Synthesis and Applications of β-Aminocarboxylic Acids Containing a Cyclopropane Ring

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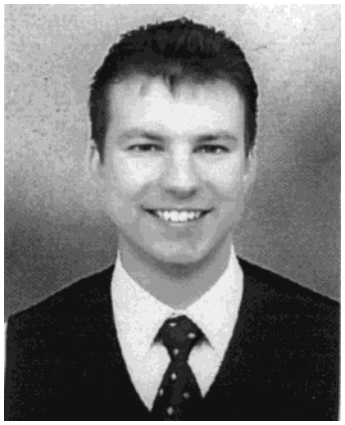
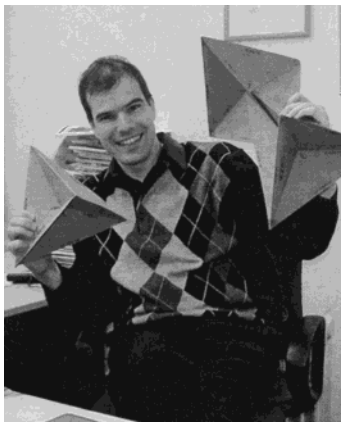


Frieder Gnad, born 1974 in Germany, received his Diploma in chemistry in 2000 from University Regensburg. Currently, he is a Ph.D. student at University Regensburg under the supervision of Oliver Reiser.



Oliver Reiser was born 1962 in Hamburg, Germany. He studied chemistry at the Universities of Hamburg, Jerusalem, and Los Angeles (UCLA) and obtained his PhD in 1989 at the University of Hamburg under the supervision of Armin de Meijere. He spent one year as a postdoctoral fellow with Robert Miller at the IBM Research Center, San Jose, and one year with David Evans, Harvard University, Cambridge. In 1992 he joined the University of Göttingen as Assistant professor, finishing his habilitation in 1995. In 1996 he moved to the University Stuttgart as Associate Professor and in 1997 to the University of Regensburg as Full Professor. His research group is involved in the development of methods for stereoselective synthesis and catalysis toward the synthesis of natural products, application of non conventional methods such as high pressures in catalysis, and peptide chemistry using unnatural amino acids.

1. Introduction

The overwhelming importance of α-amino acids in biologically relevant processes has also been manifested for many cyclopropane-containing derivatives.[1] With the growing realization that some β-amino acids also display significant biological activities[2] and because the latter are valuable constituents in peptides,[3] cyclopropyl-substituted analogues have attracted widespread attention in recent years. In addition, cyclopropyl-modified β-alanines have been proved to be useful intermediates in organic syntheses, making use of the amino, the carboxyl, and the cyclopropyl group as reactive functionalities.

There are three different possibilities how β-alanine (**1**) can be fused directly with a cyclopropane ring: the cyclopropyl group can be placed like two geminal substituents in the α- or β-position of **1** as depicted in **2** or **3**, respectively, or incorporating the α- and β-position as shown in **4**. As long as the cyclopropane ring is not further substituted, no stereochemical issues arise in **2** and **3**. In contrast, the possibility of diastereomers (*E*/*Z*-position of the amino and carboxyl group) as well as of enantiomers exists in **4**, which consequently has to be addressed in synthetic strategies toward this structure.

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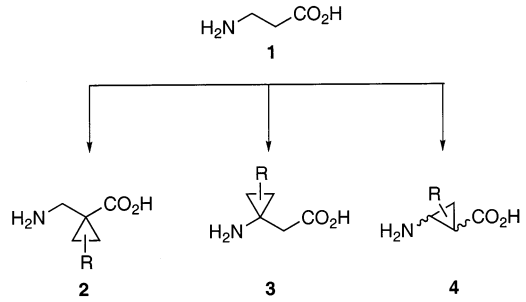
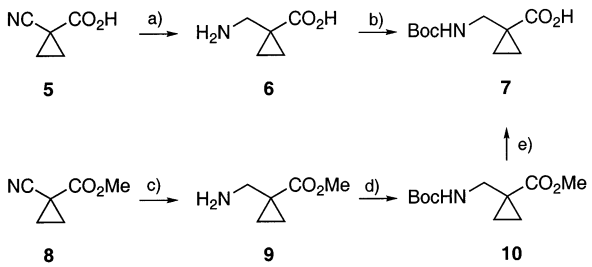
Scheme 1. Cyclopropyl-Modified β-Alanines 2−4



2. α-Cyclopropyl-Modified β-Alanines

Commercially available 1-cyanocyclopropanecarboxylic acid (**5**),[4] also easily prepared from ethyl cyanoacetate and 1,2-dibromoethane[5a−b] or from trimethylsilylacetonitrile,[5c−d] offers a simple but most effective entry into α-cyclopropyl-modified β-alanines of type **2** (Scheme 2). The cyano group can be reduced by catalytic hydrogenation in the presence of platinum dioxide to yield **6**, and subsequent protection of the amino group gives rise to the *N*-Boc-protected amino acid **7**, being suitably functionalized to be incorporated into peptides. Likewise, the methyl ester **8** can be converted to the aminoester **9** by catalytic hydrogenation over Raney-nickel, followed by *N*-Boc protection to **10** and subsequent saponification to **7**.

Scheme 2. Synthesis of α-Cyclopropyl-Modified β-Alanine 7[5,a]



[a] Reagents and conditions: (a) H_2, PtO_2, HOAc, 86%; (b) Boc_2O, NaOH, dioxane, 93%; (c) H_2, Raney-Ni, MeOH, 1 bar, r.t., 4 h; (d) Boc_2O, MeCN, NEt_3, 0 °C, 2 h, 80% (2 steps); (e) LiOH, MeOH, r.t., 3 d, 48%.

The amino acid **7** has been used in the synthesis of analogues of depsipeptides belonging to the family of the cryptophycins (**11** and **12**),[6] which exhibit high activity against a broad spectrum of solid tumors (Figure 1, Table 1). It was hypothesized that ester hydrolysis of the β-alanine unit in these molecules might be one process that would decrease their cytotoxicity. Consequently, the increase of steric bulk around the ester bond should improve stability and therefore antitumor activity. Incorporation of **6** instead of β-alanine into these structures, using standard HOBt/DCC carboxylic acid coupling methodology resulted indeed in highly active derivatives **11c**, **11d**, and **12c**, both in vitro as well as in vivo.[7] It is interesting to note that the incorporation of larger rings than cyclopropyl, such as cyclopentyl or cyclohexyl, was less well-tolerated, although the bond angles in the latter analogues are closer to the ones in the natural products.

Table 1. Cryptophycins and Cyclopropyl Analogues Exhibiting High Antitumor Activity[7]

compound **11** or **12**	R^1	R^2	X	IC_{50} (nM) **11**	IC_{50} (nM) **12**
b	Me	Me	O	0.02	0.05
c	$-(CH_2)-$	$-(CH_2)-$	O	0.16	0.014
d	$-(CH_2)-$	$-(CH_2)-$	NH	0.010	—[a]
e	Et	Et	O	1.1	1.6
f	Pr	Pr	O	8.5	8.7
g	$-(CH_2)_2-$	$-(CH_2)_2-$	O	0.3	0.4
h	$-(CH_2)_2-$	$-(CH_2)_3-$	O	63	110

[a] Not determined.

Homooligomers of **6**, up to the hexamers **16**, were prepared starting from **7** and **10** (Scheme 3).[8] X-ray crystal structures of **13**, **14a**, and **15** revealed the formation of boatlike eight-membered H-bonded rings, in which the exocyclic C−CO bonds each adopt a bisected conformation[9] with respect to the cyclopropyl moiety, which serves as an additional conformational lock in these structures (Figure 2).

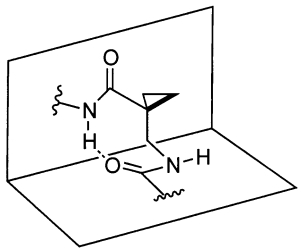
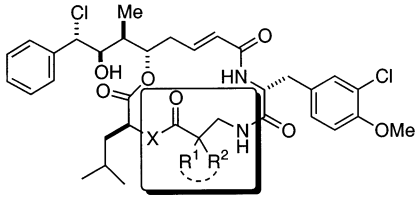
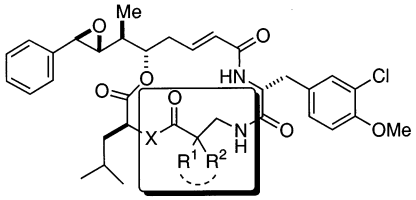


Figure 2. Boatlike eight-membered H-bonded ring in homooligomers **13**−**16**.

On the basis of this structural motif, a pleated ribbon- or stair-like structure was suggested as a model for β-peptides consisting of the building block **2** (Figure 3). It was further established that **16c** as well as β-peptides in general are stable against a broad variety of proteases, but also do not inhibit the latter.[10] Not too surprisingly, molecules specifically



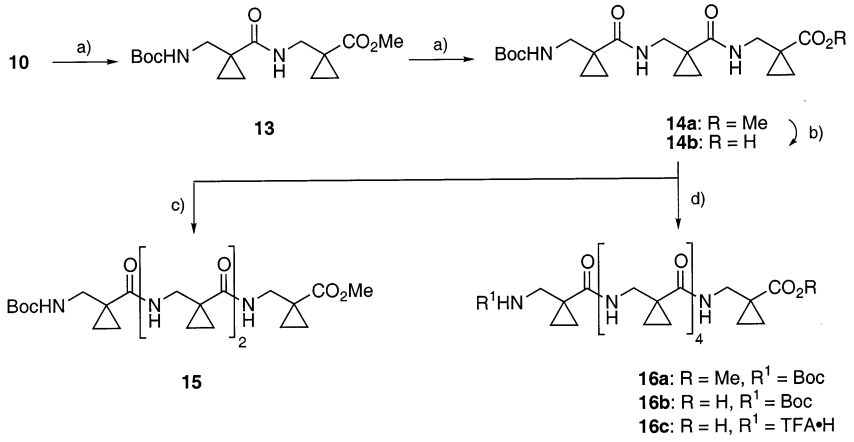
11a: R^1 = Me, R^2 = H, X = O, Cryptophycin 1
11b: R^1, R^2 = Me, X = O, Cryptophycin 52
11c - 11h: *see* Table 1



12a: R^1 = Me, R^2 = H, X = O, Cryptophycin 8
12b: R^1, R^2 = Me, X = O, Cryptophycin 55
12c - 12h: *see* Table 1

Figure 1. Cryptophycins and cyclopropyl analogues exhibiting high antitumor activity.[7]

Scheme 3. Homooligomers of α-Cyclopropyl-Modified β-Alanine 6[8,a]



[a] Reagents and conditions: (a) (i) TFA, CH_2Cl_2, 0 °C; r.t., 1.5 h. (ii) **7**, HOBt, EDC, CH_2Cl_2, NEt_3, 0 °C; r.t., 16 h, 70%. (b) LiOH, MeOH, H_2O, 79%. (c) (i) TFA, CH_2Cl_2, 0 °C; r.t., 1.5 h. (ii) **7**, HOBt, EDC, CH_2Cl_2, NEt_3, 0 °C; r.t., 16 h, 93%. (d) (i) **14a**, TFA, CH_2Cl_2, 0 °C; r.t., 1.5 h. (ii) **14b**, HOBt, EDC, DMF, NEt_3, 0 °C; r.t., 16 h, 87%.

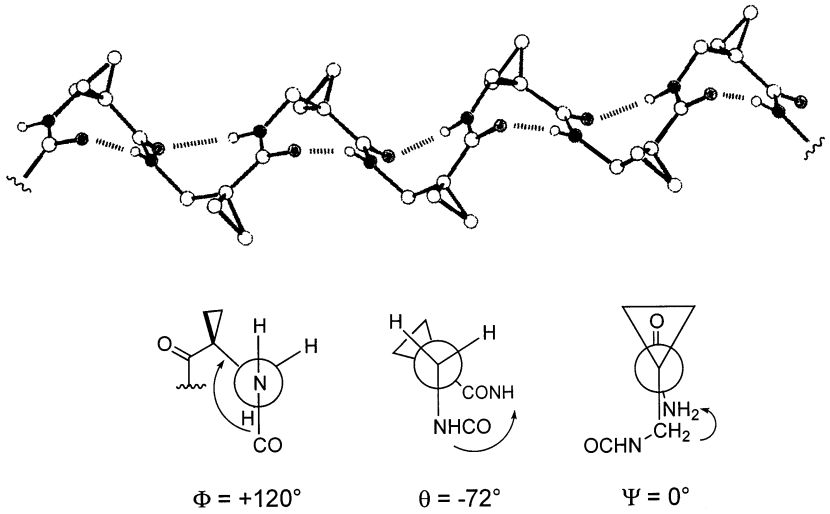
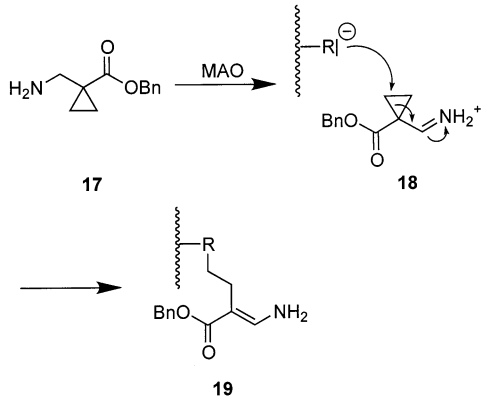


Figure 3. Model for a possible pleated-ribbon or stair-like structure of β-peptides consisting of 1-(aminomethyl)-cyclopropanecarbonyl residues; torsion angles Φ, Θ, and Ψ used for the construction of the model based on an X-ray structure of **14b**; adapted from ref 8. Copyright 1999, Wiley-VCH.

designed to interact with the world of α-peptides do not obviously recognize β-peptides.

The inherent reactivity of an acceptor-substituted cyclopropane ring toward nucleophiles was utilized in the benzyl ester **17** to inactivate the flavoenzyme monoamine oxidase (MAO) (Scheme 4),[11] a process that is linked to antidepressant[12] or anti-Parkinson[13] properties. It was proposed that MAO-induced oxidation of the aminomethyl group generates the bisactivated cyclopropane **18**, which becomes subsequently attached to the flavin coenzyme to yield a structurally modified, thus inactivated adduct **19** (Scheme 4).

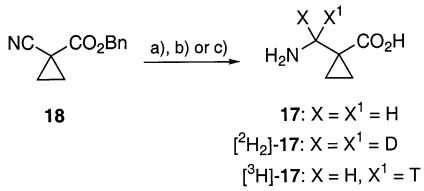
Scheme 4. α-Cyclopropyl-Modified β-Alanine 17 as an Irreversible Inhibitor of the Flavoenzyme Monoamine Oxidase (MAO)[11,14]



A detailed study[14] revealed that the oxidative modification of **17** takes place by an initial single electron transfer, followed by a rate determining α-C−H bond cleavage. To gain insight into this mechanism, derivatives of **17** labeled with ^{14}C, deuterium, or tritium isotopes in the α-position were required. While a carbon-14 label is easily introduced using ethyl ^{14}C-cyanoacetate following the protocol outlined above (cf. Scheme 2), the synthesis of the deuterium- and tritium-labeled derivatives was effectively accomplished by sodium borohydride reduction using cobalt(II)chloride as a catalyst (Scheme 5).

The inhibition of dihydroorotate dehydrogenase (DHOD), a target for chemotherapy of parasitic diseases, can be effected by 5-spirocyclopropanobarbituric acid.[15] It was envisioned that 5-spirocyclopropyldihydroorotic acid (**21**) would be the most direct

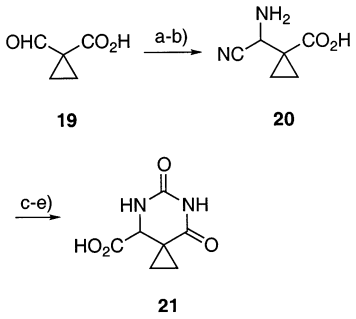
Scheme 5. Synthesis of Deuterium- and Tritium-Labeled α-Cyclopropyl-Modified β-Alanines 17[14,a]



[a] Reagents and conditions: (a) $NaBH_4/CoCl_2$.6 H_2O, MeOH, −20 °C; (b) $NaBD_4/CoCl_2 \cdot 6H_2O$, THF/D_2O, −20 °C; (c) $NaBT_4/CoCl_2 \cdot 6H_2O$, H_2O, 0 °C.

analogue containing the cyclopropane group for activation and irreversible inhibition. Its synthesis was achieved[16] by subjecting the cyclopropanecarboxaldehyde **19**[17] to a modified Strecker protocol. The resulting amino acid **20** was cyclized with sodium cyanate, followed by nitrile hydrolysis to give rise to the target compound. However, so far no data on the biological activity of **21** have been reported.

