Synthesis of N-Protected β-Aminocyclopropanedicarboxylates and Their Ring Transformation to *N*-Benzhydryl-3-alkoxycarbonyl-4,4-dialkyl-pyrrolidin-2-ones

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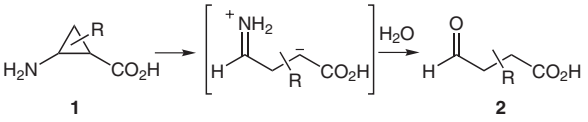
Abstract: An easy and short synthesis of new N-protected β-aminocyclopropanedicarboxylates, a rather unexplored class of highly activated conformationally constrained β-amino acid derivatives, is described. Michael-induced ring closure (MIRC) of diphenylmethylidenamine to 2-bromoalkylidenemalonates leads to 3,3-dialkyl-2-(diphenylmethylidenamino)cyclopropane-1,1-dicarboxylates, the reactivity of which with hydrides was investigated, yielding 3-(alkoxycarbonyl)pyrrolidin-2-ones.

Key words: Michael-induced ring closure, rearrangement, cyclopropanes, β-amino acids, N-heterocycles

One of the most conformationally constrained classes of β-amino acids are 2-aminocyclopropanecarboxylic acids (β-ACCs) **1**, which readily undergo ring opening to γ-oxo-carboxylates **2**, due to the 1,2-push-pull substitution on the cyclopropane ring (Scheme 1).[1] Therefore, an appropriate N-protecting group has to be introduced during the synthesis of β-aminocyclopropanecarboxylic acid derivatives, and special procedures are necessary to incorporate these donor-acceptor cyclopropanes (D-A cyclopropanes) into β-peptide structures, which has limited their use.[2] Besides their incorporation in β-peptide structures, it can be envisioned that the intrinsic characteristic of β-ACCs to ring open could be used as an advantage in the synthesis of N-heterocyclic compounds under appropriate conditions. However, contrary to D-A cyclopropanes with an oxygen substituent as donor,[1a] only relatively few examples of the heterocyclic synthetic use of ring-opening of β-ACCs are known. Moreover, often further functionalisation in the β-ACC structure is required to make the synthesis of the N-heterocycle possible. These examples include hydrolysis of a cyclopropanated enaminocarboxanilide to a pyrrolidone,[3] transformation of ring-opened 3-acyl-2-aminocyclopropane-1-carboxylates to tetrahydrocyclopenta[*b*]pyrroles and tetrahydroindoles,[4] electrocyclic ring enlargement of cyclopropanated uridines to 1,3-diazepinediones,[5] ring transformation of β-ACC derivatives during the synthesis of the alkaloid (±)-eburnamonine,[6,7] thermal rearrangement of 6-ethyl 2-methyl 2-azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate in the presence of CuBr to ethyl *N*-methoxycarbonylpyrrole-2-acetate or gas pyrolysis to 2-ethyl 1-methyl pyridine-1,2(2*H*)-dicarboxylate,[8] and the photochemical rearrangement of 2-diphenylmethylidenamino-2-methylcyclopropane-1-carboxylates to the corresponding 1-pyrrolines.[9]

In the present article results are disclosed on the synthesis of N-protected 2-aminocyclopropane-1,1-dicarboxylates, a class of highly activated β-ACCs, of which only few related compounds have been synthesised, i.e. β-purinyl,[10] β-imidazolyl,[11] β-nitro,[12] and β-*N*,*N*-(bistrimethylsilyloxy)aminocyclopropanedicarboxylates.[13] Furthermore, the synthetic use of the newly prepared β-aminocyclopropanedicarboxylates as interesting building blocks for functionalised γ-lactams is described. 3-(Alkoxycarbonyl)pyrrolidin-2-ones are highly desirable targets in organic synthesis, as they exhibit physiological activities, e.g. scytalone dehydratase inhibition.[14] Moreover, they also have been used in the synthesis of other interesting compounds, e.g. the antidepressant rolipram,[15] dienophilic pyrrolin-2-ones,[16] 3-alkylpyrrolidin-2-ones,[17] 3-alkylpyrrolinium salts,[18] ene-pyrrolidine carbamates useful in radical cyclisations[19] and intramolecular Diels–Alder cyclisations,[20] γ-lactam-constrained amino acids[21] and dipeptides,[22] cyclic five-membered non-proteinogenic amino acids,[23,24] 5,6-dihydropyrrolo[2,3-*d*]pyrimidines,[25] octahydropyrrolo[2,3-*b*]pyrroles,[26] fused oxazolidinones,[27] polyheterocyclic systems,[28–30] and polymers.[31]



