, d, J = 6.6 Hz); 4.16 (2H, q, J = 7.2 Hz); 4.38 (1H, d, J = 6.6 Hz); 7.26-7.60 (10H, m). ^{13}C NMR (CDCl₃, 75 MHz): δ 13.9; 14.0; 22.0; 23.4; 40.8; 44.3; 54.3; 61.4; 61.6; 65.9; 127.9; 128.1; 128.6; 128.76; 128.82; 130.2; 135.6; 139.7; 167.9; 168.2; 169.3. IR (ATR, cm⁻¹): $\nu_{\text{C=O}}$ = 1727; $\nu_{\text{C=N}}$ = 1626. MS (ES, pos. mode): m/z (%): 488/90 (M+H⁺, 100). Anal. Calcd for C₂₅H₃₀BrNO₄: C 61.48, H 6.19, N 2.87. Found: C 61.39, H 6.06, N 2.88.

Diethyl 2-[3-chloro-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate 7d:

Yield 67%. White crystals. Mp = 83.9-84.1 °C. ^1H NMR (CDCl₃, 300 MHz): δ 0.91 (3H, s); 1.04 (3H, t, J = 6.9 Hz); 1.04 (3H, s); 1.23 (3H, t, J = 6.9 Hz); 3.36 (1H, d, J = 11.1 Hz); 3.47 (1H, d, J = 11.0 Hz); 3.94 (2H, q, J = 7.0 Hz); 3.99 (1H, d, J = 6.0 Hz); 4.16 (2H, q, J = 6.8 Hz); 4.36 (1H, d, J = 6.6 Hz); 7.26-7.59 (10H, m). ^{13}C NMR (CDCl₃, 75 MHz): δ 13.9; 14.0; 21.0; 22.3; 41.4; 53.4; 54.2; 61.4; 61.6; 65.8; 127.9; 128.0; 128.6; 128.77; 128.85; 130.2; 135.6; 139.8; 168.0; 168.2; 169.3. IR (ATR, cm⁻¹): $\nu_{\text{C=O}}$ = 1723; $\nu_{\text{C=N}}$ = 1627. MS (ES, pos. mode): m/z (%): 444/46 (M+H⁺, 100). Anal. Calcd for C₂₅H₃₀ClNO₄: C 67.63, H 6.81, N 3.15. Found: C 67.59, H 6.85, N 3.17.

Synthesis of diethyl 2-[2,2-dimethyl-3-(diphenylmethylenamino)propylidene]malonate 8b. In a flame-dried flask, triethylamine (1.7 mmol, 1.05 equiv) was added to a mixture of diethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate **6c** (1.6 mmol, 1 equiv) and benzophenone imine (1.7 mmol, 1.05 equiv). The reaction mixture was stirred at 60 °C under solvent-free conditions for 20 hours. Subsequently, dry diethyl ether was added, the solution was filtered and the solvent was removed *in vacuo*. Pure diethyl 2-[2,2-dimethyl-3-(diphenylmethylenamino)propylidene]malonate **8b** was obtained after recrystallization from diethyl ether in a yield of 38%.

Diethyl 2-[2,2-dimethyl-3-(diphenylmethylenamino)propylidene]malonate 8b: Yield 38%. White crystals. Mp 75.6-77.0 °C. ^1H NMR (CDCl₃, 300 MHz): δ 1.18 (6H, s); 1.28 (3H, t, J = 7.2 Hz); 1.31 (3H, t, J = 7.2 Hz); 3.31 (2H, s); 4.22 (2H, q, J = 7.2 Hz); 4.24 (2H, q, J = 7.2 Hz); 7.07 (1H, s); 7.11-7.15 (2H, m); 7.29-7.50 (6H, m); 7.61-7.65 (2H, m). ^{13}C NMR (75 MHz, CDCl₃): δ 14.0; 14.1; 24.7; 39.4; 61.26; 61.35; 64.2; 126.4; 127.8; 128.0; 128.4; 128.5; 128.6; 130.0; 136.8; 139.8; 153.7; 164.5; 167.0; 168.7. IR (ATR, cm⁻¹): $\nu_{\text{C=O}}$ = 1725; $\nu_{\text{C=C}}$ =

1646, $\nu_{C=N} = 1626$.). MS (ES, pos. mode): m/s (%): 408 ($M+H^+$, 100). Anal. Calcd for $C_{25}H_{29}NO_4$: C 73.68, H 7.17, N 3.44. Found: C 73.28, H 7.17, N 3.41.