Scheme 6. Synthesis of 5-Spirocyclopropyldihydroorotic Acid (21)[16,a]

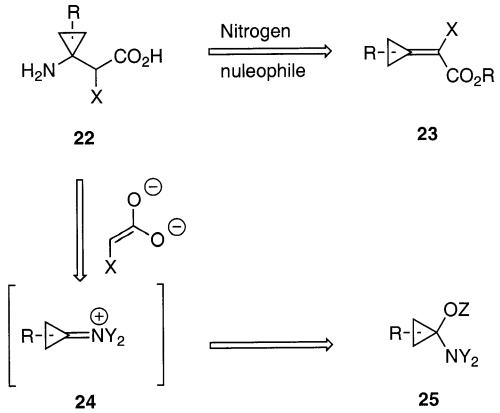


[a] Reagents and conditions: (a) TMSCN, KCN, 18-crown-6; (b) NH_3, MeOH; 50% (2 steps); (c) NaOCN, HCl aq., 78%; (d) LDA, THF, 36%; (e) 3 M HCl aq., 54%.

3. β-Cyclopropyl-Modified β-Alanines and Other β-Amino Acids with Cyclopropyl Groups

There are two general strategies toward β-cyclopropyl-modified β-alanines **22**. Cyclopropylideneacetates **23** have been proved to be highly reactive Michael acceptors, making facile 1,4-additions of nitrogen nucleophiles possible. Most notably the group of de Meijere developed this strategy,[18] utilizing the resulting amino acids as conformationally restricted building blocks for peptidomimetics, but also as bifunctional starting materials to a great variety of spiroanellated heterocycles. In an alternative approach toward **22**, cyclopropylideneiminium ions **24**, being generated in situ from cyclopropanone-N,O-acetals **25**, can be reacted with carbon nucleophiles such as enolates.

Scheme 7. Retrosynthetic Analysis of β-Cyclopropyl-Substituted β-Alanines

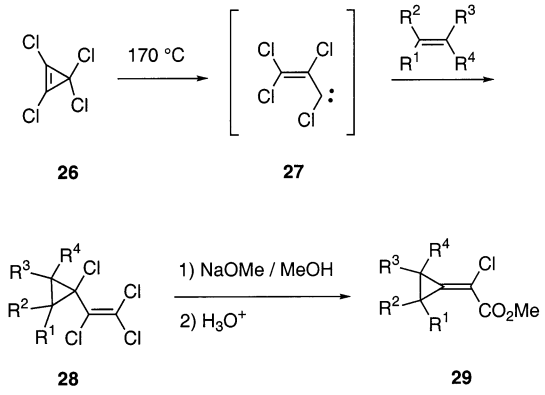


3.1. β-Cyclopropyl-Modified β-Amino Acids from Cyclopropylideneacetates

Due to its excellent reactivity toward nitrogen nucleophiles, cyclopropylideneacetates are most valuable starting materials toward the title compounds. Their synthesis can be achieved in large quantities by two general routes.

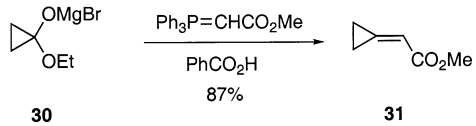
Tetrachlorocyclopropene (**26**), readily available from tetrachloroethene and sodium trichloroacetate,[19] undergoes thermal ring opening to perchlorovinylcarbene **27**, which can be efficiently trapped with a large number of alkenes to form 1-chloro-1-(trichloroethenyl)cyclopropanes **28**.[20] From these intermediates, 2-chloro-2-cyclopropylideneacetates **29** can be obtained by treatment with potassium hydoxide or sodium methoxide in methanol followed by hydrolysis of the resulting ortho esters (Scheme 8).

Scheme 8. Synthesis of Methyl 2-Chlorocyclopropylideneacetates 29 from Tetrachlorocyclopropene (26)[20]



Alternatively, the cyclopropanone hemiacetal magnesium salt **30** can be transformed to the cyclopropylideneacetate **31** by a Wittig−Horner−Emmons olefination[21] or, more efficiently, by benzoic acid-catalyzed Wittig olefination (Scheme 9).[22]

Scheme 9. Synthesis of Cyclopropylideneacetates 31 by Olefination of the Hemiacetal Magnesium Salt 30[22]



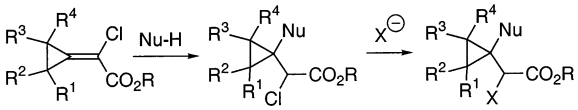
Due to the electron-withdrawing chlorine substituent in the α-position and the angle strain in the double bond caused by the attached cyclopropyl moiety, chlorocyclopropylideneacetates **29** are par-

Table 2. Addition of Nitrogen Nucleophiles to 2-Chloro-2-cyclopropylideneacetates 29 (see Scheme 10)[23]

entry	R	R^1	R^2	R^3	R^4	R^5	Nu	X	yield (%)	ref
1	Me	Me	Me	Me	Me	Cl	piperidine	piperidinyl	57	23a
2	Me	Me	Me	Me	H	Cl	piperidine	piperidinyl	67	23a
3	Me	Me	H	H	Me	Cl	piperidine	piperidinyl	59	23a
4	Me	Me	H	Me	H	Cl	piperidine	piperidinyl	51	23a
5	Me	H	H	H	H	Cl	piperidine	piperidinyl	71	23a
6	Me	Me	H	H	Me	Cl	$HNEt_2$	Cl	–	23a
7	Me	H	H	H	H	Cl	$HNEt_2$	Cl	78	23a
8	Me	Me	H	H	Me	Cl	$HNEt_2$	NEt_2	32	23a
9	Me	H	H	H	H	Cl	$HNEt_2$	NEt_2	56	23a
10	Me	Me	Me	Me	H	Cl	$HNEt_2$	OMe	30	23a
11	Me	Me	H	H	Me	Cl	$HNEt_2$	OMe	21	23a
12	Me	Me	Me	Me	Me	Cl	$HNMe_2$	NMe_2	64	23a
13	Me	Me	H	H	Me	Cl	$HNMe_2$	NMe_2	67	23a
14	Me	Me	H	H	Me	Cl	NaN_3	Cl	62	23a
15	Me	H	H	H	H	Cl	NaN_3	Cl	56	23a
16	*t*-Bu	H	H	H	H	Cl	HNPhMe	Cl	67	23b
17	Me	H	H	H	H	Cl	$HN{=}CPh_2$	Cl	98	23c/23d
18	Me	H	H	H	H	H	$HN{=}CPh_2$	H	90–100	23c
19	Et	H	H	H	H	Br	$HN{=}CPh_2$	Br	70	23c
20	Me	H	H	H	H	H	$HN{=}CPh_2$	H	40	23e
21	Me	H	H	H	H	Cl	$HN{=}CPh_2$	Cl	–	23e
22	Me	H	H	H	H	Cl	$HNBn_2$	Cl	89	23f
23	Me	H	H	H	H	Cl	$HN{=}CPh_2$	Cl	91	23f
24	Bn	H	H	H	H	Cl	$HNBn_2$	Cl	91	23f
25	Bn	H	H	H	H	Cl	$HN{=}CPh_2$	Cl	88	23f
26	Me	Me	H	H	H	Cl	$HN{=}CPh_2$	Cl	66	23d
27	Me	Me	H	H	Me	Cl	$HN{=}CPh_2$	Cl	–	23d
28	Me	H	H	H	H	Cl	$HNMe_2$	Cl	93	23g
29	Me	H	H	H	H	Cl	$HNBn_2$	Cl	88–96	23h
30	Me	H	H	H	H	Cl	H_2NBn	Cl	88–96	23h/23i
31	Me	H	H	H	H	Cl	$H_2NCH_2CO_2tBu$	Cl	88–96	23h

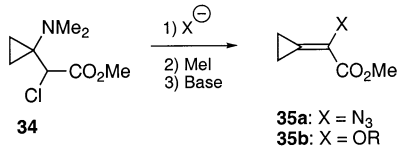
ticularly reactive toward 1,4-addition of nucleophiles. Thus, rapid addition of nitrogen nucleophiles at room temperature or below takes place (Scheme 10), giving rise to the β-amino-α-chloroacetates **32** (Table 2, entries 6, 7, 14–17, and 21–31) or to their substitution products **33** (Table 2, entries 1–5, 8–13, and 18–20) depending on the reaction conditions.[23]

Scheme 10. Addition of Nucleophiles to 2-Chloro-2-cyclopropylideneacetates 29[23]



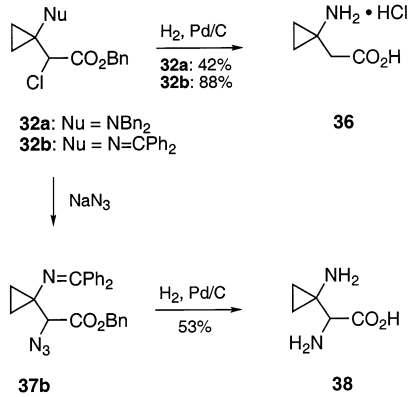
Dialkyl- or arylalkylamines, diphenylmethylideneamine, or azide can be added in a highly efficient manner. A dimethylamino or diethylamino group introduced in this way is not only a nitrogen functionality but can also be used as a leaving group, allowing the synthesis of novel cyclopropylideneacetates **35** (Scheme 11).[24]

Scheme 11. Synthesis of 2-Substituted 2-Cyclopropylideneacetates 35[24]



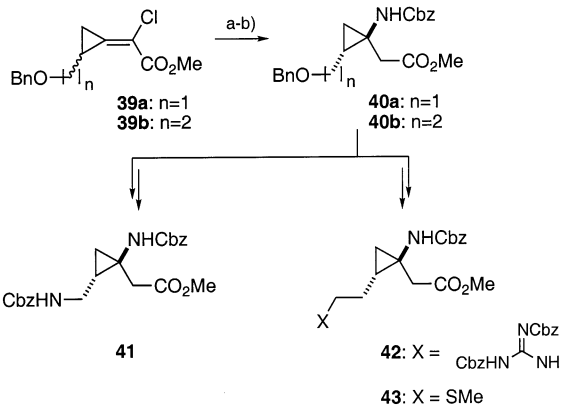
Following the strategy of nitrogen nucleophile addition to access aminocyclopropyl acetates of type **32**, it was possible to synthesize the parent alanine analogue **36** as well as the α,β-diamino acid **38** (Scheme 12).[25] It should be noted that diphenylmethylideneamine is an especially useful nitrogen nucleophile, being reactive enough in 1,4-additions to α,β-unsaturated carbonyl compounds as well as being easily cleaved subsequently to produce a free amino group.

Scheme 12. Synthesis of β-Cyclopropyl-Modified β-Alanines[25]



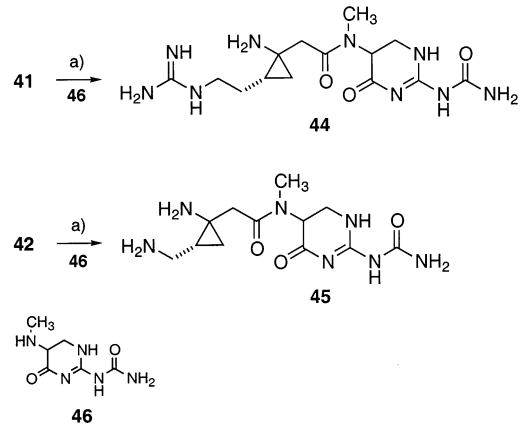
A particular useful application of this synthetic route is also the conversion of **39** to **40** (Scheme 13), not only giving rise to cyclopropyl-modified β-alanines with a serine side chain mimic, but also allowing the subsequent synthesis of the lysine mimic **41**, the arginine mimic **42**, and the cysteine mimic **43**.[26] The compounds **41** and **42** were converted to 3′,4′-methano-analogues **44** and **45** of the antiobiotics TAN-1057[27] A and B (Scheme 14).

Scheme 13. Synthesis of Cyclopropyl-Modified *β*-Alanines with α-Amino Acid Side Chain Functionality[26,a]



[a] Reagents and conditions: (a) HBn_2, MeOH, 79% ($n = 1$), 77% ($n = 2$). (b) (i) Pd/C, H_2 (4.5 bar), 4−7 d, (ii) Cbz-Cl, Na_2CO_3 aq., 48% ($n = 1$), 78% ($n = 2$).

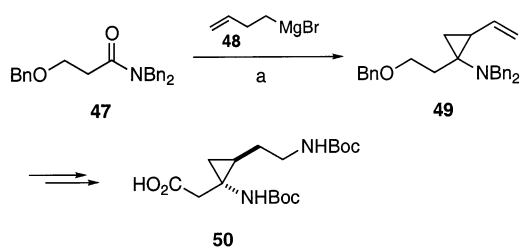
Scheme 14. Synthesis of 3′,4′-Methano-Analogues 44 and 45 of the Antiobiotics TAN-1057 A and B[26,a]



[a] Reagents and conditions: (a) (i) 2N NaOH, dioxane, 1 h, (ii) HATU, (*i*Pr)$_2$NEt, DMF, **46**, (iii) $PdCl_2$, H_2, MeOH, 93% (**44**), 66% (**45**).

The lysine mimic **50**, being a homologue of **41**, was synthesized making use of the titanium(IV)-mediated cyclopropanation of amides (Scheme 15). Starting from the *β*-benzyloxyamide **47** and homoallylmagnesiumbromide (**48**), **49** was directly obtained in good yield as a 2.5:1 mixture of *E*/*Z*-diastereomers.[28] Hydroboration of the vinyl group allowed the subsequent introduction of the amino functionality, while oxidation of the hydroxy function to the carboxylic acid completed the synthesis of **50**.

Scheme 15. Synthesis of Cyclopropyl-Modified *β*-Alanine 49 via Cyclopropanation of Amide 46[28,a]



[a] Reagents and conditions: (a) **48**, MeTi(O*i*Pr)$_3$, 12 h, THF, 56%.

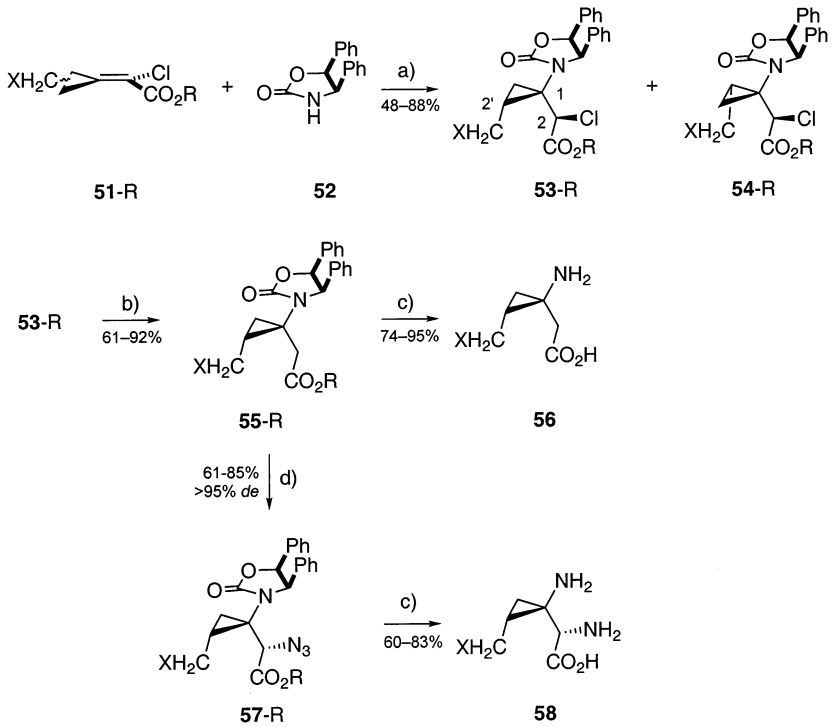
The enantioselective synthesis of *β*-cyclopropyl-modified *β*-alanines and higher homologues was achieved using (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**52**) as a chiral auxiliary (Scheme 16, Table 3).[29] Despite the fact that **52** is a poor nucleophile, in the presence of 10 mol % KH/DB-18-C-6, addition to racemic **51**-R already takes place at −20 to 0 °C with 48−88% yield, demonstrating again the high reactivity of the latter type of acrylate in 1,4-additions. Excellent trans selectivity with respect to the substitutent on the three-membered ring, but apparently also quite good diastereoselectivity with respect to the newly formed stereocenter at C-2, is observed, although selectivities in the latter case were difficult to establish. The resulting diastereomers **53**-R and **54**-R can be separated by chromatography, thus allowing the resolution of the racemic starting material due to the stereogenic center at C-2′, and further individual transformation as exemplified with **53**-R. Dehalogenation with zinc−copper couple, removal of the chiral auxiliary by catalytic hydrogenation and saponification leads to the free amino acid **56**. Alternatively, the lithium enolate of **55**-R can be highly diastereoselectively (≥19:1) substituted with trisyl azide, giving rise to enantiomerically pure diamino acids **58** after removal of the protecting groups. The amino acids obtained by this strategy appear to be useful as conformationally restricted building blocks for peptides with the added bonus of side chains of naturally occurring α-amino acids being attached to the cyclopropyl group, mimicking serine (Table 3, entries 5−7), cysteine (Table 3, entry 8), or lysine (Table 3, entry 9).