1 **2**

Scheme 1

Under appropriate reaction conditions, in analogy with other nucleophiles, e.g. methoxide, cyanide, thiolates, hydride, phosphites,[32] 4-formylimidazole,[11] or aminopurines,[10] diphenylmethylidenamine proved to be a suitable nucleophile for the Michael-induced ring-closure (MIRC) of dialkyl 2-bromoalkylidenemalonates **3**, prepared via a Knoevenagel condensation of the corresponding aldehyde and malonate, followed by radical allylic bromination (Scheme 2). Treatment of dialkyl 2-bromoalkylidenemalonates **3** with one equivalent of diphenylmethylidenamine and triethylamine in *tert*-butyl alcohol under reflux conditions, for a period of time as indicated by consumption of the starting material on TLC, resulted in

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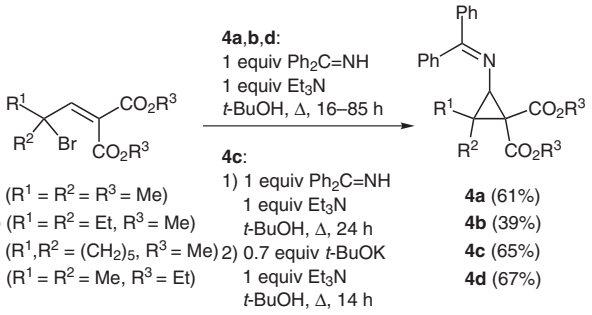
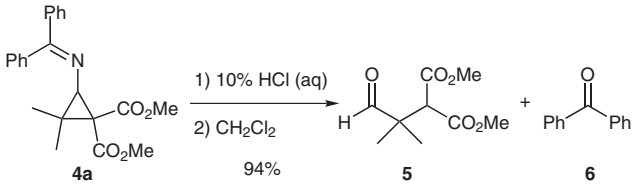
the formation of 3,3-dialkyl-2-(diphenylmethylidenamino)cyclopropane-1,1-dicarboxylates **4a–d** in moderate to good isolated yield.[33,34] With this methodology, for the first time 2-aminocyclopropane-1,1-dicarboxylates come available with an easily deprotectable group on nitrogen. Extensive chromatography was necessary to separate compounds **4** from benzophenone **6**, present in the reaction mixtures and formed on column due to hydrolysis of some residual diphenylmethylidenamine. Benzophenone **6** together with γ-oxodicarboxylate **5** were also formed in good yield upon acid hydrolysis of **4a** (Scheme 3). In the synthesis of cyclopropane **4c**, an additional treatment with potassium *tert*-butoxide in *tert*-butyl alcohol under reflux conditions overnight was necessary to complete the sterically hindered ring-closure after the initial Michael addition of diphenylmethylidenamine.



Scheme 2

When methanol was used instead of *tert*-butyl alcohol for the cyclization of 2-bromoalkylidenemalonate **3a** an important side reaction occurred, which resulted in less formation of cyclopropane **4a** (Scheme 4). After prolonged heating, compound **7** was isolated, resulting from ring-opening of cyclopropane **4a** under the given reaction conditions, followed by nucleophilic attack of methanol (path a). Besides **7**, also a significant amount of 1-pyrroline **8** was observed in the reaction mixture.[35] The formation of the latter can be explained via an azavinylcyclopropane–cyclopentene rearrangement similar to the thermal rearrangement of comparable *N*-cyclopropylimines to 1-pyrrolines (path b).[9,36] Ring expansions of *N*-arylidenecyclopropylamines often require harsh conditions such as vacuum pyrolysis above 350 °C.[9a] However, ring expansion rates increase significantly if substituents are present at the cyclopropane ring.[9a,36b] Therefore, it seems reasonable that the methyl substituents and the ester functions in *N*-(diphenylmethylidene)cyclopropylamine (**4a**) reduce the activation energy for ring expansion. However, for *N*-cyclopropylimines with an electron-withdrawing group at C-2, formed by irradiation of imine carbene complexes with alkenes, the rearrangement has only been reported under photochemical conditions.[9c] In the conversion of 2-bromoalkylidenemalonates **3** to cyclopropanes **4**, increasing the amount of diphenylmethylidenamine or the use of other bases like potassium carbonate or potassium *tert*-butoxide, or other solvents like dimethylformamide or acetonitrile only led to the formation of more unidentifiable side products besides cyclopropanes **4** and 1-pyrroline **8**, which made the isolation of the cyclopropanes **4** impossible.



