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Two-Step Stereocontrolled Synthesis of Densely Functionalized Cyclic β-Aminoesters Containing Four Stereocenters, Based on a New Cerium(IV) Ammonium Nitrate Catalyzed Sequential Three-Component Reaction

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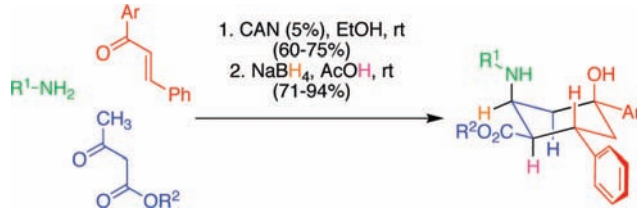
ABSTRACT



The cerium(IV) ammonium nitrate (CAN)-catalyzed sequential, one-pot reaction between alkylamines, β-ketoesters, and chalcones afforded *cis*-4,6-disubstituted 2-alkylaminocyclohexene-1-carboxylic esters with complete diastereoselectivity. The carbon−carbon double bond of these compounds was reduced with sodium triacetoxyborohydride, again with complete diastereoselectivity. This novel two-step route allows the transformation of very simple acyclic starting materials into tetrasubstituted cyclohexane derivatives bearing four functional groups, including a *cis*-β-aminoester moiety, and generates four stereocenters, three of which are adjacent and one of which is quaternary.

β-Amino acids and their esters have attracted much attention in recent years[1] due to their biological and pharmacological relevance. Although they are less widely distributed than their α counterparts, a considerable number of bioactive natural products contain β-amino acid moieties, including, among many others, the β-lactam antibiotics,[2] antitumor compounds such as taxol,[3] cryptophycin 1,[4] and dolastatin 11,[5] the antibiotics nodularin and microcistin,[6] the marine antifungal agent jasplakinolide,[7] and the aminopeptidase inhibitors bestatin and amastatin.[8] In addition, β-amino acids are very important in medicinal chemistry because they allow the creation of peptidomimetics that not only have potent biological activity but also are resistant to proteolysis[9,10] and hence have improved pharmacokinetic properties with regard

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to the natural peptides. Peptides composed of β-amino acids (β-peptides) fold into three-dimensional structures similar to those of the natural peptides and often exhibit important pharmacological properties. For example, some peptides related to the general structure **1** (Figure 1) are antibiotics,

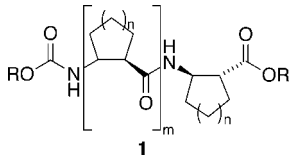

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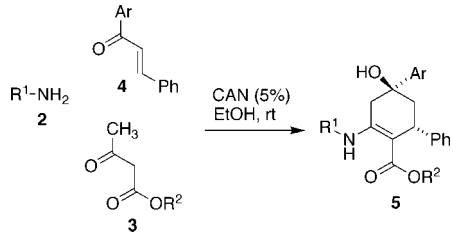
Figure 1. Example of a biologically active β-peptidic structure.

and most interestingly, they have shown activity against vancomycin-resistant bacteria.[11]

In spite of the importance of cyclic β-amino acid derivatives, exemplified by the components of **1**, there are relatively few methods that allow their preparation. We present here a new procedure for the synthesis of highly substituted and functionalized derivatives of 2-amino-1-cyclohexene-1-carboxylic acid bearing up to four stereocenters, three of which are adjacent and the fourth which is quaternary. This method involves a new three-component reaction[12] from acyclic precursors, catalyzed by cerium(IV) ammonium nitrate, for the diastereoselective construction of a tetrasubstituted cyclohexene derivative containing an unsaturated β-aminoester moiety, followed by the stereoselective reduction of a double bond within the initial (cyclized) reaction product.

