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Optically Active Oxazolidinones as Michael Donors for the Short and Efficient Synthesis of β-Amino Acids Containing a Cyclopropane Ring[1,2]

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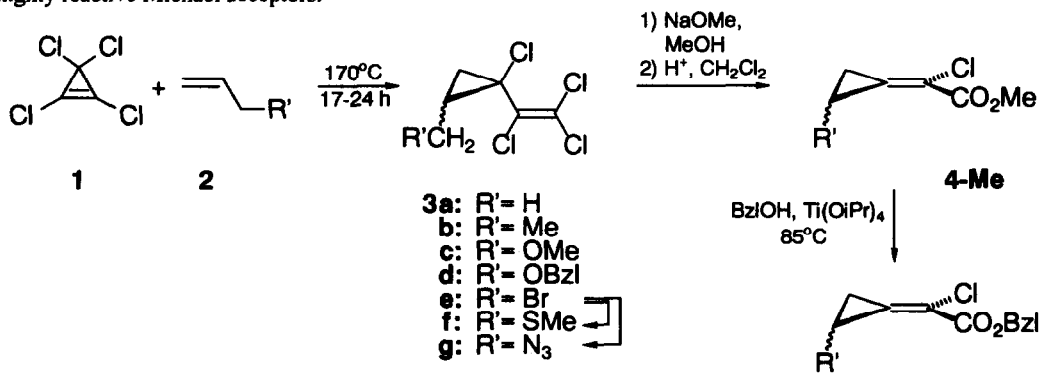
Abstract: The Michael addition of optically active 3,4-diphenyloxazolidinone **5** to 2'-substituted 2-chloro-2-cyclopropylideneacetates yields 2'-substituted 2-cyclopropyl-1'-(2-oxo-3,4-diphenyloxazolidin-3-yl)acetates **6-R** with excellent *trans*-selectivity, which upon reductive dehalogenation and subsequent hydrogenolysis give free 2-(1'-amino-cyclopropyl)acetic acids **9**.

Besides the large number of α-amino acids found in nature, β-amino acids are gaining an ever increasing interest.[3] Amino acids of this type are found in the side chain of taxol,[4] or in sperabillin, an antibiotic effective against gram-positive and gram-negative bacteria.[5] Especially (-)-*cis*-2-aminocyclopentane-1-carboxylic acid (2-ACPC) produced by *Streptomyces setonii* is of interest as it shows excellent *in vitro* and *in vivo* antifungal activity against *Candida albicans*.[6] ACPC is also found in amipurimycin, a nucleoside antibiotic, active against rice blast disease.[7] In addition, ACPC containing dipeptides are being tested as sugar surrogates.[8] In continuing our studies towards the synthesis of various β-amino acids,[9] and of amino acids containing a cyclopropane ring,[10] we found a very efficient way for the preparation of cyclopropyl group containing β-alanine analogues.

The key reaction is a Michael addition of a suitable ammonia equivalent to 2-chloro-2-cyclopropylideneacetates **4**, which can easily be prepared on a multigram scale from adducts **3** of thermally ring-opened tetrachlorocyclopropene **1** to alkenes and functionally substituted alkenes **2** (Scheme 1), and have been found to be highly reactive Michael acceptors.[10-12]



Scheme 1

As previously shown,[10,11] 2-chloro-2-cyclopropylideneacetates of type **4** with a variety of substituents at the C-2' position can be obtained by treatment of 1-chloro-1-(trichloroethenyl)cyclopropanes **3** with sodium methoxide in methanol and subsequent cleavage of the resulting orthoesters with acid (Table 1). Other functional groups like methylthiomethyl and azidomethyl can be generated at the stage of **3** by nucleophilic substitution on