Scheme 3

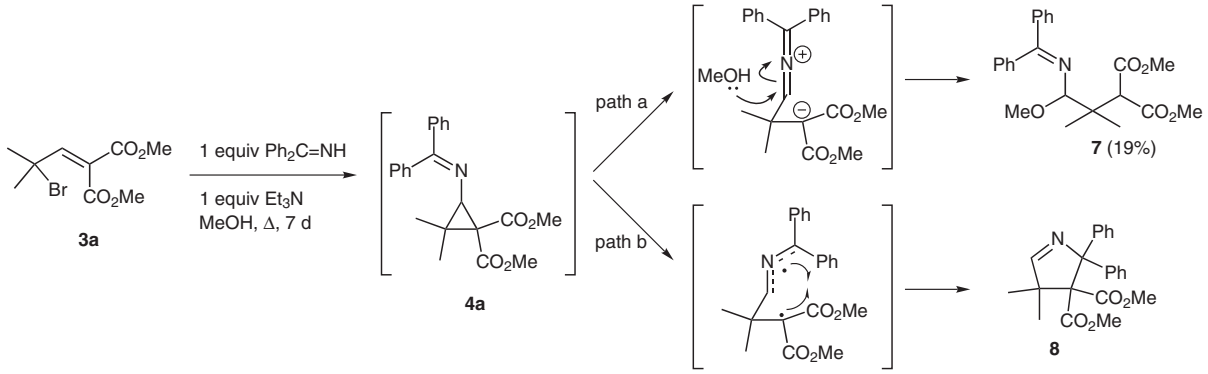
With the 3,3-dialkyl-2-(diphenylmethylidenamino)cyclopropane-1,1-dicarboxylates **4a–d** in hand, their reactivity under reducing conditions was investigated with cyclopropane **4a** as preliminary substrate (Table 1). At first, reduction was attempted using sodium borohydride in methanol, since the diphenylmethylidenamino moiety normally is reduced under these conditions.[37] However, refluxing cyclopropane **4a** in methanol with one molar equivalent of sodium borohydride resulted in an almost 1:1 mixture of starting material and 1-pyrroline **8** (entry 1). Apparently, heating of cyclopropane **4a** with sodium borohydride lead to formation of 1-pyrroline **8**, while sodium borohydride is not a strong enough reducing agent in this case, confirmed by the absence of reaction at room temperature (entry 2). Therefore, sodium cyanoborohydride under acidic conditions was used in further experiments as a stronger reducing system at room temperature. When 2.5 molar equivalents of sodium cyanoborohydride was used, a clean and complete ring transformation of the starting cyclopropane **4a** to *N*-benzhydryl-3-methoxycarbonyl-4,4-dimethylpyrrolidin-2-one (**12a**) was observed (entry 3). In the same way, γ-lactams **12b**,**c** were formed, whereas reduction of cyclopropane **4d** resulted in a 2:1 mixture of γ-aminodiester **11d** and γ-lactam **12d** (Scheme 5).[38,39] The formation of γ-lactams **12** can be explained by first reduction of the imino function via the corresponding protonated iminium ion, followed by spontaneous ring-opening of the intermediate 2-aminocyclopropane-1,1-dicarboxylates **9** to the γ-iminodicarboxylates **10**. Further reduction then occurs by the excess of hydride and the resulting γ-aminodiesters **11** cyclise to the corresponding lactams **12**, with the cyclization being slower with diethyl ester **11d**. When the reduction of cyclopropane **4a** with sodium cyanoborohydride was not allowed to proceed long enough, the intermediate γ-aminodiester **11a** together with the lactam **12a** could be detected in the reaction mixture. A complex mixture of aminodiester **11a** together with starting compound **4a** and heterocycles **8** and **12a** was formed when the reduction was performed using sodium borohydride in combination with cerium(III) chloride (Luche's reagent, entry 6).[40]

The use of only a small excess of sodium cyanoborohydride (entry 4) or one molar equivalent of the sterically more demanding sodium triacetoxyborohydride (entry 5) only lead to mixtures of starting product **4a** and pyrrolidin-2-one **12a** without any evidence for the formation of