Synthesis of dialkyl 3,3-dimethyl-2-(diphenylmethylenamino)cyclobutane-1,1-dicarboxylates 9. As a representative example, the synthesis of dimethyl 3,3-dimethyl-2-(diphenylmethylenamino)cyclobutane-1,1-dicarboxylate **9a** is described. To a solution of dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylenamino)propyl]malonate **7a** (0.9 mmol, 1 equiv) in dry THF (10 mL), 1.2 equiv $KOtBu$ (1.08 mmol) was added. After stirring the reaction mixture at reflux temperature for three hours, an aqueous saturated solution of ammoniumchloride (10 mL) was added and this mixture was extracted with EtOAc (3x 10 mL). The combined organic layers were dried over $MgSO_4$. The drying agent was removed by filtration and the filtrate was concentrated *in vacuo*. After recrystallization from MeOH, pure dimethyl 3,3-dimethyl-2-(diphenylmethylenamino)cyclobutane-1,1-dicarboxylate **9a** was obtained as white crystals in a yield of 94%.

Dimethyl 3,3-dimethyl-2-(diphenylmethylenamino)cyclobutane-1,1-dicarboxylate 9a:
 Yield 94%. White crystals. Mp 123.4.9-124.2 °C. 1H NMR ($CDCl_3$, 300 MHz): δ 0.82 (3H, s); 1.11 (3H, s); 1.86 (1H, d, $J = 12.7$ Hz); 2.91 (1H, d, $J = 12.6$ Hz); 3.67 (3H, s); 3.72 (3H, s); 4.43 (1H, s); 7.15-7.64 (10H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.8; 29.5; 37.0; 38.0; 52.4; 52.5; 53.7; 67.7; 128.0; 128.1; 128.3; 128.47; 128.51; 130.1; 136.5; 139.4; 167.9; 170.3; 172.1. IR (ATR, cm^{-1}): $\nu_{C=O} = 1725$; $\nu_{C=N} = 1628$. MS (ES, pos. mode): m/z (%): 380 ($M+H^+$, 100). Anal. Calcd for $C_{23}H_{25}NO_4$: C 72.80, H 6.64, N 3.69. Found: C 72.49, H 6.24, N 3.72.

Diethyl 3,3-dimethyl-2-(diphenylmethylenamino)cyclobutane-1,1-dicarboxylate 9b:
 Yield 75%. White crystals. Mp 57.9-59.7 °C. 1H NMR ($CDCl_3$, 300 MHz): δ 0.84 (3H, s); 1.10 (3H, t, $J = 7.2$ Hz); 1.12 (3H, s); 1.20 (3H, t, $J = 7.2$ Hz); 1.86 (1H, dd, $J = 12.8$ Hz, 1.4 Hz); 2.92 (1H, d, $J = 12.8$ Hz); 4.04-4.27 (4H, m); 4.42 (1H, s); 7.15-7.65 (10H, m). ^{13}C

¹H NMR (CDCl₃, 75 MHz): δ 14.0; 14.2; 23.9; 29.4; 36.9; 38.1; 53.7; 61.1; 61.2; 67.7; 127.9; 128.1; 128.3; 128.4; 128.6; 130.0; 136.6; 139.5; 167.7; 169.8; 171.6. IR (ATR, cm⁻¹): $\nu_{C=O}$ = 1726; $\nu_{C=N}$ = 1661. MS (ES, pos. mode): *m/z* (%): 408 (M+H⁺, 100). Anal. Calcd for C₂₅H₂₉NO₄: C 73.68, H 7.17, N 3.44. Found: C 73.58, H 7.33, N 3.35.