Table 3. Addition of (4*S*,5*R*)-4,5-Diphenyloxazolidin-2-one (52) to Racemic Cyclopropylideneacetates 51-R (See Scheme 16)[29]

entry	**51**-R R	**53**-R/**54**-R X	yield (%)
1	Me	H	73
2	Bn	H	48
3	Me	Me	64
4	Bn	Me	79
5	Me	OMe	68
6	Bn	OMe	69
7	Me	OBn	57
8	Me	SMe	59
9	Me	NHCbz	88

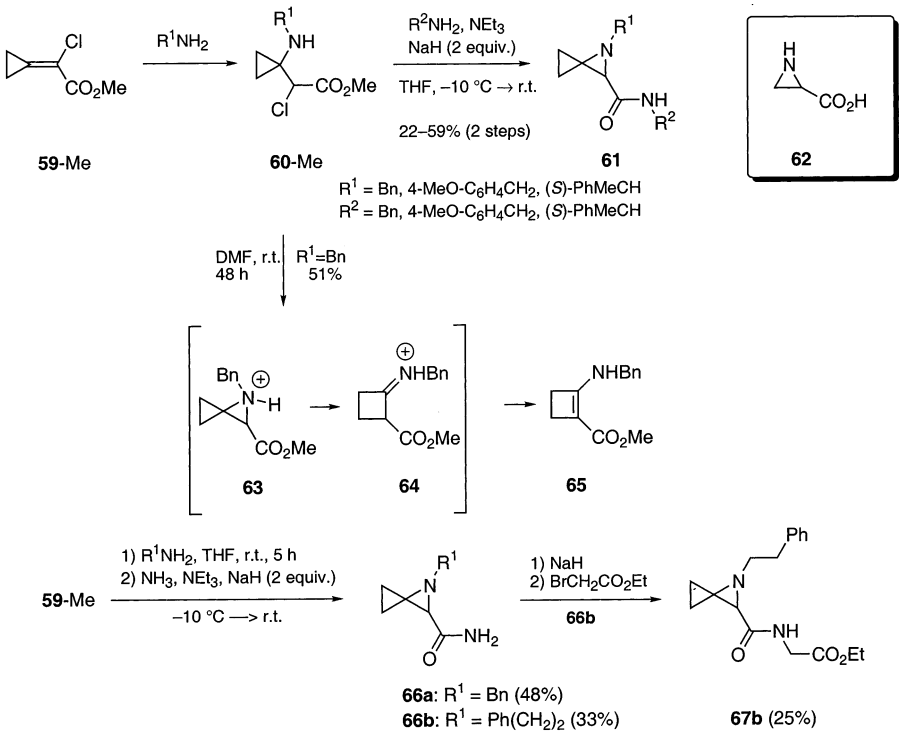
Rather than participating in intermolecular substitutions, a secondary amino group in compounds of type **32** can also act as a nucleophile intramolecularly. This way, spirocyclopropane derivatives **61** of aziridinecarboxylic acid (**62**), which has been used as a unique conformationally restricted amino acid in peptidomimetics, become accessible (Scheme 17).[30] However, for the success of this synthesis it was necessary to discover that the carboxamide functionality in **61** greatly enhances the stability of the azaspiropentane ring system. Simple stirring of the esters **60**-Me in DMF at room temperature results in the predominant formation of 2-aminocyclobutenecarboxylates of type **65**. However, the ring closure of **60**-Me to yield **61** can be achieved by treatment of **60**-Me with a combination of a primary amine, triethylamine, and sodium hydride, thus presumably first transforming the methyl ester to the corresponding amide before the intramolecular nucleo-

Scheme 16. Asymmetric Synthesis of β-Cyclopropyl-Modified β-Amino Acids 56 and 58 (For Details, See Table 3)[29,a]



[a] Reagents and conditions: (a) (i) DB-18-C-6, THF, 10 mol % KH, −20 → 0 °C, 4−12 h. (ii) Separation by chromatography. (b) Zn/Cu, THF/H_2O (100:1), 12 h. (c) (i) 4 bar H_2, 10% Pd/C, MeOH, H^+. (ii) NaOH, Dowex 50. (d) (i) LiHMDS, THF, trisyl azide, −78 °C. (ii) CH_3CO_2H, r.t.

Scheme 17. Synthesis of 1-Azaspiropentane-2-carboxamides[30]

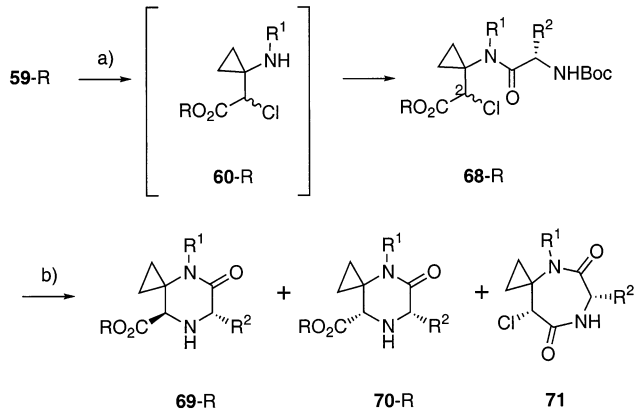


philic substitution takes place. Alternatively, the direct spiroaziridination of cycloalkylidene acetates with larger than three-membered rings under high pressure has also been developed.[31]

Following the protocol by de Meijere et al.,[30] the primary amides **66** are obtained when ammonia is used for the second step, thus opening the possibility to incorporate the carboxy-terminus of **66** into peptides as suggested with the successful synthesis of **67b**. However, all attempts to deprotect the *N*-terminus in the azaspiropentane unit have failed so far.

The *N*-alkylated amine adducts **60**-R can also efficiently be used in cyclization reactions to yield spirocyclopropane-anellated four, five-, six-, and seven-

Scheme 18. Six-Membered Ring Amino Esters 69-R/70-R and Seven-Membered Ring Lactams 71 Obtained from 59-R (For Details, See Table 4)[32,a]



[a] Reagents and conditions: (a) (i) R^1NH_2, THF, 0 °C, (ii) NBoc-amino acid, DCC, py, THF; (b) (i) TFA, CH_2Cl_2, 0 °C, (ii) $NaHCO_3$ (aq.), CH_2Cl_2, 0 °C.

Table 4. Six-Membered Ring Amino Esters 69-R/70-R and Seven-Membered Ring Lactams 71 Obtained from 59-R (see Scheme 15)[32]

				yield[a] (%)		
entry	R	R^1	R^2	**69**-R	**70**-R	**71**
1	Me	*n*-pentyl	H	22	—[b]	60
2	Me	2-furfuryl	H	n.r.[c]	—[b]	55
3	Me	Bn	H	18	—[b]	60
4	Me	4-$MeOC_6H_4CH_2$	H	n.r.[c]	—[b]	53
5	Me	4-$ClC_6H_4CH_2$	H	n.r.[c]	—[b]	61
6	Me	$PhCH_2CH_2$	H	18	—[b]	63
7	*t*-Bu	$PhCH_2CH_2$	H	61	—[b]	0
8	Me	Me	Bn	20	2	19
9	Me	Me	(indol-3-yl)CH_2	21	2	22
10	Me	Me	$(CH_2)_2SMe$	n.r.[c]	0	20
11	Me	Me	*i*-Bu	n.r.[c]	0	19

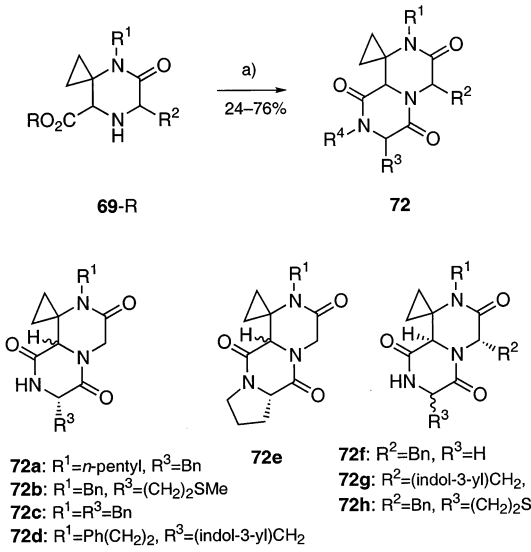
[a] Overall yields from **59**-R. [b] Not applicable. [c] Not reported.

membered rings, leading to interesting templates for peptidomimetics or analogues of natural products.

Starting from **59**-R, the addition of an amine followed by the acylation with an amino acid can be carried out in a one-pot procedure to yield **68**-R almost quantitatively (Scheme 18, Table 4).[32] After removal of the *N*-Boc protecting group, cyclization takes place, leading predominantly to the seven-membered ring lactams **71** for R = Me and R^2 = H. The six-membered ring amino ester **69**-*t*Bu was obtained exclusively (Table 4, entry 6) by using the *t*-butyl ester **59**-*t*Bu as starting material, thus preventing lactamization due to steric hindrance. A quite remarkable kinetic resolution takes place when chiral amino acids ($R^2 \neq$ H) were used in this sequence. While in the initial addition to yield **68**-R no induction at C-2 is observed, the (2*S*)-isomer cyclizes exclusively to the amino ester **69**-R, while the (2*R*)-isomer forms mainly the chlorolactams **71** along with only traces of **70**-R.

A broad variety of geometrically defined bi- and tricyclic small peptides **72** can be obtained by a second coupling/cyclization sequence carried out with **69**-Me and *N*-Boc amino acids (Scheme 19).[32a] Although in the case of the highly complex diketopiperazines **72f**−**72h** only moderate yields are achieved and forcing reaction conditions are necessary, resulting in partial epimerization at the position of R^3, this strategy opens the possibility for the rapid assembly of a variety of peptide β-turn mimetics.[33]

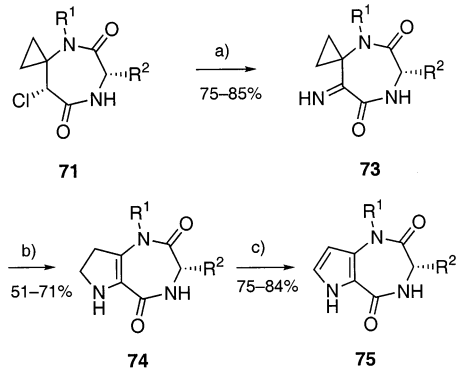
Scheme 19. Confromationally Restricted, Small Bi- and Tricyclic Peptides 72[32a,a]



[a] Reagents and conditions: (a) (i) (*S*)-$HO_2CCHR^3NR^4Boc$, DCC or EDC, py, CH_2Cl_2, (ii) TFA, CH_2Cl_2, 0 °C, (iii) DMF, 60−130 °C.

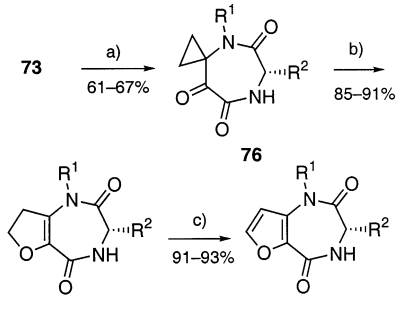
The chlorolactams **71** can be efficiently converted to heteroarene-anellated [1,4]-diazepinediones **75** and **78** utilizing the Cloke rearrangement[34] of cyclopropylketimines **73** (Scheme 20) and cyclopropyl ketones **76** (Scheme 21).[32b]

Scheme 20. Synthesis of Pyrrolo[3,2-*e*][1,4]-diazepinediones 75[32b,a]



[a] Reagents and conditions: (a) NaN_3, DMSO, 80−90 °C, 5 h; (b) $<5 \times 10^{-5}$ mbar, 170−220 °C, 30−60 min; (c) DDQ, $CHCl_3$, 40 °C, 16 h.

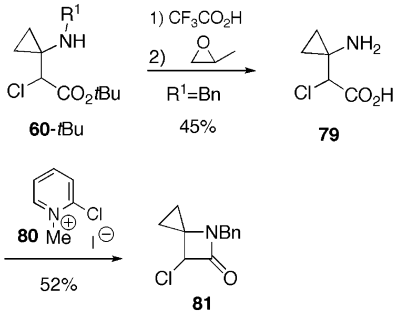
Scheme 21. Synthesis of Furo[1*H*][1,4]-diazepinediones 78[32b,a]



[a] Reagents and conditions: (a) HCl aq., MeOH, 2 h; (b) $<5 \times 10^{-5}$ mbar, 200 °C, 30 min; (c) DDQ, $CHCl_3$, reflux, 72 h.

The synthesis of a spirocyclopropane anellated β-lactam has also been accomplished starting from **60**-*t*Bu (Scheme 22).[35] Upon liberation of the amino acid **79** using nonbasic conditions, cyclization to **81** was successful using 2-chloro-1-methylpyridinium iodide (**80**) as condensing agent.

Scheme 22. Formation of Spirocyclopropane Anellated β-Lactam 81[35]



A very useful variant of the addition of nitrogen nucleophiles to chlorocyclopropylideneacetates is their direct reaction with amides **83** (Scheme 23, Table 5),

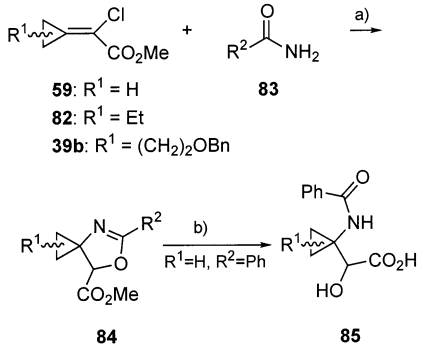
Table 5. Addition of Amides 83 to Chlorocyclopropylideneacetates[36]

entry	cyclopropylidene–acetate	amide R^2	**83** yield (%)	dr
1	**59**	Ph	60	—[a]
2	**59**	3-C_5H_4N[b]	38	—[a]
3	**59**	2-C_4H_3O[c]	49	—[a]
4	**59**	*p*-CN-C_6H_4	74	—[a]
5	**59**	*o*-Me-C_6H_4	70	—[a]
6	**59**	*m*-Me-C_6H_4	58	—[a]
7	**59**	*p*-Me-C_6H_4	50	—[a]
8	**59**	*m*-F-C_6H_4	75	—[a]
9	**59**	*p*-Br-C_6H_4	73	—[a]
10	**59**	*o*-NO_2-C_6H_4	47	—[a]
11	**59**	*p*-NO_2-C_6H_4	47	—[a]
12	**59**	*o*-Cl-C_6H_4	77	—[a]
13	**59**	*p*-Cl-C_6H_4	68	—[a]
14	**59**	*o*-I-C_6H_4	72	—[a]
15	**59**	*m*-I-C_6H_4	49	—[a]
16	**82**	Ph	56	9:1
17	**82**	*o*-Me-C_6H_4	68	17:1
18	**82**	*o*-I-C_6H_4	55	17:1
19	**82**	*p*-NO_2-C_6H_4	40	2:1
20	**82**	*m*-F-C_6H_4	46	7:1
21	**82**	3-C_5H_4N[b]	25	5:1
22	**39b**	*p*-NO_2-C_6H_4	41	2:1
23	**59**	Me	6	—[a]
24	**59**	Et	24	—[a]
25	**59**	*n*-Pr	24	—[a]
26	**59**	*t*-Bu	25	—[a]

[a] Not applicable. [b] Nicotinic acid amide. [c] Furan-2-carboxamide.

ultimately opening a very short route to α-hydroxy-β-cyclopropyl-modified β-alanines **85**.[36] Initially, the oxazoline carboxylates **84** are formed, introducing both the amino and the hydroxy functionality through the amide. Aromatic amides **83** give superior results in these formal cycloaddition reactions (entries 1−22), moreover, they add to ring-substituted chlorocyclopropylideneacetates **82** or **39b** with moderate to high trans selectivity (entries 16−22).