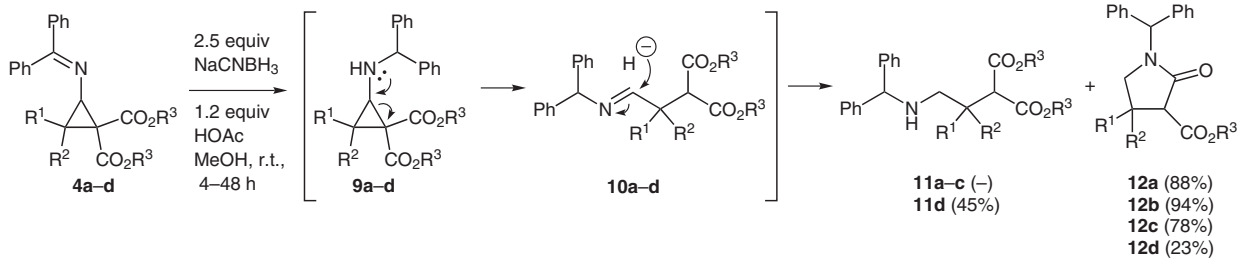
Table 1 Overview on the Reduction of Cyclopropane **4a**

Entry	Reaction conditions	Yield (%)[a,b]
1	1 equiv $NaBH_4$, MeOH, Δ, 20 h	47 (**4a**) + 53 (**8**)
2	0.33 equiv $NaBH_4$, MeOH, 0 °C to r.t., 14 h	100 (**4a**)
3	2.5 equiv $NaCNBH_3$, 1.2 equiv HOAc, MeOH, r.t., 17 h	100 (**12a**, 88)
4	0.34 equiv $NaCNBH_3$, 1.2 equiv HOAc, MeOH, r.t., 3 h	86 (**4a**) + 14 (**12a**)
5	1 equiv $NaBH(OAc)_3$, HOAc–THF, –78 °C to r.t., 22 h	38 (**4a**) + 62 (**12a**)
6	2 equiv $NaBH_4$, 0.5 equiv $CeCl_3$, MeOH, –78 °C to r.t., 21 h	23 (**4a**) + 15 (**12a**) + 26 (**8**) + 36 (**11a**)[c]

[a] Ratio of reaction products based on integrations of ^{1}H NMR spectra of the reaction mixtures.
[b] Isolated yield.
[c] Not isolated, identification based on signals of the ^{1}H NMR spectrum of the reaction mixture.

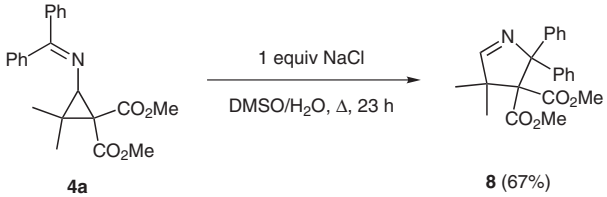


Scheme 4



Scheme 5

the intermediate γ-iminodicarboxylate **10a**. Clearly, the reduction of the starting imino moiety of cyclopropane **4a** is slower then the ring-opening of the aminocyclopropane **9a** and the subsequent reduction of the γ-iminodicarboxylate **10a**. This can be explained by steric hindrance during the reduction of the diphenylmethylidenamino moiety and the strong tendency of the highly activated D-A-cyclopropane ring to ring open by the two electron-withdrawing ester functions of 2-aminocyclopropane-1,1-dicarboxylate (**9a**). In an attempt to make the β-ACC derivate **4a** less prone towards ring-opening, a decarboxylation reaction was attempted under Krapcho conditions, which yielded, however, the 1-pyrroline **8** in moderate isolated yield (Scheme 6).



Scheme 6

In conclusion, a short synthesis of functionalised β-aminocyclopropanecarboxylates via a Michael-induced ring closure was described. These compounds proved very sensitive towards different ring-opening reactions, but upon reduction under the appropriate conditions a clean

and efficient transformation was accomplished towards 4,4-dialkyl-3-(methoxycarbonyl)pyrrolidin-2-ones which are useful building blocks in heterocyclic chemistry.