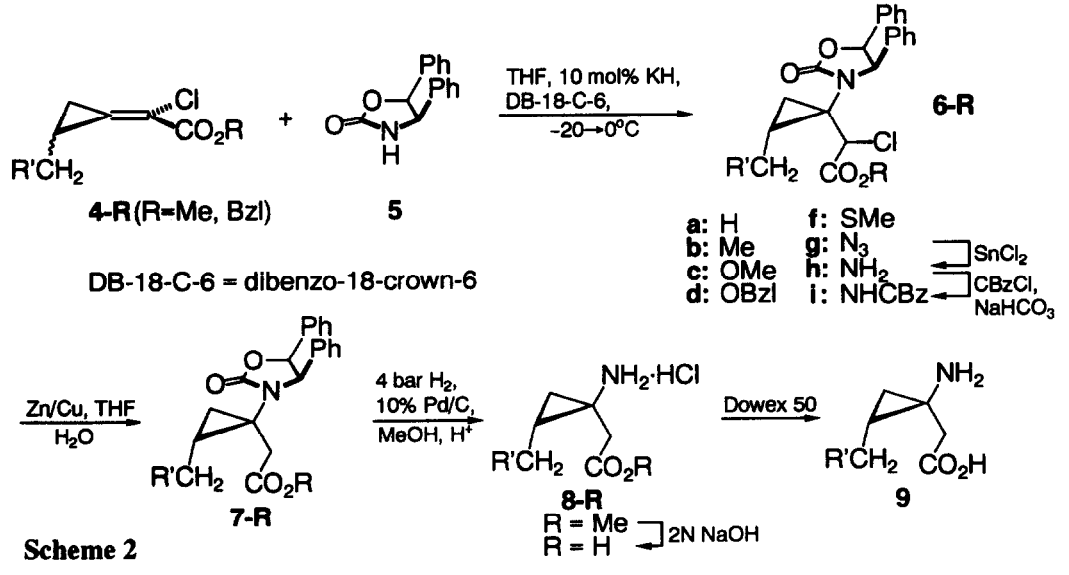
the bromomethyl derivative **3e** with sodium methylthiolate or sodium azide in DMF, respectively, and treatment of the resulting **3f,g** according to the standard protocol.[11] Methyl esters **4-Me** can be transesterified to benzyl esters **4-Bzl** in good yields with titanium tetraisopropoxide in benzyl alcohol (Table 1).[13]

Table 1. 2'-Substituted 2-Chloro-2-cyclopropylideneacetates **4-R** from Alkenes **2** and Tetrachlorocyclopropene **1** via 1-Chloro-1-(trichloroethenyl)cyclopropanes **3**.

1-Chloro-1-trichloroethenylcyclopropanes **3**				Cyclopropylideneacetates **4-R**			
Product	Yield [%]	Product	Yield [%]	Product	Yield [%]	Product	Yield [%]
3a	87			**4a-Me**	52	**4a-Bzl**	70
3b	66			**4b-Me**	51	**4b-Bzl**	91
3c	71			**4c-Me**	50	**4c-Bzl**	73
3d	38			**4d-Me**	50		
3e	38	**3f**[a]	78	**4f-Me**	50		
		3g[a]	82	**4g-Me**	52		

[a] **3f** and **3g** were prepared from **3e**.

The Michael addition of optically active (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one (**5**)[14] in tetrahydrofuran in the presence of 10 mol% potassium hydride to different racemic 2-chloro-2-cyclopropylideneacetates **4-R** gave 1,4-adducts **6-R** not only with excellent *trans*-selectivity with respect to the three-membered ring but also quite good diastereoselectivity with respect to the second newly formed stereogenic center at C-2 (Table 2).[15] Apparently, the protonation of the intermediate enolate occurs with high diastereoselectivity, in spite of the fact that protonation reactions are usually very fast,[16] and the Michael addition had to be carried out at -20 to 0°C.[17] It is noteworthy that the substituent at C-2' appears to be very important for the diastereoselectivity at C-2. The unsubstituted methyl or benzyl 2-chloro-2-cyclopropylideneacetates add **5** with only moderate selectivity.[18]



Scheme 2

Table 2. Michael Addition of (4*S*,5*R*)-4,5-Diphenyloxazolidin-2-one **5** to 2-Chloro-2-cyclopropylidene-acetates **4-R**, Reductive Dehalogenation of the Adduct **6-R**, and Deprotection of the Products **7-R** to give Free β-Amino Acids **9** (Scheme 2).