Scheme 23. Synthesis of α-Hydroxy-β-cyclopropyl-Modified β-alanines 85[36,a]



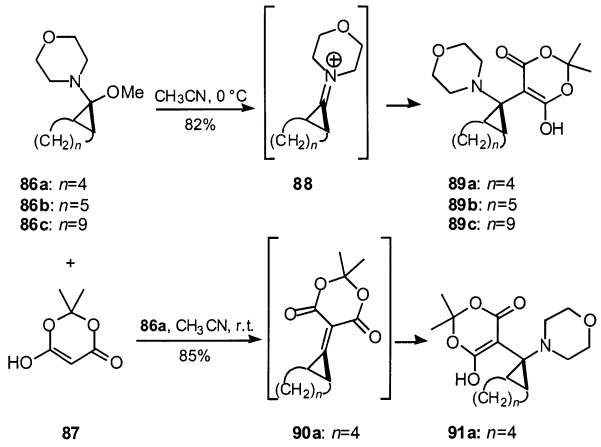
[a] Reagents and conditions: (a) NaH, MeCN, 0 → 20 °C, 24 h; (b) (i) 1N HCl, 100 °C, 30 min, (ii) 5 N NaOH, PhCOCl, 0 °C, 2 h, 70% over 2 steps.

3.2. β-Cyclopropyl-Modified β-Alanine Derivatives from Cyclopropanone-N,O-acetals

As an alternative to the addition of nitrogen nucleophiles to cyclopropylideneacetates, the coupling of enolates with cyclopropanone-N,O-acetals offers an efficient way to the title compounds. Early on, Vilsmeier et al. executed this strategy with morpholino-substituted bicyclo[*n*.1.0]alkanes, which undergo clean reactions with sufficiently C,H-acidic compounds.[37]

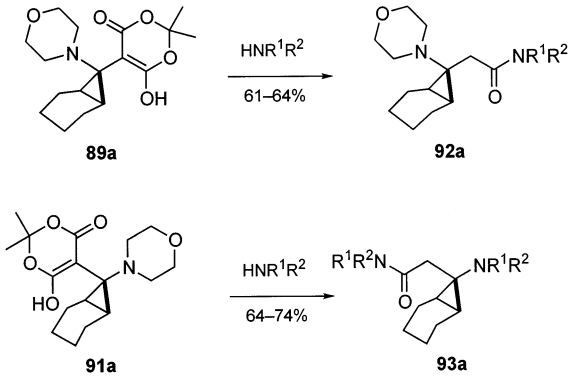
In particular, **86** reacts with Meldrum's acid (**87**) at 0 °C to give **89** in high yields (Scheme 24). The

Scheme 24. Aminobicycloalkyl Meldrum's Acid Derivatives[37]



stereochemical outcome of this transformation can be rationalized by assuming the formation of the intermediate iminium cation **88**, which is attacked by **87** from the sterically less hindered exo face of the bicyclic system. Consequently, to account for the reversal of stereoselectivity by carrying out the reaction at room temperature, as demonstrated with **86a**, it is assumed that elimination of morpholine in **89a** can take place to give rise to **90a**, which is again attacked from the exo face by morpholine to ultimatively lead to the thermodynamically favored product **91a**. The Meldrum's acid residue can be efficiently degraded to a carboxylic acid or carboxamide functionality, e.g., treatment of **89a** or **91a** with a wide variety of amines leads to the amides **92a** or **93a**, respectively (Scheme 25).[38] Only in the latter case, an additional substitution of the morpholino group by amine takes

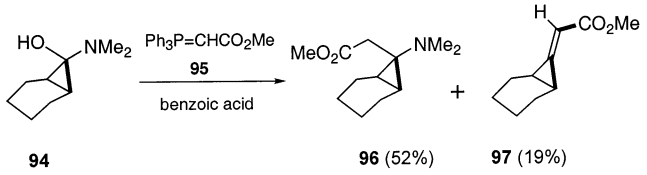
Scheme 25. Synthesis of Bicyclic β-Cyclopropyl-Modified β-Alanine Amides[38]



place, again most likely via the intermediate **90a**. Once the Meldrum's acid unit is degraded, no further exchange with amines, e.g., in **93a**, was observed.

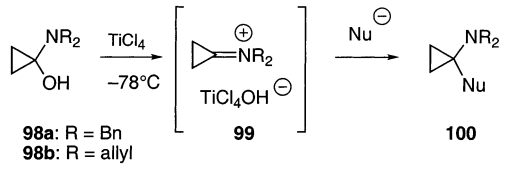
In a related approach, the reaction of the N,O-hemiacetal **94** with the stabilized ylide **95** in the presence of catalytic amounts of benzoic acid leads to the amino ester **96** (Scheme 26).[39] This product is formed by a 1,4-addition of dimethylamine, being liberated from **94**, to the bicyclic cyclopropylideneacetate **97**.

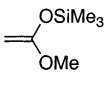
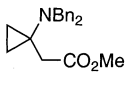
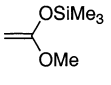
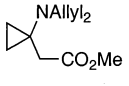
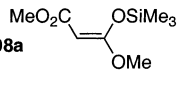
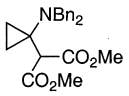
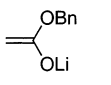
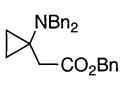
Scheme 26. Synthesis of the Bicyclic β-Cyclopropyl-Modified β-Alanine Ester 96[39]



The coupling of enolates with cyclopropyliminium ions also offers an efficient entry to β-cyclopropyl-modified β-alanines (Scheme 27).[40] Treatment of the N,O-acetals **98** with $TiCl_4$ generates an iminium ion best described as **99**, which reacts in moderate yields with ketene silyl acetals or lithium ester enolates to the amino esters **100**.

Scheme 27. Ti(IV)-Mediated Reactions of N,O-acetals 98 and Ketene Silyl Acetals or Lithium Ester Enolates[40]

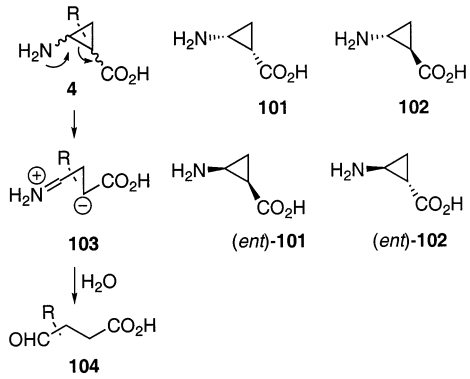


Starting Material	Nu	Product	Yield (%)
98a			57
98b			40
98a			56
98a			40

4. 2-Aminocyclopropanecarboxylic Acids (β-ACCs)

The bridging of the carbon atoms in β-alanine bearing the amino and the carboxylic acid functionality by a methylene group creates the most severely conformationally restricted β-alanine analogues that can be envisioned. Therefore, the 2-aminocyclopropanecarboxylic acids (β-ACCs) **4** appear to be attractive as constituents of peptides; however, their synthesis and utilization as building blocks in peptide synthesis poses a number of challenges. In contrast to the cyclopropyl-modified amino acids discussed so far, even the parent 2-aminocyclopropanecarboxylic acid contains two stereogenic centers, giving rise to cis/trans diastereomers **101** and **102**, which each exist as a pair of enantiomers **101**/(*ent*)-**101** and **102**/(*ent*)-**102**, respectively (Scheme 28). Moreover, β-ACCs **4** belong to the class of vicinally donor−acceptor substituted cyclopropanes,[41] which are extremely prone to undergo ring opening, resulting in their degradation as exemplified in the sequence **4**→**103**→**104**. Therefore, they are generally only stable if the amino group is protected by at least one electron-withdrawing group.

Scheme 28. Stereoisomers and Inherent Reactivity of 2-Aminocyclopropanecarboxylic Acids

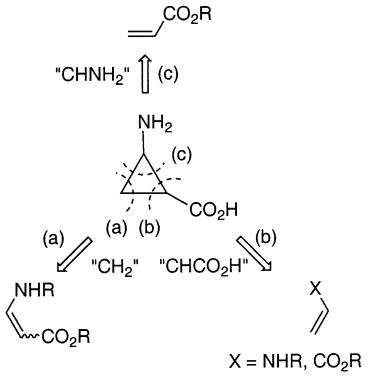


4.1. Synthesis of 2-Aminocyclopropanecarboxylic Acids (β-ACCs)

The common strategy toward β-ACCs is the direct cyclopropanation of a suitably functionalized alkene with a carbene or a carbenoid, mostly generated in situ from a diazo compound. Nucleophilic addition to an alkene with an electron-withdrawing group (EWG) and concurrent 1,3-elimination is also possible, requiring a suitable leaving group either on the nucleophile or in γ-position to the EWG of the alkene. The stepwise synthesis of starting materials, being appropriately functionalized to undergo base-induced 3-*exo*-tet ring closure, has also been executed toward β-ACC derivatives.[42]

In principle, three different approaches toward the parent structure from acyclic starting materials are possible, which indeed all have been successfully realized (Scheme 29): (a) (formal) addition of a carbene to a β-dehydroamino acid, requiring the efficient and ideally stereoselective synthesis of the latter; (b) (formal) addition of a carbene, bearing a carbonyl group, to an enamine or to an acrylate, subsequently transforming in the latter case one of the carboxyl groups to an amino group by a Curtius degradation, or (c) (formal) addition of a *N*-substituted carbene to an acrylate.

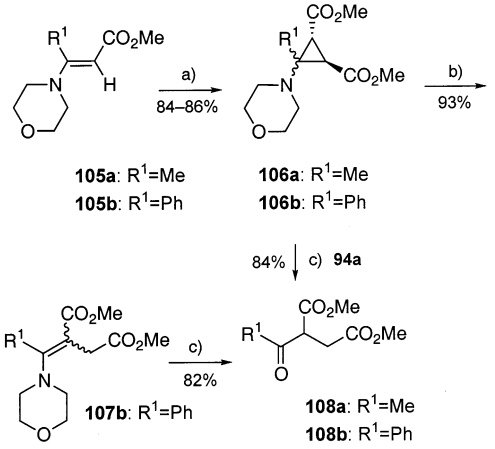
Scheme 29. Retrosynthetic Analysis of β-ACCs



4.1.1. β-ACCs from β-Dehydroamino Acids

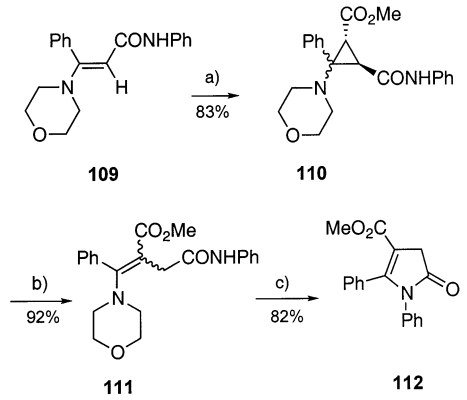
Copper(I)-catalyzed[43] cyclopropanations with diazoacetates of acyclic enaminoesters **105** and enaminocarboxanilide **109** proceed in high yields to the β-ACC derivatives **106** and **110**, respectively (Schemes 30 and 31).[44] Already on contact with dry silica, ring opening to **107** and **111** occurs, leading to the ketoester **108** and the pyrrolidone **112** upon hydrolysis. The delicate balance of the stability of 2-aminocyclopropanecarbonyl compounds became evident from the fact that the analogous cyclopropanation of enaminoketones immediately led to ring-opened products.

Scheme 30. Cyclopropanation of Acyclic Tertiary Enaminoesters 93[44,a]



[a] Reagents and conditions: (a) $Cu(acac)_2$ (3 mol %), ethyl acetate, 80 °C, $N_2{=}CHCO_2Me$; (b) silica gel, ethyl acetate; (c) HCl aq., CH_2Cl_2.

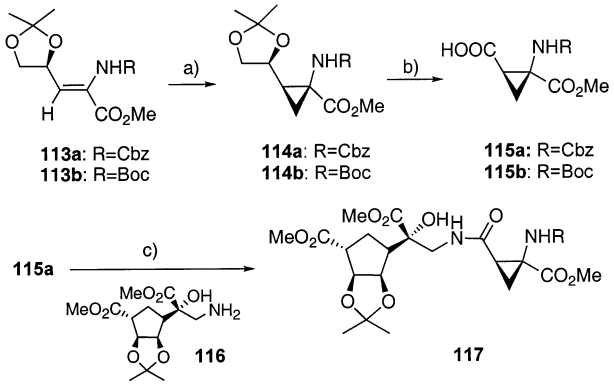
Scheme 31. Cyclopropanation of Acyclic Tertiary Enaminocarboxanilide 97[44,a]



[a] Reagents and conditions: (a) $Cu(acac)_2$ (3 mol %), ethyl acetate, 80 °C, N_2CHCO_2Me; (b) silica gel, ethyl acetate; (c) HCl aq., CH_2Cl_2.

Cyclic aspartic acid analogues **115** were obtained in a highly stereoselective manner from the masked β-dehydroamino acid **113**, readily available from glyceralaldehyde in both enantiomeric forms.[45] Cyclopropanation of **113** was achieved by 1,3-dipolar cycloaddition of diazomethane followed by photochemical extrusion of nitrogen from the corresponding intermediate pyrazolines (Scheme 32). Remarkable is not only the high yield (75−100%), but also the perfect 1,2-stereoinduction[46] with which this transformation takes place. The aminoester **115** was further transformed to the highly constrained peptide surrogate **117**.

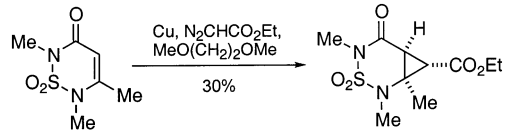
Scheme 32. Synthesis and Application of Cyclo-Asp Derivatives 115[46,a]



[a] Reagents and conditions: (a) CH_2N_2, *hν*, 100%; (b) (i) HCl, MeOH, (ii) $RuO_2{\cdot}xH_2O$, $NaClO_4$, 63%; (c) **116**, EDC, HOBt, CH_2Cl_2, 87%.

Cyclopropyl-modified pyrimidine nucleosides have found widespread interest for application as antivirus and anticancer agents.[47] Thus, copper-catalyzed cyclopropanation of thiadiazinone **118** with ethyl diazoacetate proceeds to the bicyclic system **119** with complete exo selectivity (Scheme 33).[48] The relatively low yield of 30% in which **119** was isolated is most likely due to the use of copper bronze for the generation of the carbene. Only more recently the much higher activity of copper(I) triflate for the decomposition of diazoacetates was discovered, which is today

Scheme 33. Cyclopropanation of Thiadiazinone 118[48]

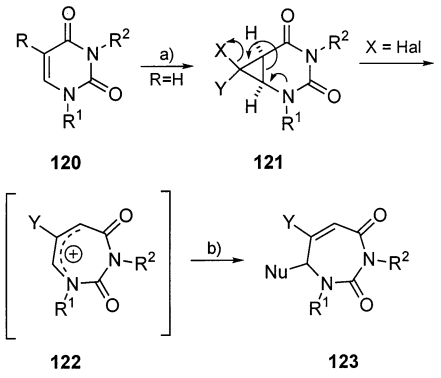


118 119

the copper salt of choice for cyclopropanation reactions. Not surprisingly, **119** is a stable compound due to the electron withdrawing sulfonyl group on nitrogen.