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References

(1) (a) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.
(2) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.
(3) Maas, G.; Müller, A. *J. Prakt. Chem.* **1998**, *340*, 315.
(4) Müller, A.; Maier, A.; Neumann, R.; Maas, G. *Eur. J. Org. Chem.* **1998**, 1177.
(5) (a) Thieller, H. P. M.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, *33*, 2603. (b) Thieller, H. P. M.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, *33*, 2609. (c) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3478.
(6) (a) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586. (b) Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197.
(7) Wenkert, E.; Hudlick, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893.
(8) Tanny, S. R.; Grossman, J.; Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 6495.
(9) (a) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodriguez, M. A. *Tetrahedron Lett.* **2002**, *43*, 8811. (b) Campos, P. J.; Soldevilla, A.; Sampedro, D.; Rodriguez, M. A. *Org. Lett.* **2001**, *3*, 4087. (c) Campos, P. J.; Sampedro, D.; Rodriguez, M. A. *Organometallics* **2002**, *21*, 4076.
(10) (a) Geen, G. R.; Kincey, P. M.; Choudary, B. M. *Tetrahedron Lett.* **1992**, *33*, 4609. (b) Geen, G. R.; Harnden, M. R.; Parratt, M. J. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 347. (c) Geen, G. R.; Grinter, T. J.; Moore, S. Eur. Pat. Appl. EP 420559, **1991**; *Chem. Abstr.* **1991**, *115*, 28993. (d) Hayashi, T.; Yasuoka, J.; Nishikawa, J. Jpn. Kokai Tokkyo Koho JP 2000327593, **2000**; *Chem. Abstr.* **2000**, *133*, 362933. (e) Hayashi, T.; Yasuoka, J.; Nishiura, A. Eur. Pat. Appl. EP 916674, **1999**; *Chem. Abstr.* **1999**, *131*, 5268. (f) Kim, H. S.; Barak, D.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **2001**, *44*, 3092.
(11) Su, Q.; Wood, J. L. *Synth. Commun.* **2000**, *30*, 3383.
(12) (a) Trukhin, E. V.; Makarenko, S. V.; Berestovitskaya, V. M. *Russ. J. Org. Chem.* **1998**, *34*, 59; *Chem. Abstr.* **1998**, *130*, 3661. (b) Villemin, D.; Thibault-Starzyk, F.; Hachemi, M. *Synth. Commun.* **1994**, *24*, 1425. (c) Le Menn, J. C.; Tallec, A.; Sarrazin, J. *Can. J. Chem.* **1991**, *69*, 761. (d) Sopova, A. S.; Bakova, O. V.; Metelkina, E. L.; Perekalin, V. V. *Zh. Org. Khim.* **1975**, *11*, 68; *Chem. Abstr.* **1975**, *83*, 9406. (e) Sopova, A. S.; Yurchenko, O. I.; Perekalin, V. V. *Zh. Obshch. Khim.* **1965**, *1*, 1707; *Chem. Abstr.* **1966**, *64*, 3726. (f) Kohler, E. P.; Darling, S. F. *J. Am. Chem. Soc.* **1930**, *52*, 424.
(13) (a) Smirnov, V. O.; Tishkov, A. A.; Lyapkalo, I. M.; Ioffe, S. L.; Kachala, V. V.; Strelenko, Y. A.; Tartakovsky, V. A. *Russ. Chem. Bull.* **2001**, *50*, 2433; *Chem. Abstr.* **2002**, *137*, 279247. (b) Danilenko, V. M.; Tishkov, A. A.; Ioffe, S. L.; Lyapkalo, I. M.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **2002**, 635. (c) Tishkov, A. A.; Kozintsev, A. V.; Lyapkalo, I. M.; Ioffe, S. L.; Kachala, V. V.; Strelenko, Y. A.; Tartakovsky, V. A. *Tetrahedron Lett.* **1999**, *40*, 5075.
(14) Basarab, G. S.; Jordan, D. B.; Gehret, T. C.; Schwartz, R. S. *Bioorg. Med. Chem.* **2002**, *10*, 4143.
(15) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097.
(16) (a) Vedejs, E.; Campbell, J. B. Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534. (b) Craven, A. P.; Dyke, H. J.; Thomas, E. J. *Tetrahedron* **1989**, *45*, 2417.
(17) Swan, G. A.; Wilcock, J. D. *J. Chem. Soc., Perkin Trans. 1* **1974**, 885.
(18) Rueppel, M. L.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 7021.
(19) Cossy, J.; Cases, M.; Gomez Pardo, D. *Tetrahedron Lett.* **1998**, *39*, 2331.
(20) (a) Leonard, J.; Fearnley, S. P.; Finlay, M. R.; Knight, J. A.; Wong, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2359. (b) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.
(21) Boisbrun, M.; Kovács-Kulyassa, A.; Jeannin, L.; Sapi, J.; Toupet, L.; Laronze, J.-Y. *Tetrahedron Lett.* **2000**, *41*, 9771.
(22) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631.
(23) Lee, D. L.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 893.
(24) (a) Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M. *Synlett* **1995**, 1159. (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069.
(25) (a) Taylor, E. C.; Liu, B. *J. Org. Chem.* **2001**, *66*, 3726. (b) Taylor, E. C.; Liu, B. *Tetrahedron Lett.* **1999**, *40*, 5291.
(26) Thorsett, E. D.; Harris, E. E.; Patchett, A. A. *J. Org. Chem.* **1978**, *43*, 4276.
(27) Padwa, A.; Prein, M. *J. Org. Chem.* **1997**, *62*, 6842.
(28) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556.
(29) Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339.
(30) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947.
(31) (a) Kim, J.-B.; Jung, M.-H.; Chang, K.-H. *Eur. Polym. J.* **1997**, *33*, 1239. (b) Kim, S.-T.; Kim, J.-B.; Jung, M.-H.; Ahn, K.-D. *Polym. Bull.* **1997**, *39*, 423. (c) He, W.; Gonsalves, K. E.; Pickett, J. H.; Halberstadt, C. *Biomacromolecules* **2003**, *4*, 75.
(32) (a) Verhé, R.; De Kimpe, N.; De Buyck, L.; Courtheyn, D.; Schamp, N. *Bull. Soc. Chim. Belg.* **1977**, *86*, 215. (b) Kristensen, J.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 609. (c) Walborsky, H. M.; Topolski, M. *Tetrahedron Lett.* **1993**, *34*, 7681. (d) Stevens, C. V.; Van Heecke, G.; Barbero, C.; Patora, K.; De Kimpe, N.; Verhé, R. *Synlett* **2002**, 1089.
(33) **General Experimental Procedure.**
t-BuOH was dried by distillation over CaH_2. To a mixture of malonate **3** (10 mmol) and anhyd *t*-BuOH (15 mL) was added diphenylmethylidenamine (10 mmol) and Et_3N (10 mmol). The reaction mixture was stirred at reflux temperature (**4a**: 16 h; **4b**, **4d**: 85 h; **4c**: 24 h). For **4c**, 0.7 equiv of *t*-BuOK were added and the reaction mixture was stirred at reflux temperature overnight. The reaction mixture