As shown in Scheme 1 and Table 1, the reaction at room temperature between primary amines **2**, β-ketoesters **3**, and

Scheme 1. Sequential Three-Component Reaction between Primary Amines, β-Ketoesters, and Chalcones



chalcones **4**, in the presence of a catalytic amount (5 mol %) of cerium(IV) ammonium nitrate (CAN), afforded 2-aminocyclohex-1-ene-1-carboxylic esters **5**[13] in good yields, with a molecule of water as the only byproduct. The reaction proceeded with complete selectivity in favor of the diastereoisomer having a *cis*-arrangement for the aryl substituents at C-4 and C-6, with both substituents placed in an equatorial position. The choice of CAN as the catalyst was based on its low oxophilicity in comparison to other Lewis acids,[14] which prevented loss of the hydroxyl group by elimination. The use of chiral amines as starting materials

Table 1. CAN-Catalyzed Preparation of 2-Alkylamino-1-cyclohexene-1-carboxylic Esters

entry	compd	R^1	R^2	Ar	time, h	yield, %
1	**5a**	*n*Bu	Et	Ph	30	63
2	**5a**	*n*Bu	Et	Ph	42	77
3	**5b**	*n*Bu	Et	4-ClC_6H_4	42	73
4	**5c**	*n*Bu	*t*Bu	Ph	42	80
5	**5d**	*n*Bu	*t*Bu	4-ClC_6H_4	42	81
6	**5e**	nC_6H_{13}	Et	Ph	45	71
7	**5f**	nC_7H_{15}	Et	Ph	45	73
8	**5g**	nC_6H_{13}	Et	4-ClC_6H_4	42	68
9	**5h**	nC_7H_{15}	Et	4-ClC_6H_4	42	72
10	**5i**[a]	(±)-2-Me-Bu	Et	Ph	45	71
11	**5i**[a]	(*S*)-2-Me-Bu	Et	Ph	48	74
12	**5j**[a]	(±)-sec-Bu	Et	Ph	96	74
13	**5j**[a]	(*R*)-sec-Bu	Et	Ph	96	72

[a] As a 1:1 diastereomeric mixture.

did not lead to any observable enantioselection, as shown by the absence of optical rotation and the comparison of the products arising from the racemic and enantiomerically pure amines (e.g., entries 10 and 11 and 12 and 13),[15] which were studied by NMR techniques and also by HPLC with conventional and chiral columns. All attempts to extend the scope of the reaction by using α,β-unsaturated ketones different from chalcones or γ-substituted β-ketoesters have been unsuccessful so far. The structural and stereochemical assignment of compound **5** was based on spectroscopic data and confirmed by the single-crystal X-ray diffraction study of **5c** (Figure 2).

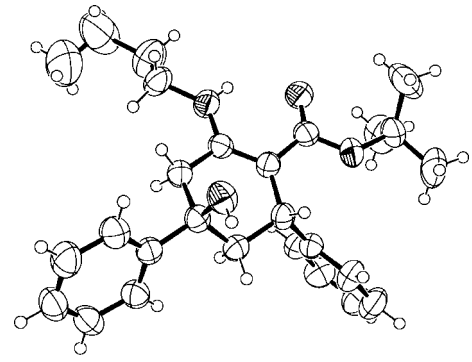
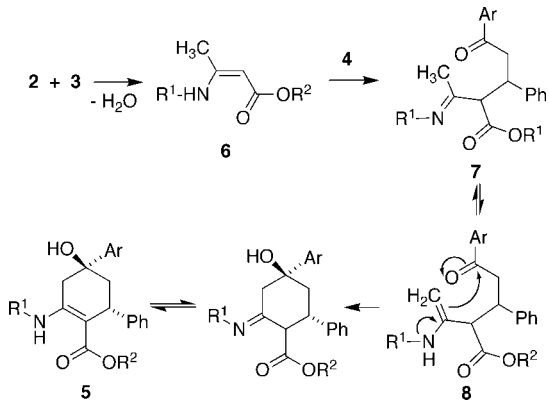


Figure 2. X-ray diffraction structure of compound **5c**.

Cyclohexene derivatives **5** are proposed to arise from an initial CAN-catalyzed reaction[16] between amines **2** and β-ketoesters **3** to give β-enaminones **6**, followed by a Michael addition to the enone system in substrates **4** to give **7**, imine−enamine tautomerism to **8**, and a final cyclization step, where the tendency of both aromatic substituents to sit in equatorial positions controls the stereochemistry of the final products (Scheme 2). In agreement with this hypothesis, a control experiment run from an isolated enaminone **6**

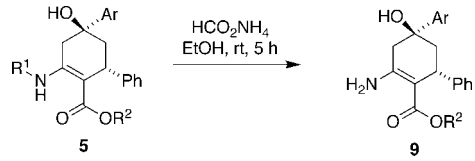
Scheme 2. Mechanism Proposed for the Three-Component Reaction Leading to Compounds **5**



generated from butylamine **2a** and ethyl acetoacetate **3a** gave a result identical to that obtained in the corresponding three-component reaction (78% yield of compound **5a**).