Likewise, addition of dihalocarbenes (Scheme 34, Table 6, entries 6−9 and 11−13), generated from the corresponding phenylmercurymethyl trihalides, to uridines **120** proceeds in good yields to the adducts **121**.[49] Assisted by the nitrogen donor and the carboxy acceptor on the three-membered ring, in the presence of nucleophiles, the 7-halo-substituted bicyclo[4.1.0]-heptanes undergo facile electrocyclic ring opening with concurrent expulsion of the endo halogen,[50] leading to 1,3-diazepinediones **123**.[51] The cyclopropanation of **120** via thermal decomposition of ethyl diazoacetate gave inferior results (Table 6, entries 1−5 and 10).

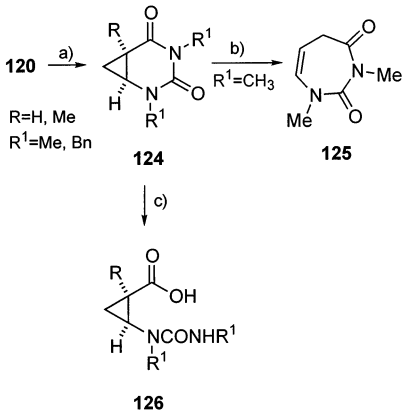
Scheme 34. Cyclopropanation of Uridines 120 and Ring Enlargement to 1,3-Diazepinediones 123[49,51,a]



120 121 122 123

[a] Reagents and conditions: (a) carbene source (see Table 6), DMF, Δ*T*; (b) MeOH, 110 °C, sealed tube, 5 h, 5−30%.

Scheme 35. Cyclopropanation of Uridines 120 with Dimethylsulfoxonium Methylide[52,a]



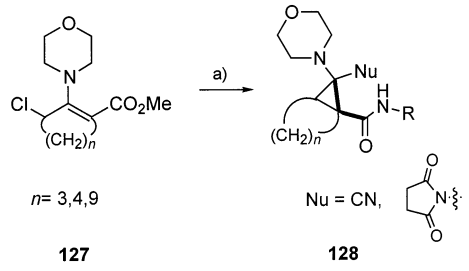
124 125 126

[a] Reagents and conditions: (a) trimethylsulfoxonium chloride, NaH, THF, reflux, 58−66%; (b) *hν*, 45%; c) NaOH, H_2O, r.t., 83−98%.

Cyclopropanation of **120** was also successfully carried out with dimethylsulfoxonium methylide to give rise to thymine mimics **124**, which can not only be photochemically rearranged to 1,3-diazepinediones **125**, but also hydrolyzed to the cis-*β*-ACC derivatives **126** in excellent yields (Scheme 35).[52] In this approach the amino group is part of a urea moiety, which prevents ring opening of the cyclopropane.

The cyclic chloroenamines **127** can elegantly be converted to *β*-ACC derivatives **128** by a domino 1,4-addition-cyclization sequence (Scheme 36). Addition

Scheme 36. Domino 1,4-Addition−Cyclization Sequence to *β*-ACCs 128[53,a]

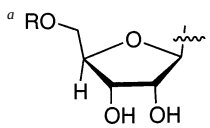


127 128

[a] Reagents and conditions: (a) NaCN, (nBu$_4$)Cl, H_2O, 65%, or succinimide, MeCN/H_2O, 60 °C, 32−84%.

Table 6. Addition of Carbenes to Uridines 120[49,51]

						yield (%)	
entry	R^1	R^2	carbene source	X	Y	exo	endo
1	Me	Me	N_2CHCO_2Et	CO_2Et	H	43	29
2	$PhCH_2$	$PhCH_2$	N_2CHCO_2Et	CO_2Et	H	27	14
3	$PhCH_2OCH_2$	Me	N_2CHCO_2Et	CO_2Et	H	7	7
4	$Ph(CH_2)_3$	Me	N_2CHCO_2Et	CO_2Et	H	23	40
5	$PhCH_2OCH_2$	$PhCH_2$	N_2CHCO_2Et	CO_2Et	H	4	2.5
6	$PhCH_2$	$PhCH_2$	$PhHgCBrCl_2$	Cl	Cl	80	
7	$PhCH_2$	$PhCH_2$	$PhHgCBr_3$	Br	Br	38	
8	$PhCH_2$	$PhCH_2$	$PhHgCCl_2F$	Cl	F	38	43
9	AcRib[a]	H	$PhHgCBrCl_2$	Cl	Cl	72	
10	CH_2CO_2EtRib[a]	H	N_2CHCO_2Et	CO_2Et	H	0	<5
11	AcRib[a]	Me	$PhHgCBrCl_2$	Cl	Cl	50−70	
12	AcRib[a]	Me	$PhHgCBr_3$	Br	Br	50−70	
13	AcRib[a]	Me	$PhHgCCl_2F$	Cl	F	50−70	

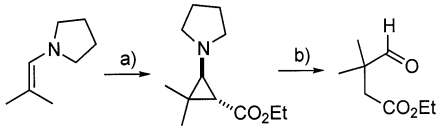
[a]  R=Ac, CH_2CO_2Et

of cyanide[53] or succinimide[54] proceeded with high stereoselectivity, placing the nucleophile on the exo side of the bicyclic framework. Quite instructively, the amino function in **128** is not protected by an acceptor group; nevertheless, the geminally located electron-withdrawing group obviously is sufficient to render the molecules stable.

4.1.2. β-ACCs from Enamines

Initially, the cyclopropanation of enamines with diazoacetates did not appear to be an efficient route toward β-ACCs. An early example was reported by Wenkert et al.[55] in which the β-ACC derivative **130** could be isolated starting with **129** as a single diastereomer, albeit only in 14% yield. Upon exposure to HCl, the γ-formylester **131** was obtained (Scheme 37).

Scheme 37. Cyclopropanation of 2-Methyl-1-pyrrolidinylpropene (129)[55,a]

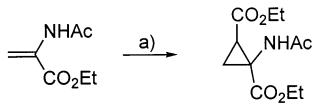


129 **130** **131**

[a] Reagents and conditions: (a) ethyl diazoacetate, CuCl, hexane, reflux, 14%; (b) HCl, EtOH, H_2O, no yield given.

Also, the reaction of α,β-dehydroalaninate **132** with ethyl diazoacetate initiated by copper led only in low yield to **133** as a single isomer of undetermined configuration (Scheme 38).[56]

Scheme 38. Cyclopropanation of α,β-Dehydroalaninate 132[56,a]



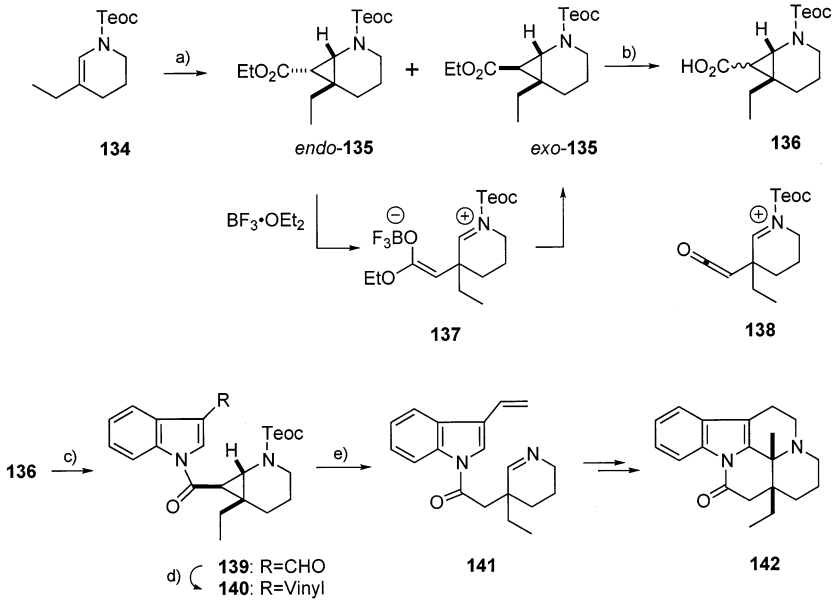
132 **133**

[a] Reagents and conditions: (a) N_2CHCO_2Et, Cu, CH_2Cl_2, 55 °C, 12.5%.

Nevertheless, under more forcing conditions, copper bronze was shown to be quite effective as a catalyst for the cyclopropanation of the enamine **134** with ethyl diazoacetate (Scheme 39).[57] Without a solvent and at a reaction temperature of 135 °C, **135** was obtained in 64% yield as a mixture of exo and endo isomers in almost equal amounts. The diastereomers could be separated by chromatography, but more interestingly, it was discovered that upon treatment with boron trifluoride etherate *endo*-**135** can be converted to *exo*-**135**, most likely via the zwitterion **137**. Saponification of **135** leads to the carboxylic acid **136**, which upon activation as its acid chloride reacted with indole-3-carboxaldehyde. No matter whether *endo*-**136** or *exo*-**136** was employed in this amide coupling, only the exo isomer **139** was obtained, suggesting that isomerization via the ketene **138** had taken place. After alkenylation of **139**, ring opening of **140** was achieved by removal of the Teoc group with fluoride to give rise to **141**, which served as a precursor to the alkaloid (±)-eburnamonine (**142**).

The bistrimethylsilyl-protected enamine (*E*)-**143** was found to undergo cyclopropanation to **144** with methyl diazaoacetate in high yields if copper(II) acetylacetonate[43] was employed as a catalyst (Scheme 40).[58] Good trans selectivity was observed, and using the chiral copper catalyst **146**, moderate enantioselective (trans-**144**, 20% *ee*; cis-**144**, 56% *ee*) induction was achieved. In contrast, the corresponding *(Z)*-**143** failed to give a cyclopropanation product, and moreover, dirhodiumtetraacetate, usually a most successful cyclopropanation catalyst, failed completely in these transformations. Not surprisingly, deprotection of the amino group in **144** was not possible without destruction of the cyclopropane moiety, but after reduction of the ester group, the amino alcohol **145** could be obtained in good yields. However, with **144**

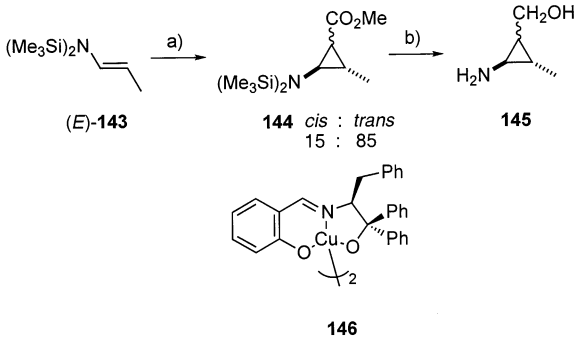
Scheme 39. β-Acc 135 as Key Intermediate for the Synthesis of (±)-Eburnamonine (142)[59,a]



134 *endo*-**135** *exo*-**135** **136** **137** **138** **141** **142**

[a] Reagents and conditions: (a) Cu-bronze, N_2CHCO_2Et, 135 °C, 64%; (b) NaOH, EtOH, H_2O, THF (3:1:1), r.t., 66%-quant.; (c) (i) $(COCl)_2$, NEt_3, Et_2O, (ii) indole-3-carboxaldehyde, LDA, THF, −78 °C, 52%; (d) NaHMDS, Ph_3PCH_3Br, 86%; (e) $Bn(Me)_3NF$, THF, sieves, 45°C, 81%.

Scheme 40. Cyclopropanation of Bistrimethylsilyl-Protected Enamines[58,a]

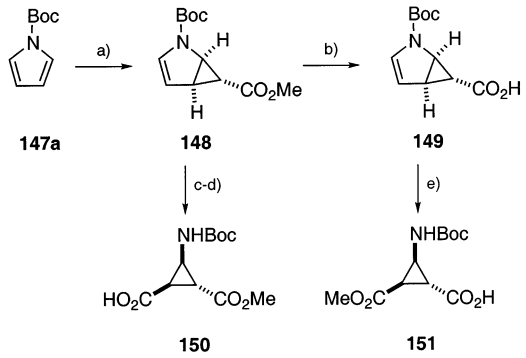


[a] Reagents and conditions: (a) N_2CHCO_2Me, $Cu(acac)_2$, $Cl(CH_2)_2Cl$, 80 °C, 77%; (b) (i) $LiAlH_4$, THF, r. t., 90%, (ii) MeOH, reflux, 86%.

it was demonstrated for the first time that the amino function in a β-ACC can be liberated in situ, thus allowing peptide coupling with amino acids via the *N*-terminus (cf. Section 4.2).

N-protected pyrroles, which are readily available in bulk quantities, have proved to be versatile starting materials for a broad variety of β-ACC derivatives. Their cyclopropanation with alkyl diazoacetates was pioneered by Fowler et al. using copper bronze,[59] but later on it was discovered that copper(II) triflate activated by phenylhydrazine is a more active catalyst. Thus, **147a** can be cleanly converted to the monocyclopropanated product **148**, which is obtained exclusively as the exo diastereomer in 39−45% yield on a multigram scale (Scheme 41).[60] By appropriate

Scheme 41. Selective Synthesis of *cis*- (150) and *trans*-β-ACCs (151) from N-Boc-pyrrole (147)[60,a]



[a] Reagents and conditions: (a) N_2CHCO_2Me, $Cu(OTf)_2$/Ph-$NHNH_2$ (0.2 mol %), CH_2Cl_2, 39−45% (70−74% after recovery of **147a**; (b) KOH/MeOH/H_2O, 79%; (c) (i) O_3, CH_2Cl_2, −78 °C, (ii) Me_2S, −78 °C → r.t., 79−88%; (d) (i) $NaClO_2$, H_2O_2, 96−100%, (ii) DEAEA, acetonitrile, 87%; (e) (i) O_3, MeOH, −78 °C, (ii) Ac_2O, NEt_3, CH_2Cl_2, −78 °C → r.t., (iii) DEAEA, MeCN, 66% overall.

manipulation of the ester group and oxidative cleavage of the cyclic Boc-protected enamines **148** or **149**, either the *cis*-amino acid **150** or the *trans*-amino acid **151** can be synthesized. As with **144** (cf. Scheme 40), an in situ coupling of the *N*-terminus of *N*-Boc protected β-ACC derivatives of type **150** or **151** could be developed, allowing their full incorporation into peptides (cf. section 4.2). Furthermore, the remaining ester group in **151** has been transformed into side chain mimics of α-amino acids, giving rise to novel trifunctional β-ACC derivatives **152**−**155** (Figure 4).[61]

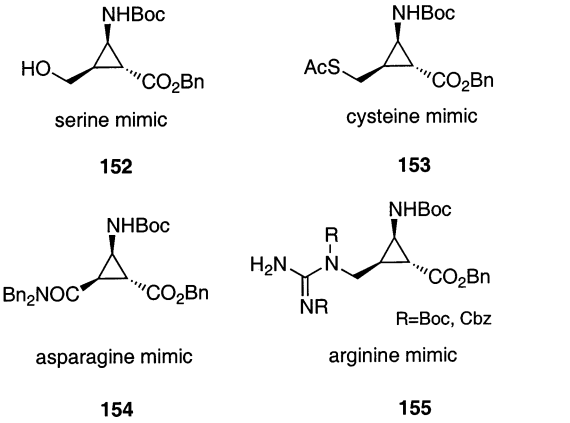


Figure 4. β-ACC derivatives with α-amino acid side chain functionality.[61]

Moreover, the amino aldehyde **156**, being obtained after ozonolysis and reductive workup of **148** (cf. Scheme 41), undergoes highly diastereoselective nucleophile additions following the Felkin-Anh[46] paradigm, giving rise to a broad variety of trans-β-ACC derivatives **145** (Scheme 42, Table 7).[62]

Scheme 42. Synthesis of β-ACC Derivatives by Addition of Nucleophiles to Aldehyde 156 (For Reagents and Conditions, See Table 7)[62]