was then evaporated, diluted with dry Et_2O (40 mL), filtered and concentrated. The pure cyclopropanes **4** were obtained by flash column chromatography (neutral Al_2O_3, hexane–Et_2O, 2:1) and recrystallisation (Et_2O–hexane) for **4a**; repeated flash column chromatography (basic Al_2O_3, hexane–Et_2O, 9:1) for **4b–d**.

(34) All compounds gave satisfactory analytical and spectral data.

Dimethyl 3-[(Diphenylmethylidene)amino]-2,2-dimethylcyclopropane-1,1-dicarboxylate (4a).
White crystals. R_f (neutral Al_2O_3, hexane–Et_2O 2:1) = 0.32. Mp 87.3–87.7 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.56 (s, 3 H), 3.47 (s, 1 H), 3.68 (s, 3 H), 3.74 (s, 3 H), 7.22–7.59 (m, 10 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 18.5, 20.5, 34.4, 46.2, 52.2, 52.5, 55.8, 128.0, 128.35, 128.41, 128.44, 128.8, 130.0, 136.2, 139.3, 166.9, 168.5, 169.2. IR (KBr): ν = 1745, 1731, 1618 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 366 (100) [M + H$^+$]. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; N, 3.83. Found: C, 72.04; N, 3.70.

Dimethyl 3-[(Diphenylmethylidene)amino]-2,2-diethylcyclopropane-1,1-dicarboxylate (4b).
Viscous oil. R_f (silica gel, hexane–Et_2O, 9:1) = 0.03. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.4 Hz, 3 H), 1.01 (t, *J* = 7.4 Hz, 3 H), 1.28–1.57 (m, 2 H), 1.95–2.19 (m, 2 H), 3.51 (s, 1 H), 3.68 (s, 3 H), 3.72 (s, 3 H), 7.25–7.64 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8, 10.6, 20.3, 21.7, 44.2, 47.2, 52.1, 52.5, 55.9, 128.0, 128.3, 128.4, 128.5, 128.8, 129.9, 136.2, 139.5, 166.9, 167.0, 168.7. IR (NaCl): ν = 1732, 1622 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 394 (100) [M + H$^+$]. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; N, 3.56. Found: C, 73.02; N, 3.47.

Dimethyl 2-[(Diphenylmethylidene)amino]spiro[2.5]octane-1,1-dicarboxylate (4c).
White crystals. R_f (silica gel, hexane–Et_2O, 2:1) = 0.29. Mp 92.8–94.2 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.41–2.11 (m, 10 H), 3.50 (s, 1 H), 3.68 (s, 3 H), 3.72 (s, 3 H), 7.26–7.57 (m, 10 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 25.3, 25.5, 26.1, 28.7, 30.1, 41.2, 47.1, 52.2, 52.5, 54.9, 128.0, 128.3, 128.4, 128.5, 128.8, 129.9, 136.2, 139.5, 166.9, 168.3, 168.7. IR (KBr): ν = 1749, 1728, 1623 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 406 (100) [M + H$^+$]. Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; N, 3.45. Found: C, 73.91; N, 3.41.