Starting Material	R'	Product	Yield[a] [%]	Product	Yield [%]	Product	Yield [%]	$[\alpha]_D^{25}$ [°]
4a-Me	H	**6a-Me**	73	**7a-Me-1**[d]	78	**8a-Me-1**	95	
4a-Bzl[b]	H	**6a-Bzl**	48	**7a-Bzl-2**[d]	83	**9a-H-2**	95	+9.5(c=1.0)[c]
4b-Me	Me	**6b-Me**	64	**7b-Me-1**	92	**8b-Me-1**	95	
				7b-Me-2	91	**8b-Me-2**	95	
4b-Bzl	Me	**6b-Bzl**	79	**7b-Bzl-1**	77	**9b-H-1**	95	+3.7(c=1.0)
				7b-Bzl-2	86	**9b-H-2**	94(67)[e]	-3.3(c=1.0)
4c-Me	OMe	**6c-Me**	68	**7c-Me-1**	84	**8c-Me-1**	95	
				7c-Me-2	89	**8c-Me-2**	95	
4c-Bzl	OMe	**6c-Bzl**	69	**7c-Bzl-1**	61	**9c-H-1**	95	+13.5(c=1.0)
				7c-Bzl-2	84	**9c-H-2**	91(80)[e]	-15.4(c=1.0)
4d-Me	OBzl	**6d-Me**	57	**7d-Me-1**	80	**8d-Me-1**	95	-6.1(c=1.0)
				7d-Me-2	71	**9j-H-1**	74	-7.3(c=0.9)[c,f]
4f-Me	SMe	**6f-Me**	59	**7f-Me-1**	91			
4i-Me	NHCBz	**6i-Me**	88	**7i-Me-2**	88	**8h-Me-2**	95	

[a] Yields are those of the sums of both diastereomers related to the racemic starting material. - [b] Bzl = Benzyl. - [c] Solvent: H_2O. - [d] Suffixes 1 and 2 denote the first and second diastereomer obtained upon chromatographic separation of the Michael adducts **6-R**. - [e] Yields in parentheses are those obtained by hydrogenolysis and saponification of methyl esters **8-Me**. - [f] Rotation for **9j** (R' = OH) is that for a mixture of the β-amino acid **9j** (75%) and the corresponding lactone (25%).

The two major diastereomers of **6-R** formed in the Michael addition can be purified by simple flash column chromatography, thus allowing the resolution of the racemate due to the stereogenic 2'-center in the starting material (Table 2).[19] The reductive dehalogenation of the purified diastereomers of **6-R** with zinc copper couple in aqueous tetrahydrofuran[20] leads to the protected precursors of 2'-substituted 2-(1-aminocyclopropyl)acetic acids. The methyl esters **7-Me** can be deprotected in two steps to give free amino acids **9** by first removing the chiral auxiliary by catalytic hydrogenation, and secondly saponifying the methyl ester with 2 N sodium hydroxide. This has been exercised for two examples, namely **8a-Me**, **8b-Me** and **8c-Me**, with overall yields ranging from 67 to 80%. The benzyl esters **7-Bzl** obtained when starting with benzyl 2-chloro-2-cyclopropylideneacetates **4-Bzl** yield free β-amino acids **9** almost quantitatively in a single operation by catalytic hydrogenation.[21] The overall yields in sequences via benzyl esters **4-Bzl** are much higher (Table 2), which makes this route the more favorable one.