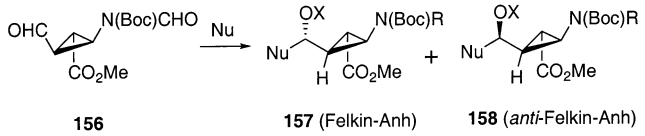
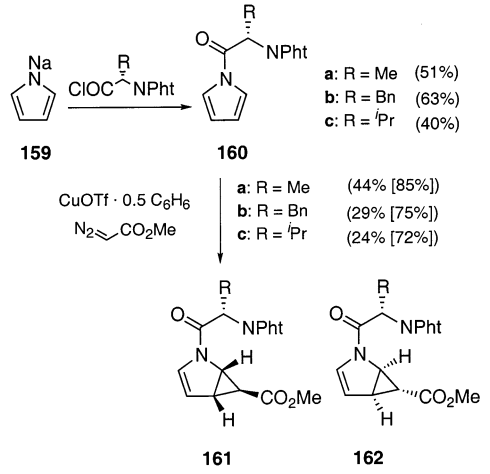


Table 7. Synthesis of β-ACC Derivatives by Addition of Nucleophiles to Aldehyde 156[62]

Entry	Nucleophile	Catalyst	Temp [°C]	Product X	Product R	Product 157 : 158	Yield [%]
1		NEt_3	0	CHO	H	≥ 99:01	91
2		NEt_3	0	CHO	H	≥ 99:01	84
3	TMSCN	–	25	TMS	CHO	91:09	100
4	TMSCN	BF_3•OEt_2	–78	H	CHO	89:11	94
5		BF_3•OEt_2	–78	CHO	H	≥ 99:01	71
6		BF_3•OEt_2	–78	CHO	H	≥ 99:01	92
7		BF_3•OEt_2	–78	CHO	H	≥ 99:01	93

In contrast to the cyclopropanation of the corresponding furans,[63] this reaction could not be rendered enantioselective for pyrroles **147**. However, an enzymatic resolution of **148** was developed,[60b] allowing the synthesis of all β-ACC derivatives obtained via this route in enantiomerically pure form. Alternatively, pyrroles **160**, in which the nitrogen is acylated by the C-terminus of an amino acid, can be employed as starting materials (Scheme 43).[64] Although there is no selectivity in the initial cyclopropanation, the diastereomers **161** and **162** can readily be separated by chromatography to yield them as single stereo-

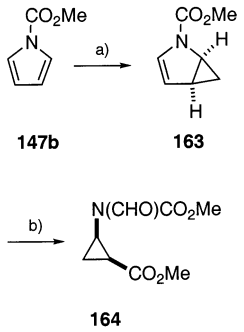
Scheme 43. Cyclopropanation of Pyrroles 148[64]



isomers. Following oxidative cleavage of the bicyclic system as outlined in Scheme 41, peptides containing the β-ACC unit can be obtained.

Cyclopropanation of pyrroles has been also carried out with diiodomethane/zinc−copper couple according to the Simmons−Smith protocol, leading to the cis-β-ACC ester **152** after ozonolysis and in situ acylation of the resulting carbonyl oxide intermediate and elimination of acetic acid with triethylamine (Scheme 44).[65]

Scheme 44. Synthesis of β-ACC 164 by Simmons−Smith Cyclopropanation of *N*-Methoxycarbonylpyrrole (147b)[65,a]

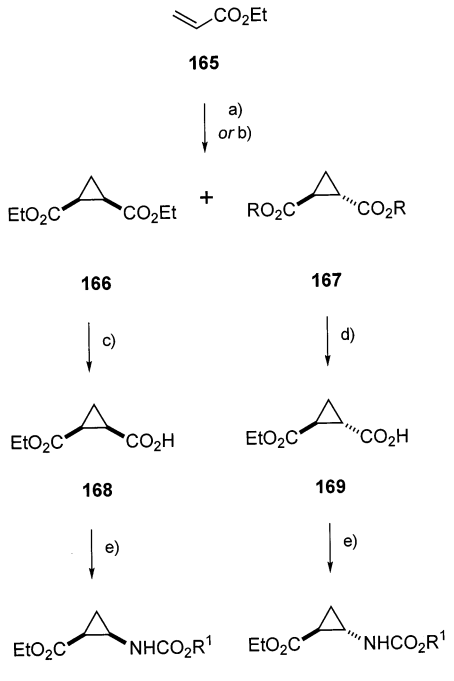


[a] Reagents and conditions: (a) Et_2Zn, CH_2I_2, 45%; (b) (i) O_3, MeOH, −78 °C, (ii) Ac_2O, NEt_3, CH_2Cl_2, −78 °C → r.t., 60%.

4.1.3. β-ACCs from Acrylates

Acrylates have served as precursors for β-ACCs in a variety of strategies. Key intermediates were *cis*- and *trans*-cyclopropane-1,2-dicarboxylic acid derivatives **166** or **167**, respectively, which are accessible either by cyclopropanation of acrylates **165** with diazoacetates in a formal [2+1]-cycloaddition,[66] or with α-chloroacetic acid esters in a Michael addition/1,3-elimination sequence (Scheme 45).[67] Selective saponification of only one ester group to the monoester **168** and **169**, respecitively, is possible with sodium hydroxide, moreover, enzymatic hydrolysis of the meso diester **166** with pig liver esterase affords in 90% yield enantiomerically pure **168**.[68] Curtius degradation with trapping of the intermediate isocyanates of the mono acids completes the synthesis of the β-ACC derivatives **170** and **171**, respectively. All attempts to deprotect the amino group in these

Scheme 45. Synthesis of *cis*- and *trans*-β-ACC Derivatives from Acrylates 165[66−68,a]

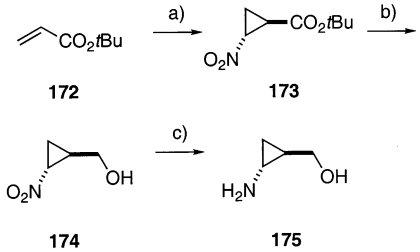


[a] Reagents and conditions: (a) N_2CHCO_2Et, heptane, molecular sieves, 30 °C, 1 h, 72%; (b) $ClCH_2CO_2Et$, NaOMe, MeOH, 70%; (c) PLE, 0.1M KH_2PO_4, pH 7, 20 °C; (d) NaOH/H_2O, EtOH, reflux, 2 h, 70%; (e) (i) $SOCl_2$, r.t., 85%, (ii) NaN_3, toluene, reflux, 45%.

compounds to obtain the free amino acids or esters resulted only in ring opening.

In a related approach, the nitrocyclopropanecarboxylic acid **173** was envisioned as a promising precursor toward β-ACCs (Scheme 46).[69] Reduction of the acid and the nitro functionality proceeded in good yield, giving rise to the amino alcohol **175**, which should prove to be a useful building block for organic synthesis. However, all attempts to protect the amino group and subsequently oxidize the alcohol to the acid were not successful, and only products resulting from ring opening could be obtained.

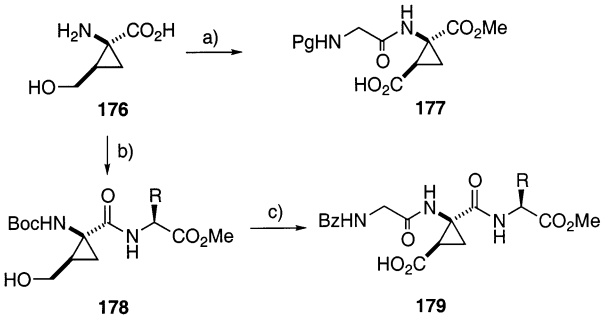
Scheme 46. Acid 173 as Potential Precursor toward β-ACCs[69,a]



[a] Reagents and conditions: (a) (i) Br_2, $CHCl_3$, (ii) CH_3NO_2, Na_2CO_3, DMF, 31%; (b) $AlCl_3$, $NaBH_4$, DME, 67%; (c) H_2/Pd−C, MeOH, 78%.

In contrast, in 2,3-methanohomoserine **176**[20b,45a,70] the oxidation of the hydroxymethylene group is successful after protection of the amino and carboxylic acid group (Scheme 47).[69] Following this strategy, it has been especially possible to synthesize peptides **177** and **178** of 2,3-methanoaspartic acid. Quite obviously, it would be also possible to couple the carboxylic acid in **177** with another amino acid, thus

Scheme 47. Synthesis of Peptides 179 Containing 2.3-Methanoaspartic Acid[70,a]



[a] Reagents and conditions: (a) (i) HCl, MeOH, (ii) $PgNHCH_2CO_2Me$, (iii) $NaIO_4$/cat. $RuCl_3$, 27−40%; (b) (i) Boc_2O/NaOH, (ii) DCC/HOBt *or* IIDQ, NEt_3, HCl-Xxx-OMe (Xxx = Gly, Phe), 33−78%; (c) (i) excess TFA, (ii) DCC/HOBt, NEt_3, Bz-Gly-OMe, (iii) $NaIO_4$/cat. $RuCl_3$, 26−37%.

achieving the incorporation of a β-ACC unit into peptides (cf. Chapter 4.2).

After reduction of the ester groups of N-protected β-ACC derivatives to the corresponding amino alcohols, the amino group can be manipulated by standard procedures. This way, **170** and **171** (cf Scheme 45) have been converted to a variety of carbocyclic nucleoside analogues such as **180**−**181** (Figure 5).[71]

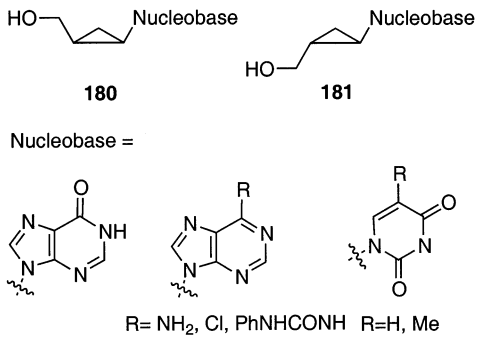
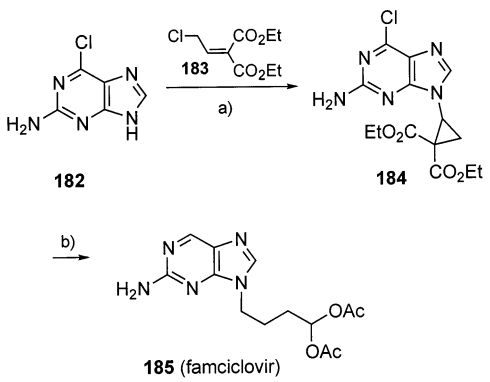


Figure 5. Carbocyclic nucleoside analogues derived from β-ACCderivatives **170** and **171**.[71]

The aminopurine-substituted cyclopropanedicarboxylate **184** was synthesized from diethyl 2-chloroethylidenemalonate (**183**) by conjugate addition of **182** with concurrent cyclization by 1,3-elimination (Scheme 48).[72] Selective 1,2-cyclopropane ring fission

Scheme 48. Synthesis of Famciclovir (165)[72,a]

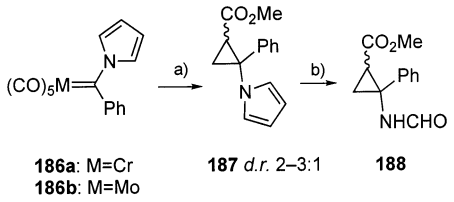


[a] Reagents and conditions: (a) **183**, K_2CO_3, DMF, 87%; (b) (i) H_2, Pd/C, NEt_3, 74%, (ii) $NaBH_4$, (iii) Ac_2O, pyridine, DMAP, 82% (2 steps).

was achieved by catalytic hydrogenation, subsequent hydride reduction and acylation gave rise to the antiherpes virus agent famciclovir (**185**).

Chromium, molybdenum, and tungstencarbene complexes with a pyrrole group as the heteroatom-containing substituent on C-1 have been shown to react as masked aminocarbenes with electron deficient alkenes.[73] Thus, methyl acrylate and **186** yield the diastereomeric cyclopropane derivatives **187** (Scheme 49). The pyrrole group could be cleaved to a formyl-protected amino group by ozonolysis, resulting in the β-ACC derivative **188** in good yield.

Scheme 49. Cyclopropanation of Acrylates with Group 6 Pyrroleocarbene Complexes[73,a]



[a] Reagents and conditions: (a) methyl acrylate, DBHT, THF, 65−90%; (b) (i) O_3, CH_2Cl_2, (ii) $(H_2N)_2C{=}S$, MeOH, 73% (2 steps).

A few other reaction sequences with group VI metal carbene complexes leading to amino-substituted cyclopropane carboxylic acid derivatives have also been reported.[74]

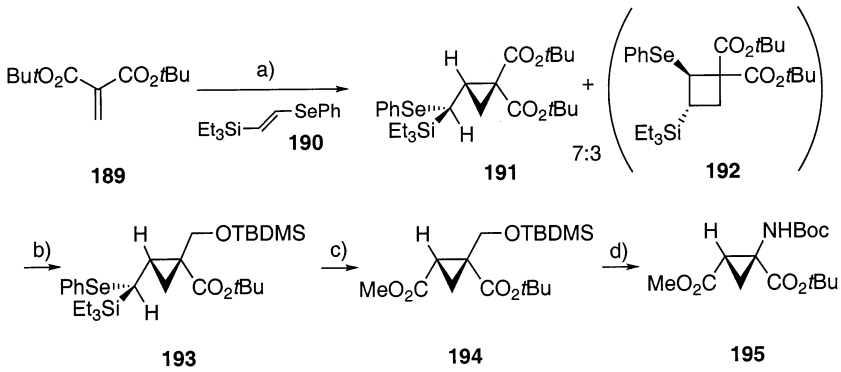
The highly functionalized cyclopropane **191** is formed along with the cyclobutane derivative **192** by the reaction of 1-seleno-2-silylethene (**190**) with the methylenemalonate ester **189** (Scheme 50).[75] Selective reduction of the sterically less shielded ester group in **191** gives rise to **193**. The selenosilylmethyl group can be converted with $RuCl_3/NaIO_4$ directly to a carboxylic acid; thus, **194** was obtained from **193** by oxidation and subsequent esterification. Oxidation of the hydroxymethylene group followed by Curtius rearrangement finally led to the 2,3-methanoaspartic acid **195** (cf. also Scheme 32 and Scheme 53).

4.1.4. β-ACCs from Other Cyclopropane and Cyclopropene Derivatives

In certain cases, amino or carboxy groups can be directly introduced into suitably functionalized cyclopropanes and cyclopropenes to accomplish the synthesis of β-ACCs. Due to the high ring strain, cyclopropene carboxylates are highly reactive toward nucleophiles. Therefore, 1,4-addition of morpholine to methylcyclopropene-1-carboxylate **196** occurred readily at room temperature to give the addition products **197** (Scheme 51). Remarkably, even **197c**, being substituted not only by the electron-donating morpholino group, but in addition with a methyl group on the same carbon atom was reported to be stable.[76]

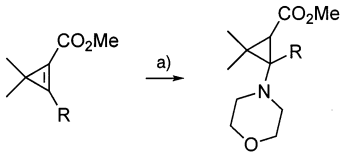
Dimethyl cyclopropenedicarboxylate **199** has been generated and in situ trapped with ammonia. However, the initial report that the synthesis of the diastereomeric β-ACC derivatives **200** (Scheme 52) followed by transformation to the cyclic asparagines analogues **202** was achieved[77] turned out to be an error.[78] Instead, the methoxy derivative **201**, being formed by addition of methanol, produced from

Scheme 50. Synthesis of 2,3-Methanoaspartic Acid 195[75,a]



[a] Reagents and conditions: (a) $ZnBr_2$, −78 °C, CH_2Cl_2, 93%; (b) (i) $LiAlH_4$, −78 °C, Et_2O, 45 min, (ii) $NaBH_4$, −30 °C, *i*PrOH, 1 h, 87% (2 steps), (iii) TBDMSCl, imidazole, CH_2Cl_2, 25 h, 95%; (c) (i) $NaIO_4$, $RuCl_3.H_2O$, CCl_4,/CH_3CN/H_2O (2:2:1), 5 h, 69%, (ii) TBAF, CH_3CO_2H, THF, 42 °C, 1 h, 95%; (d) (i) $NaIO_4$, $RuCl_3$*H_2O, CCl_4,/CH_3CN/H_2O (2:2:3), 5 h, 78%, (ii) DPPA, NEt_3, *t*BuOH, 110 °C, 6 h, 38%.