Diethyl 3-[(Diphenylmethylidene)amino]-2,2-dimethylcyclopropane-1,1-dicarboxylate (4d).
White crystals. R_f (silica gel, hexane–Et_2O, 9:1) = 0.08. Mp 56.2–58.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.16 (t, *J* = 7.15 Hz, 3 H), 1.23 (t, *J* = 7.15 Hz, 3 H), 1.59 (s, 3 H), 3.46 (s, 1 H), 4.06–4.23 (m, 4 H), 7.21–7.61 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 14.2, 18.5, 20.5, 34.2, 46.4, 55.6, 60.8, 61.3, 127.9, 128.4, 128.8, 129.9, 136.3, 139.4, 166.4, 168.1, 169.1. IR (KBr): ν = 1738, 1716, 1619 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 394 (100) [M + H$^+$]. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; N, 3.56. Found: C, 73.04; N, 3.44.

(35) These new compounds **7** and **8** gave satisfactory analytical and spectral data. Selected characterisation data.

Dimethyl {2-Methoxy-1,1-dimethyl-2-[(diphenylmethylidene)amino]ethyl}malonate (7).
Viscous oil. R_f (petroleum ether–EtOAc, 4:1) = 0.24. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.01 (s, 3 H), 1.31 (s, 3 H), 3.16 (s, 3 H), 3.50 (s, 3 H), 3.67 (s, 3 H), 3.81 (s, 1 H), 4.46 (s, 1 H), 7.16–7.19 (m, 2 H), 7.31–7.47 (m, 6 H), 7.66–7.70 (m, 2 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 20.3, 20.9, 42.7, 51.7, 51.8, 56.0, 56.6, 94.9, 128.0, 128.1, 128.2, 128.4, 129.0, 130.6, 136.4, 139.2, 168.7, 168.8, 170.8. IR (NaCl): ν = 1756, 1732, 1620 cm^{-1}. MS (70 eV): *m/z* (%) = no M$^+$, 365 (60), 223 (83), 216 (72), 192 (81), 181 (44), 180 (100), 166 (57), 165 (78), 104 (39), 77 (38). Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; N, 3.52. Found: C, 69.38; N, 3.44.

Dimethyl 4,4-Dimethyl-2,2-diphenyl-2,4-dihydro-3*H*-pyrrole-3,3-dicarboxylate (8).
White crystals. R_f (silica gel, petroleum ether–EtOAc, 7:3) = 0.22. Mp 112.6–113.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 6 H), 3.46 (s, 6 H), 7.12–7.26 (m, 6 H), 7.64 (br d, *J* = 7.71 Hz, 4 H), 7.71 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 51.9, 55.7, 75.2, 89.1, 126.8, 127.4, 128.9, 143.4, 169.7, 170.8. IR (KBr): ν = 1737, 1719, 1652 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 366 (100) [M + H$^+$]. Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; N, 3.83. Found: C, 72.07; N, 3.75.

(36) (a) Caramella, P.; Huisgen, R.; Schmolke, B. *J. Am. Chem. Soc.* **1974**, *96*, 2997. (b) Caramella, P.; Huisgen, R.; Schmolke, B. *J. Am. Chem. Soc.* **1974**, *96*, 2999.

(37) Dejaegher, Y.; Mangelinckx, S.; De Kimpe, N. *Synlett* **2002**, 113.

(38) **General Experimental Procedure.**
To a mixture of cyclopropane **4** (0.5 mmol) and MeOH (3 mL) was added $NaCNBH_3$ (1.25 mmol) and HOAc (0.6 mmol). The reaction mixture was stirred at r.t. (**12a**: 17 h; **12b**: 42 h; **12c**: 4 h; **12d** and **11d**: 48 h). The reaction mixture was poured into aq NaOH (0.5 N, 10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). After drying of the organic layer ($MgSO_4$), filtration and evaporation, the pure pyrrolidin-2-ones **12a–c**, or the mixture of **12d** and **11d** was obtained. Analytically pure samples could be obtained upon recrystallisation (Et_2O–hexane) for **12a**; flash column chromatography (silica gel, petroleum ether–EtOAc, 4:1) for **12b**,**c**; flash column chromatography (silica gel, hexane–Et_2O, 4:1) for **12d** and **11d**.

(39) All compounds gave satisfactory analytical and spectral data.