The reported simple protocol allows the preparation of a number of 2'-substituted 2-(1-aminocyclopropyl)acetic acids from correspondingly substituted 2-chloro-2-cyclopropylideneacetates. It demonstrates the advantage of using optically active (4*S*,5*R*)-4,5-diphenyloxazolidin-2-one as a Michael donor, as it allows the formation of two chiral centers from the prochiral centers at C-2 and C-1' in the starting material with excellent and good selectivity in one pot. At the same time the chirality introduced during the Michael addition can be used as the auxiliary for the resolution of the third chiral center at C-2', which is racemic in the starting material **4**. Further applications of this protocol to other highly reactive Michael acceptors are underway.

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(17) (4*S*,5*R*)-4,5-Diphenyloxazolidin-2-one is a very poor nucleophile. This still holds for the anion generated by deprotonation at the carbamate position and activation by addition of dibenzo-18-crown-6 to the reaction mixture, and causes that the Michael addition is still very slow at -78°C. The best temperature is -20 → 0°C. The higher the temperature the more decomposition product is formed during the Michael addition.
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(19) All new compounds were fully characterized by spectroscopic techniques (^{1}H NMR, ^{13}C NMR, IR, MS) and their molecular formulas in general established by microanalysis or high resolution mass spectrometry. ^{1}H NMR (250 MHz, $CDCl_3$) data of representative products are as follows: **6b-Et** (1st isomer): 0.18 (dd, 1 H, J = 6.3, J = 8.0 Hz), 0.68 (dd, 1 H, J = 6.1, J = 9.6 Hz), 0.93 (t, 1 H, J = 7.2 Hz), 1.01-1.19 (m, 1 H), 1.65-1.78 (m, 1 H), 1.82-1.98 (m, 1 H), 4.17 (s, 1 H), 5.13 (d, 1 H, J = 11.9 Hz), 5.22 (d, 1 H, J = 11.9 Hz), 5.52 (d, 1 H, J = 7.8 Hz), 5.55 (d, 1 H, J = 7.9 Hz), 6.74- 6.83 (m, 2 H), 6.84-6.89 (m, 2 H), 6.93-7.06 (m, 6 H), 7.21-7.32 (m, 3 H), 7.39-7.43 (m, 2 H). - **6b-Et** (2nd isomer): 0.68 (t, 1 H, J = 7.3 Hz), 0.66-0.75 (m, 1 H), 0.98 (t, 1 H, J = 7.1 Hz), 0.99-1.14 (m, 1 H), 1.23-1.40 (m, 1 H), 1.66 (dd, 1 H, J = 6.6, J = 9.7 Hz), 4.08 (s, 1 H), 5.19 (s, 2 H), 5.53 (d, 1 H, J = 7.7 Hz), 5.90 (d, 1 H, J = 7.7 Hz), 6.76-6.78 (m, 2 H), 6.87-6.91 (m, 2 H), 6.93-7.17 (m, 6 H), 7.25-7.33 (m, 3 H), 7.41-7.44 (m, 2 H). - **7b-Et-2**: 0.52 (t, 1 H, J = 6.4 Hz), 0.75 (t, 3 H, J = 7.3 Hz), 0.80-0.87 (m, 1 H), 0.98-1.19 (m, 1 H), 1.20-1.39 (m, 1 H), 2.42 (d, 1 H, J = 16.6 Hz), 3.12 (d, 1 H, J = 16.6 Hz), 5.12 (d, 1 H, J = 6.3 Hz), 5.13 (d, 1 H, J = 0.8 Hz), 5.65 (d, 1 H, J = 7.9 Hz), 6.78-6.89 (m, 4 H), 7.01-7.06 (m, 6 H), 7.40-7.45 (m, 5 H). - **9b-Et-2** (in D_2O): 0.36 (t, 1 H, J = 6.3 Hz), 0.82 (t, 3 H, J = 7.1 Hz), 0.92 (dd, 1 H, J = 6.9, J = 9.7 Hz), 1.01-1.31 (m, 4 H), 2.30 (d, 1 H, J = 17.6 Hz), 2.44 (d, 1 H, J = 17.6 Hz).
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