Scheme 51. Addition of Morpholine to Cyclopropenes 196[76,a]

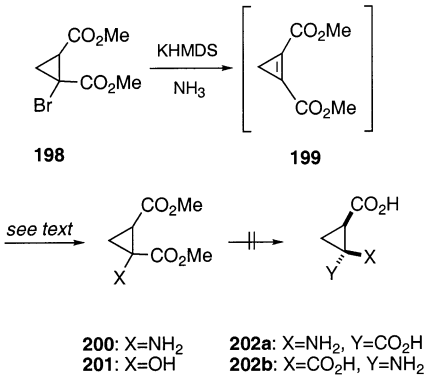


196a: R=H
196b: R=CO_2Me
196c: R=Me

197a: R=H
197b: R=CO_2Me
197c: R=Me

[a] Reagents and conditions: (a) morpholine, Et_2O, 20 °C, 54−80%

Scheme 52. Attempted Synthesis of Cyclic Asparagines Analogues 202[77,78]

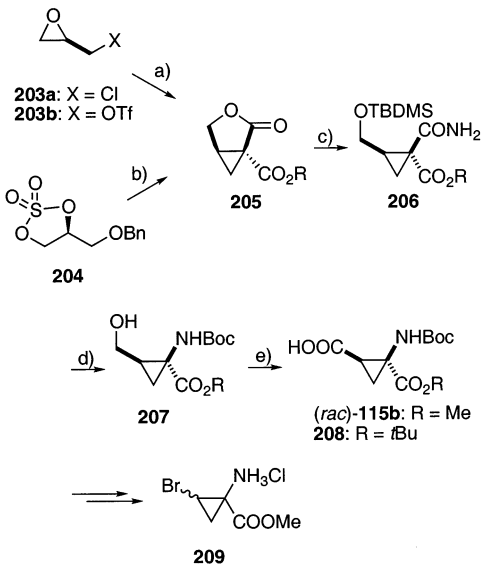


200: X=NH_2
201: X=OH

202a: X=NH_2, Y=CO_2H
202b: X=CO_2H, Y=NH_2

aminolysis of one of the methyl ester groups, to **199** had taken place. Nevertheless, the synthesis of the protected cyclic asparagines analogues (*rac*)-**115b** and **208** could be accomplished in racemic form by yet another route (Scheme 53, see also Scheme 32): cyclopropanation of racemic epichlorohydrin **203a**—being analogously possible with (*R*)-**203a**,[79] the corresponding triflate (*R*)-**203b**[80] or with **204**[73]—can be carried out with malonates.[81] The bicyclic lacton **205** was hydrolyzed followed by oxidation of the resulting hydroxymethylene group to the acids (*rac*)-**115b** and **208**. These compounds have been converted to the monobrominated ACC derivatives **209** as potential substrates or inhibitors of ACC oxidase.[82] However, the attempt to synthesize **202a** by TFA-induced deprotection of the *N*-Boc protected *tert*-butyl derivative **208** failed again, resulting only in ring opening products.[83]

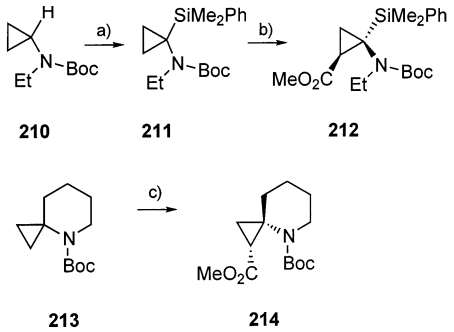
Scheme 53. Protected Cyclic Asparagines Analogues (*rac*)-115b and 208[79−83,a]



[a] Reagents and conditions: (a) $CH_2(CO_2R)_2$, NaOMe, MeOH, r.t., 30−50% (R Me, *t*Bu); (b) (i) $CH_2(CO_2tBu)_2$, NaH, DME, (ii) H_2, Pd/C, (iii) cat. TsOH, 53%; (c) (i) NH_3/MeOH, (ii) TBDMSCl, DMF, imidazole, 4 Å, 81%; (d) (i) *t*BuOH, $Pb(OAc)_4$, 62%, (ii) Bu_4NF*$3H_2O$, THF, 85%; (e) $NaIO_4$, $RuCl_3$*H_2O, CCl_4/CH_3CN/H_2O (2:2:3), 62%.

Stepwise lithiation of *N*-Boc protected cyclopropylethylamine **210** occurs first on the more acidic α-position of the cyclopropane ring. After blocking

Scheme 54. β-Lithiation of Cyclopropylamines as Key Step in the Synthesis of cis-β-ACCs[84,a]



[a] Reagents and conditions: (a) *s*-BuLi, TMEDA, $SiMe_2PhCl$, THF, −78 °C, 83%; (b) (i) *s*-BuLi, TMEDA, THF, −78 °C, (ii) dimethyl carbonate, 61%; (c) same as condition b, 64%.

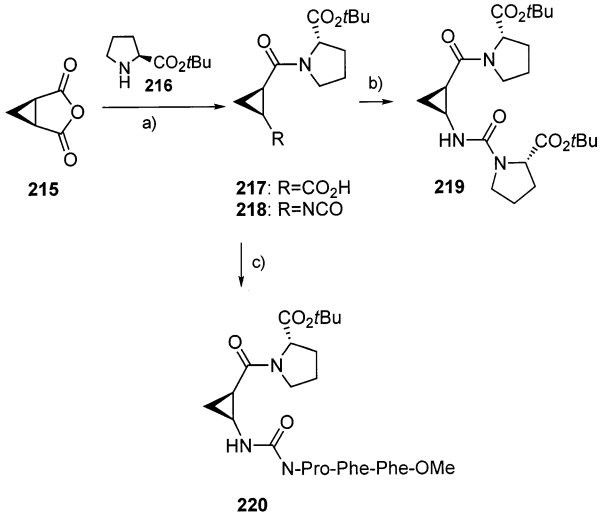
that position by a silyl substitutent, β-lithiation directed by the *N*-Boc group becomes feasible (Scheme 54).[84] Trapping of the anion with dimethyl carbonate yielded stereoselectively the cis-β-ACC derivative **212**. Analogously, the spiro anellated β-ACC **214** could be synthesized from **213**.

4.2. β-ACC Building Blocks in Peptides

Because of their rigid structure, β-ACCs are attractive building blocks to induce defined conformations in peptides. However, the high susceptibility of β-ACCs toward ring opening when an electron-withdrawing group does not protect the *N*-terminus makes their incorporation into peptides possible only by special strategies.

The synthesis of pseudo-peptides incorporating a β-ACC residue into a string of α-amino acids by a urea linkage was accomplished starting with the *meso*-anhydride **215** (Scheme 55).[85] Desymmetrization by the proline ester **216** occurred with moderate selectivity to give predominantly the acid **217**, which was subjected to a Curtius degradation. The resulting isocyanate **218** could be efficiently reacted with amino esters or *N*-unprotected peptides to yield **219** and **220**, respectively.

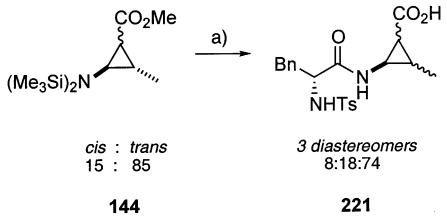
Scheme 55. Pseudopeptides 219 and 220 with Incorporated β-ACC Residue[85,a]



[a] Reagents and conditions: (a) (i) CH_2Cl_2, 40%, (ii) NaN_3, isopropenyl chloroformate, NEt_3, THF, −20 °C, 67%, (iii) benzene, 80 °C, 100%. (b) *N*-Boc-proline, CH_2Cl_2, r.t. 65−74%. (c) TFA, NEt_3, HN−Pro-Phe-Phe-OMe, CH_2Cl_2, 0 °C; 20 °C, 16 h, 74%.

The *N*-bis(silyl)-substituted β-ACC derivative **144** (cf. Scheme 40) could be deprotected by fluoride in the presence of an amino acid chloride to give rise to the dipeptide **221** (Scheme 56).[86] This study suggested for the first time that the lifetime of β-ACC derivatives having an unprotected amino group might be sufficient to allow coupling with acyl donors. Nevertheless, under the reaction conditions employed epimerization on the stereocenters of the cyclopropane moiety took place to some extent, indicating that heterolytic ring opening/ring closure sequences had taken place during the coupling.

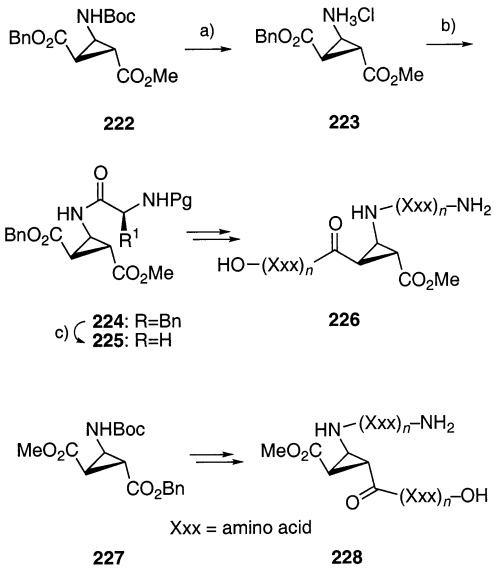
Scheme 56. In Situ Coupling of *N*-Bissilyl-Substituted β-Acc 144 with N-Ts-PheCl[86,a]



[a] Reagents and conditions: (a) (i) CsF, *N*-Ts-Phe-Cl, $(CH_2Cl)_2$, reflux, 77%, (ii) LiOH, H_2O/THF, 20 °C, (iii) 2N HCl, 95% (2 steps).

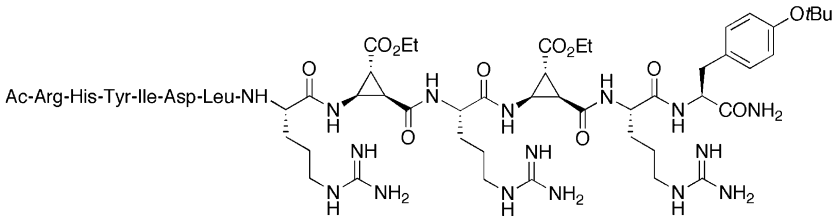
Using *N*-Boc protected β-ACC **222** (Scheme 57, cf. Scheme 41), an alternate in situ coupling approach could be developed. Deprotection of the *N*-Boc group with anhydrous HCl resulted in the stable hydrochloride **223**, which can be isolated and stored indefinitely.[60] In contrast, deprotection of **222** with trifluoroacetic acid immediately leads to ring opening: presumably the equilibrium amine/ammonium salt is shifted to liberate enough free amine to decompose the material. Treatment of the hydrochloride salt **223** with triethylamine in the presence of a DCC or EDC/HOBt activated *N*-Fmoc or *N*-Boc amino acids cleanly results in dipeptides **224** with no significant epimerization noticeable. Cleavage of the benzyl ester by catalytic hydrogenation gives rise to the C-terminal free dipeptides **225**, which have been used as building blocks for the synthesis of larger peptides of type **226** with an incorporated cis-β-ACC unit, either in solution or on solid phase. Analogously, starting from **227**, peptides of type **228** become accessible, in which a trans-β-ACC is incorporated.

Scheme 57. Synthesis of Peptides Having Either a *cis*- or a *trans*-β-ACC Unit Incorporated[60,a]

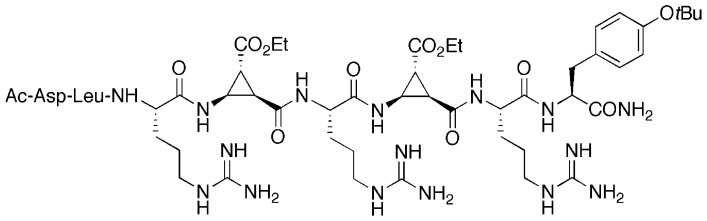


[a] Reagents and conditions: (a) HCl, EtOAc, 0 °C, 100%; (b) Pg-Xxx-OH (Pg = Fmoc or Boc), EDC, NEt_3, CH_2Cl_2, 70 to >95%; (c) Pd/C, 1,4-cyclohexadiene, 100%.

As an example for a practical application using β-ACCs, **229** and **230** have been synthesized, being the shortest known peptide ligands with nanomolar affinity and good subtype selectivity for the Neuropeptide Y1 receptor (Figure 6).[87]



229 (K_i = 29±13 nMol Y_1, 118 nmol Y_5, no activity for other NPY receptors)

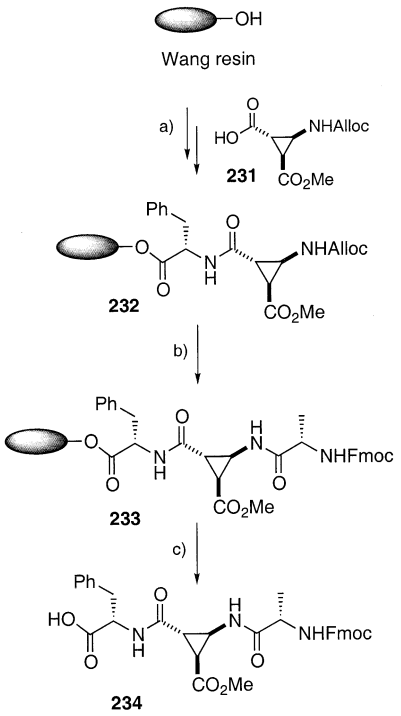


230 (K_i = 235 nMol Y_1, no activity for other NPY receptors)

Figure 6. Ligands for the NPY Y1 receptor containing two *cis*-β-ACC residues.[87]

On the basis of the use of the *N*-Alloc group, a protocol for the peptide coupling of β-ACCs has been developed starting from **231**, which is amenable to automated solid-phase synthesis.[88] Removal of the *N*-Alloc group in **232** with DABCO under palladium(0) catalysis can be carried out in the presence of amino acids, being either *N*-Boc- or *N*-Fmoc-protected and activated by EDC/HOBt, to yield the resin-bound peptide **233**. Upon cleavage from the resin with trifluoroacetic acid, the tripeptide **234** was formed without any detectable epimerization in 83−85% isolated yield. With several in situ coupling strategies being available, the elusive β-ACCs could be developed as a novel class of conformationally rigid amino acid building blocks for peptides. First structural investigations suggest that the cis-β-ACC structure incorporated into peptides induces unique turns,[89] being distinctively different from other turn-inducing amino acids such as proline or aminoisobutyric acid (AIB). In a complementary approach, 1,2-cyclopropanedicarboxylic acids and 1,2-diaminocyclopropanes have also been proved valuable peptide mimics, being able to stabilize extended peptide structures.[90]

Scheme 58. Solid Phase Peptide Coupling of β-ACC 231 Using the *N*-Alloc Protection−Deprotection Strategy[88,a]



[a] Reagents and conditions: (a) (i) Fmoc-PheOH, DIC, HOBt, DMF, (ii) piperidine, DMF, (iii) **231**, DIC, HOBt, DMF; (b) $Pd[PPh_3]_4$, DABCO *or* $PhSiH_3$ (12 equiv), Fmoc-Ala-OH, EDC, HOBt, CH_2Cl_2, 2 h, r.t.; (c) TFA, CH_2Cl_2 2:1; isolated yield based on loading of Fmoc-Phe-OH to the resin: 85% (DABCO).

5. Conclusion

There have been a number of synthetic strategies toward cyclopropyl-substituted β-alanines, resulting in structurally defined, highly functionalized amino acids. Many of these compounds have been used as reactive building blocks, utilizing the ring strain of the cyclopropane moiety as well as the amino and carboxy groups for the synthesis of complex heterocyclic systems. Only recently have the title compounds been recognized as valuable constituents in peptides, since the rigidity introduced by the cyclopropane ring not only constrains a peptide backbone, but also allows the controlled placement of functional groups, mimicking α-amino acid side chains.

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6. References

(1) (a) Salaun, J. *Top. Curr. Chem.* **2000**, *207*, 1. (b) Cativiela, C.; Diaz-de-Viellgas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.