Methyl 1-Benzhydryl-4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (12a).
White crystals. Mp 83.3–83.7 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.04 (s, 3 H), 1.11 (s, 3 H), 2.82 (d, *J* = 9.6 Hz, 1 H), 3.15 (s, 1 H), 3.23 (d, *J* = 9.6 Hz, 1 H), 3.72 (s, 3 H), 6.65 (s, 1 H), 7.21–7.35 (m, 10 H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 22.6, 28.6, 36.8, 52.0, 56.1, 58.8, 60.8, 127.4, 127.6, 128.3, 128.4, 128.5, 128.8, 138.0, 138.5, 169.4, 170.3. IR (KBr): ν = 1749, 1694 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 338 (100) [M + H$^+$], 167 (9). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; N, 4.15. Found: C, 74.36; N, 4.14.

Methyl 1-Benzhydryl-4,4-diethyl-2-oxopyrrolidine-3-carboxylate (12b).
Viscous oil. R_f (silica gel, petroleum ether–EtOAc, 4:1) = 0.18. ^{1}H NMR (300 MHz $CDCl_3$): δ = 0.68 (t, *J* = 7.4 Hz, 3 H), 0.76 (t, *J* = 7.4 Hz, 3 H), 1.26–1.56 (m, 4 H), 2.87 (d, *J* = 10 Hz, 1 H), 3.23 (d, *J* = 10 Hz, 1 H), 3.25 (s, 1 H), 3.73 (s, 3 H), 6.64 (s, 1 H), 7.22–7.49 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.6, 8.1, 24.8, 28.3, 43.4, 52.0, 53.0, 58.9, 59.1, 127.4, 127.8, 128.2, 128.4, 128.6, 129.1, 138.0, 138.6, 169.7, 170.6. IR (NaCl): ν = 1734, 1694 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 366 (100) [M +H$^+$], 167 (52). Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; N, 3.83. Found: C, 75.34; N, 3.78.

Methyl 2-Benzhydryl-3-oxo-2-azaspiro[4.5]decane-4-carboxylate (12c).
Viscous oil. R_f (silica gel, petroleum ether–EtOAc, 4:1) = 0.17. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11–1.57 (m, 10 H), 2.98 (d, *J* = 10 Hz, 1 H), 3.21 (d, *J* = 10 Hz, 1 H), 3.24 (s, 1 H), 3.72 (s, 3 H), 6.65 (s, 1 H), 7.15–7.44 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.5, 25.4, 32.1, 36.3, 40.7, 52.0, 53.1, 58.8, 60.2, 127.4, 127.7, 128.4, 128.5, 128.8, 138.1, 138.7, 169.4, 170.5. IR (NaCl): ν = 1736, 1694

cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 378 (100) [M + H^+], 167 (35). Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.36; N, 3.71. Found: C, 76.05; N, 3.61.

Ethyl 1-Benzhydryl-4,4-dimethyl-2-oxopyrrolidine-3-carboxylate (12d).

White crystals. R_f (silica gel, hexane–Et_2O, 4:1) = 0.27. Mp 94.9–96.1 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 3 H), 1.12 (s, 3 H), 1.26 (t, *J* = 7.15 Hz, 3 H), 2.81 (d, *J* = 9.63 Hz, 1 H), 3.12 (s, 1 H), 3.24 (d, *J* = 9.63 Hz, 1 H), 4.20 (q, *J* = 7.15 Hz, 2 H), 6.65 (s, 1 H), 7.21–7.38 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.6, 28.8, 36.9, 56.2, 58.9, 61.0, 61.2, 127.5, 127.8, 128.4, 128.6, 128.8, 138.1, 138.7, 169.0, 170.5. IR (KBr): ν = 1737, 1683 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 352 (100) [M + H^+]. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; N, 3.99. Found: C, 74.98; N, 3.93.

Diethyl [2-(Benzhydrylamino)-1,1-dimethylethyl]malonate (11d).

Viscous oil. R_f (silica gel, hexane–Et_2O, 1:1) = 0.23. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (s, 6 H), 1.22 (t, *J* = 7.15 Hz, 6 H), 1.63 (br s, 1 H), 2.53 (s, 2 H), 3.69 (s, 1 H), 4.14 (q, *J* = 7.15 Hz, 4 H), 4.72 (s, 1 H), 7.17–7.37 (m, 10 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 24.0, 37.5, 57.4, 57.6, 60.9, 67.8, 126.9, 127.4, 128.4, 144.2, 168.7. IR (NaCl): ν = 3351, 1755, 1732 cm^{-1}. MS (ES, pos. mode): *m/z* (%) = 398 (100) [M + H^+]. Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; N, 3.52. Found: C, 72.28; N, 3.43.

(40) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.