Synthesis of dialkyl 2-[2,2-dimethyl-3-(diphenylmethylamino)propyl]malonates 10. The synthesis of dimethyl 2-[2,2-dimethyl-3-(diphenylmethylamino)propyl]malonate **10a** is described as a representative example. To a solution of cyclobutane **9a** (0.37 mmol, 1 equiv) in MeOH (4 mL), NaCNBH₃ (0.92 mmol, 2.5 equiv) and acetic acid (0.44 mmol, 1.2 equiv) were added. The reaction mixture was stirred at room temperature for 17 hours, poured in 0.5 N NaOH (10 mL) and extracted with CH₂Cl₂ (3x 5 mL). Subsequently, the combined organic fractions were dried over MgSO₄. Removal of the drying agent through filtration and evaporation of the solvent *in vacuo* afforded dimethyl 2-[2,2-dimethyl-3-(diphenylmethylamino)propyl]malonate **10a** which was purified by column chromatography on silica gel (petroleum ether/EtOAc 1/1).

Dimethyl 2-[2,2-dimethyl-3-(diphenylmethylamino)propyl]malonate 10a: Yield 70%. Viscous oil. R_f = 0.17 (petroleum ether/EtOAc 10/1). ¹H NMR (CDCl₃, 300 MHz): δ 0.88 (6H, s); 1.54 (1H, br s); 2.03 (2H, d, *J* = 6.6 Hz); 2.31 (2H, s); 3.46 (1H, t, *J* = 6.3 Hz); 3.68 (6H, s); 4.70 (1H, s); 7.16-7.40 (10H, m). ¹³C NMR (CDCl₃, 75 MHz): δ 25.4 (CH₃); 34.1 (C); 38.2 (CH₂); 47.9 (CH); 52.6 (CH₃); 58.2 (CH₂); 68.1 (CH); 126.9 (CH); 127.3 (CH); 128.4 (CH); 144.4 (C); 170.7 (C). IR (ATR, cm⁻¹): $\nu_{C=O}$ = 1733. MS (ES, pos. mode): *m/z* (%): 384 (M+H⁺, 100). HRMS (ESI) calcd for C₂₃H₂₉NO₄ 384.2175 (M+H⁺), found 384.2157.

Diethyl 2-[2,2-dimethyl-3-(diphenylmethylamino)propyl]malonate 10b: Yield 90%. Viscous oil. R_f = 0.28 (petroleum ether/EtOAc 9/1). ¹H NMR (CDCl₃, 300 MHz): δ 0.89 (6H,

s); 1.22 (6H, t, $J = 7.2$ Hz); 1.57 (1H, br s); 2.03 (2H, d, $J = 6.1$ Hz); 2.31 (2H, s); 3.41 (1H, t, $J = 6.3$ Hz); 4.13 (2H, qxd, $J = 10.7, 7.2$ Hz); 4.15 (2H, qxd, $J = 11.0, 7.2$ Hz); 4.71 (1H, s); 7.15-7.41 (10H, m). ^{13}C NMR (CDCl₃, 75 MHz): δ 14.0 (CH₃); 25.5 (CH₃); 34.1 (C); 38.0 (CH₂); 48.3 (CH); 58.1 (CH₂); 61.4 (CH₂); 68.1 (CH); 126.9 (CH); 127.2 (CH); 128.4 (CH); 144.4 (C); 170.3 (C). IR (ATR, cm⁻¹): $\nu_{\text{C=O}} = 1748$; $\nu_{\text{C=O}} = 1729$. MS (ES, pos. mode): *m/z* (%): 412 (M+H⁺, 100). HRMS (ESI) calcd for C₂₅H₃₃NO₄ 412.2488 (M+H⁺), found 412.2473.

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