(c) Salaun, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511. (c) Burgess, K.; Ho, K. K.; Moyesherman, D. *Synlett* **1994**, 575.
(2) (a) Yamamoto, Y.; Asao, N.; Tsukada, N. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; Jai Press Inc: Stamford, CT, 1998; Vol. 3. (b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117. (c) In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (d) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3.
(3) (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) North, M. *J. Pept. Sci.* **2000**, *6*, 301.
(4) Aldrich Chemical Co., Art. No. 34,339.
(5) (a) Barthe *Bull. Soc. Chim. Fr.* **1906**, *35*, 41. (b) Carpenter *J. Chem. Soc., Perkins Trans.* **1899**, *75*, 928. (c) Jones, L. W.; Scott, A. W. *J. Am. Chem. Soc.* **1922**, *44*, 407. (d) Mitchell, A. D.; Thorpe, J. F. *J. Chem. Soc.* **1910**, *97*, 997. (d) Ohne, M.; Tanaka, H.; Komatsu, M.; Ohshiro, Y. *Synlett* **1991**, 919. (e) Wells, G. J.; Yan, T.-H.; Paquette, L. A. *J. Org. Chem.* **1984**, *49*, 3604.
(6) Schwartz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113.
(7) Varie, D. L.; Shih, C.; Hay, D. A.; Andis, S. L.; Corbett, T. H.; Gossett, L. S.; Janisse, S. K.; Martinelli, M. J.; Moher, E. D.; Schultz, R. M.; Toth, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 369.
(8) Abele, S.; Seiler, P.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1559.
(9) (a) Monti, S. A. *J. Org. Chem.* **1970**, *35*, 380. (b) de Meijere, A. *Angew. Chem.* **1979**, *11*, 867; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809.
(10) Frankepohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBiochem.* **2001**, *2*, 445.
(11) Silverman, R. B.; Ding, C. Z.; Borrillo, J. L.; Chang, J. T. *J. Am. Chem. Soc.* **1993**, *115*, 2982.
(12) Ives, J. L.; Heym, J. *Annu. Rep. Med. Chem.* **1989**, *24*, 21.
(13) Tetrud, V. W.; Langston, J. W. *Science* **1989**, *245*, 519.
(14) Silverman, R. B.; Lu, X.; Blomquist, G. D.; Ding, C. Z.; Yang, S. *Bioorg. Med. Chem.* **1997**, *5*, 297.
(15) Fraser, W.; Suckling, C. J.; Wood, H. C. S. *J. Chem. Soc., Perkin. Trans. 1* **1990**, 3137.
(16) Husbands, S.; Fraser, W.; Suckling, C. J.; Wood, H. C. S. *Tetrahedron* **1995**, *51*, *3*, 865.
(17) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelovsky, A. C.; Nolan, R. L. Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36.
(18) *Review*: de Meijere, A.; Wessjohann, L. *Synlett* **1990**, *1*, 20.
(19) (a) Glück, C.; Poignée, V.; Schwager, H. *Synthesis* **1987**, 260. (b) Sepiol, J.; Soulen, R. L. *J. Org. Chem.* **1975**, *40*, 3791. (c) Liese, T.; Jaekel, F.; de Meijere, A. *Org. Synth.* **1990**, *69*, 144. (d) Commercial source: Aldrich Chemical Co. Art. Nr. 6262.
(20) (a) Liese, T.; Seyed-Mahdavi, F.; de Meijere, A. *Org. Synth.* **1990**, *69*, 148. (b) El-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 289. (c) Wessjohann, L.; Krass, N.; Yu, D.; de Meijere, A. *Chem. Ber.* **1992**, *125*, 867. (d) Liese, T.; Teichmann, S.; de Meijere, A. *Synthesis* **1988**, 25. (e) Liese, T.; Splettstoesser, G.; de Meijere, A. *Angew. Chem.* **1982**, *94*, 799; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 784.
(21) Salaun, J.; Bennani, F.; Compain, J.-C.; Fadel, A.; Ollivier, J. *J. Org. Chem.* **1980**, *45*, 4129.
(22) Spitzner, D.; Swoboda, H. *Tetrahedron. Lett.* **1986**, *27*, 1281.
(23) (a) Liese, T.; Teichmann, S.; de Meijere, A. *Synthesis* **1988**, 25. (b) de Meijere, A.; Teichmann, S.; Yu, D.; Kopf, J.; Oly, M.; von Thienen, N. *Tetrahedron* **1989**, *45*, 2957. (c) Wessjohann, L.; McGaffin, G.; de Meijere, A. *Synthesis* **1989**, 359. (d) Wessjohann, L.; Skattebøl, L.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1990**, 574. (e) Wessjohann, L.; Krass, N.; Yu, D.; de Meijere, A. *Chem. Ber.* **1992**, *125*, 867. (f) Wessjohann, L.; Giller, K.; Zuck, B.; Skattebøl, L.; de Meijere, A. *J. Org. Chem.* **1993**, *58*, 6442. (g) de Meijere, A.; Teichmann, S.; Seyed-Mahdavi, F.; Kohlstruk, S. *Liebigs Ann. Chem.* **1996**, 1989. (h) Tamm, M.; Thutewohl, M.; Ricker, C. B.; Bes, M. T.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 2017. (i) Rulev, A.; Maddaluno, J. *Eur. J. Org. Chem.* **2001**, 2569.
(24) de Meijere, A.; Teichmann, S.; Sayed-Mahdavi, F.;. Kohlstruk, S. *Liebigs Ann. Chem.* **1996**, 1989.
(25) Wessjohann, L.; Krass, N.; Yu, D.; de Meijere, A. *Chem. Ber.* **1992**, *125*, 867.
(26) Kordes, M. Diploma thesis, University of Göttingen, Göttingen, Germany, 1999.
(27) (a) Funabashi, Y.; Tsubotani, S.; Koyama, K.; Katayama, N.; Harada, S. *Tetrahedron Lett.* **1994**, *35*, 7659. (b) Yuan, C.; Williams, R. M. *J. Am.. Chem. Soc.* **1997**, *119*, 11777. (c) Sokolov, V. V.; Kozhushkov, S. I.; Nikolskaya, S.; Belov, V. N.; El-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, *777*, 7.
(28) Brackmann, F. Diploma thesis, University of Göttingen, Göttingen, Germany, 2002.
(29) (a) El-Sayed, M.; Gratkowski, C. Krass, N.; Meyers, A. I.; de Meijere, A. *Synlett* **1992**, *3*, 962. (b) El-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 289.
(30) Tamm, M.; Thutewohl, M.; Ricker, C. B.; Bes, M. T.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, *2017*, 7.
(31) Rulev, A.; Maddaluno, J. *Eur. J. Org. Chem.* **2001**, 2569.
(32) (a) Belov, V. N.; Funke, C.; Labahn, T.; El-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, *1345*, 5. (b) Funke, C.; El-Sayed, M.; de Meijere, A. *Org. Lett.* **2000**, *2*, 4249.
(33) Golebiowski, A.; Klopfenstein, S. R.; Shao, X.; Chen, J. J.; Colson, A.-O.; Grieb, A. L.; Russell, A. F. *Org. Lett.* **2000**, *2*, 2615.
(34) Hudlicky, T.; Becker, D. A.; Fan, R. L.; Kozhushkov, S. I. In *Methods of Organic Chemistry (Houben Weyl)*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17c, p 2538.
(35) de Meijere, A.; Teichmann, S.; Yu, D.; Kopf, J.; Oly, M.; von Thienen, N. *Tetrahedron* **1989**, *45*, 2957.
(36) Nötzel, M. W.; Tamm, M.; Labahn, T.; Noltemeyer, M.; El-Sayed, M.; de Meijere, A. *J. Org. Chem.* **2000**, 65, 3850.
(37) (a) Weidner, J.; Vilsmaier, E. *Monatsh. Chem.* **1987**, *118*, 1057. (b) Weidner, J.; Vilsmaier, E.; Fries, R. *Monatsh. Chem.* **1987**, *118*, 1039.
(38) Benzing, M.; Vilsmaier, E. *Chem. Ber.* **1987**, *120*, 1873.
(39) Chowdhury, M. A.; Senboku, H.; Tokuda, M.; Masuda, Y.; Chiba, T. *Tetrahedron Lett.* **2001**, *42*, 7078.
(40) Mertin, A.; Thiemann, T.; Hanss, I.; de Meijere, A. *Synlett* **1991**, 87.
(41) *Review*: Reissig, H. U. *Chem Rev.* **2002**, *103*, 1151−1196.
(42) Kravtsov, V. Kh.; Biyushkin, V. N.; Malinovskii, T. I.; Krasnov, V. P.; Matveeva, T. V. *Dokl. Akad. Nauk SSSR* **1990**, 622.
(43) Copper(II)-salts can be employed, being in situ either reduced by the diazoester or by a reducing agent such as phenylhydrazine.
(44) Maas, G.; Mueller, A. *J. Prakt. Chem.* **1998**, *340*, 315.
(45) (a) Jimenez, J. M.; Rife, J.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 537. (b) Jimenez, J. M.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 3203. (c) Diaz, M.; Jimenez, J. M.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2465.
(46) *Review:* Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.
(47) (a) Hirota, K.; Yamada, Y.; Asao, T.; Senda, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1896. (b) Fourrey, J. L.; Henry, G.; Jouin, P. *Tetrahedron Lett.* **1979**, *11*, 951. (c) Jones, G.; Tonkinson, D. J.; Hayes, P. C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2645.
(48) Elguero, J.; Ochoa, C.; Stud, M. *Heterocycles* **1982**, *17*, 401.
(49) Thiellier, H. P. M.; Koomen, G. J.; Pandit, U. K. *Heterocycles* **1976**, *5*, 19.
(50) Ondo, T.; Hosaka, H.; Yamanaka, H.; Funasaka, W. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2013.
(51) Thiellier, H. P. M.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1977**, *33*, 2609.
(52) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1969**, *91*, 7751.
(53) (a) Vilsmaier, E.; Adam, R.; Altmeier, P.; Cronauer, R. *Tetrahedron* **1989**, *45*, 131. (b) Vilsmaier, E.; Adam, R.; Tetzlaff, C.; Cronauaer, R. *Tetrahedron* **1989**, *45*, 3683.
(54) Altmeier, P.; Vilsmaier, E.; Wolmershäuser, W. *Tetrahedron* **1989**, *45*, 3189.
(55) Wenkert, E.; McPherson, C. A.; Sanchez, E. L.; Webb, R. L. *Synth. Commun.* **1973**, *3*, 255.
(56) Hiyama, T.; Kai, M. *Tetrahedron Lett.* **1982**, 2103.
(57) (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.
(58) Paulini, K.; Reissig, H. U. *Liebigs Ann. Chem.* **1991**, *5*, 455.
(59) Tanny, S. R.; Grossman, J.; Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 6495.
(60) (a) Bubert, C.; Cabrele, C.; Reiser, O. *Synlett* **1997**, 827. (b) Beumer, R.; Bubert, C.; Cabrele, C.; Vielhauer, O.; Pietzsch, M.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 8960.
(61) Beumer, R.; Reiser, O. *Tetrahedron* **2001**, *57*, 6497.
(62) Bubert, C.; Reiser, O. *Tetrahedron Lett.* **1997**, *38*, 4985.
(63) (a) Böhm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955. (b) Boehm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315. (c) Chhor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260.
(64) Voigt, J.; Noltemeyer, M.; Reiser, O.; *Synlett* **1997**, 202.
(65) Bubert, C.; Voigt, J.; Biasetton, S.; Reiser, O. *Synlett* **1994**, 675.
(66) Sasaki, M. *Jpn. Kokai Tokkyo Koho* **2001**, 6.
(67) (a) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059. (b) McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568. (c) von der Saal, W.; Reinhardt, R.; Seidenspinner, H.-M.; Stawitz, J.; Quast, H. *Liebigs Ann. Chem.* **1989**, 703.
(68) (a) Shroff, C. C.; Stewart, W. S.; Uhm, S. J.; Wheeler, J. W. *J. Org. Chem.* **1971**, *36*, 3356. (b) Sabbioni, G.; Jones, J. B. *J. Org. Chem.* **1987**, *52*, 4565.
(69) Bremer, C. Ph.D. Thesis, University of Göttingen, Göttingen, Germany, 1994.
(70) (a) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814. (b) Guillaume, G.; Aitken, D. J.; Husson, H.-P. *Synlett* **1991**, 747. (c) Kokskinen, A. M. P.; Munos, L. *J. Org. Chem.* **1993**, *58*, 879. (d) Burgess, K.; Ho, K. K. *J. Org. Chem.* **1992**, *57*, 5931. (e) Pirrung, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301. (f) Bland. J.; Shah, A.; Bortolussi, A.; Stammer, C. H. *J. Org. Chem.* **1988**, *53*, 992.

(71) Csuk, R.; von Scholz, Y. *Tetrahedron* **1994**, *50*, 10431.
(72) Green, G. R.; Kincey, P. M. *Tetrahedron Lett.* **1992**, *33*, 4609.
(73) Merino, I.; Hegedus, L. S. *Organometallics* **1995**, *14*, 2522.
(74) (a) Tetzlaff, C.; Vilsmaier, E.; Schlag, W.-R. *Tetrahedron* **1990**, *48*, 8117. (b) Barluenga, J.; Aznar, F.; Fernandez, M. *Chem. Eur. J.* **1997**, *3*, 1629.
(75) (a) Yamazaki, S.; Inoue, T.; Hamada, T.; Takada, T. *J. Org. Chem.* **1999**, *64*, 282. (b) Yamazaki, S.; Tanaka, M.; Inoue, T.; Morimoto, N.; Kumagai, H. *J. Org. Chem.* **1995**, *60*, 6546.
(76) Franck-Neumann, M.; Miesch, M.; Kempf, H. *Tetrahedron* **1988**, *44*, 2933.
(77) Kraus, G. A.; Kim, H.; Thomas, P. J.; Metzler, D. E.; Metzler, C. M.; Taylor, J. E. *Synth. Commun.* **1990**, *20*, 2667.
(78) Taylor, E.; Hu, B. *Synth. Commun.* **1996**, *26*, 1041.
(79) (a) Pirrug, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv, Chim. Acta* **1989**, *72*, 1301. (b) Temnikova, T. I.; Semenova, S. N. *Zh. Org. Khim.* **1996**, *2*, 1171.
(80) Burgess, K.; Ho, K.-K.; Ke. C.-Y. *J. Org. Chem.* **1993**, *58*, 3767.
(81) Seebach, D.; Peleties, N. *Chem. Ber.* **1972**, *105*, 111.
(82) Wick, L.; Tamm, C. *Helv. Chim. Acta* **1995**, 78, 403.
(83) Ho, K.-K. Synthesis, Bioactivities and Conformations of Peptidomimetics Containing 2,3-Methanoamino Acids. Ph.D. Thesis, Rice University, Houston, TX.
(84) Park, Y. S.; Beak, P. *Tetrahedron* **1996**, *52*, 12333.
(85) Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *Tetrahedron* **1997**, *53*, 17417
(86) Paulini, K.; Reissig, H. U. *Liebigs Ann. Chem.* **1994**, 549.
(87) Koglin, N.; Zorn, C.; Beumer, R.; Carbele, C.; Bubert, C.; Sewald, N.; Reiser, O.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 202.
(88) Zorn, C.; Gnad, F.; Salmen, S.; Herpin, T.; Reiser, O. *Tetrahedron Lett.* **2001**, *42*, 7049
(89) Zorn, C.; Zerbe, O.; Reiser, O. Unpublished results.
(90) (a) Reichelt, A.; Gaul, C.; Frey, R.; Kennedy, A.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4062. (b) Hillier, M. C.; Davidson, J. P.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 1657. (c) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, 65, 1305. Davidson, J. P.; Martin, S. F. *Tetrahedron Lett.* **2000**, *41*, 9459. (d) Martin, S. F.; Dorsey, G. O.; Gane, T. H.; Hillier, M. C.; Kessler, H.; Baur, M.; Matha, B.; Erickson, J. W.; Bhat, N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. *J. Med. Chem.* **1998**, *41*, 1581. (e) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; DeLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710. (f) Baker, W. R.; Jae, H.-S.; Martin, S. F.; Condon, S. L.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *BioMed. Chem. Lett.* **1992**, *2*, 1405.

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