To facilitate the application of this chemistry to the peptide field, it was important to consider the preparation of *N*-unsubstituted analogues of aminoesters **5**. After some experimentation, we found an efficient method leading to this type of compound, consisting of the displacement of

Scheme 3. Displacement of the Alkylamino Group in Compound **5** by Ammonia



the alkylamino unit of **5** by ammonia through an addition−elimination mechanism. Thus, as shown in Scheme 3 and Table 2, exposure of some representative compounds **5** to a

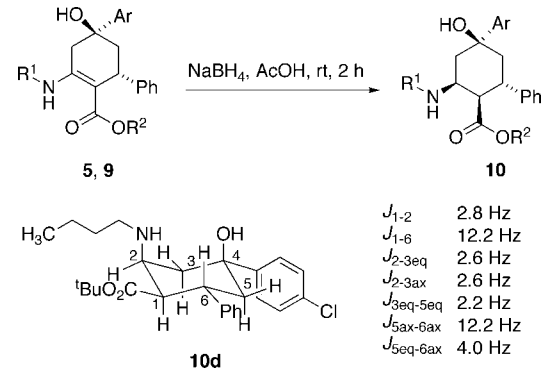
Table 2. Synthesis of 2-Amino-1-cyclohexene-1-carboxylic Esters **9** from Compounds **5**

entry	starting material	R^1	R^2	Ar	product	yield, %
1	**5a**	*n*Bu	Et	Ph	**9a**	88
2	**5b**	*n*Bu	Et	4-ClC_6H_4	**9b**	87
3	**5c**	*n*Bu	*t*Bu	Ph	**9c**	90
4	**5d**	*n*Bu	*t*Bu	4-ClC_6H_4	**9d**	88
5	**5g**	*n*C_6H_{13}	Et	4-ClC_6H_4	**9b**	85
6	**5h**	*n*C_7H_{15}	Et	4-ClC_6H_4	**9b**	87
7	**5i**	(*S*)-2-Me-Bu	Et	Ph	**9a**	90

solution of ammonium formate in ethanol at room temperature for 5 h gave the desired *N*-unsubstituted compounds **9** in excellent yields. We expect that this very simple protocol will provide a general method for the displacement of alkylamino groups in unsaturated β-aminoesters by ammonia.

Finally, we undertook the study of the reduction of the C=C double bond in compounds **5** and **9**. After some unsuccesful attempts with other reagents, we found that sodium triacetoxyborohydride, generated in situ from sodium borohydride and acetic acid,[17] effected the desired transformation in good to excellent yields, affording compounds **10** as a single diastereoisomer (Scheme 4 and Table 3). The

Scheme 4. Fully Diastereoselective Reduction of Compounds **5** and **9** by Sodium Triacetoxyborohydride



stereochemical assignment of compounds **10** was based on that previously established for **5**and also on detailed coupling

Table 3. Reduction of 2-Amino-1-cyclohexene-1-carboxylic Esters

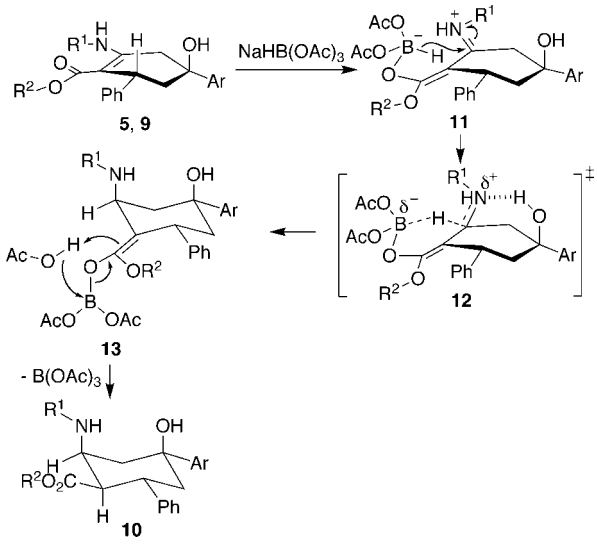
entry	starting material	R^1	R^2	Ar	product	yield, %
1	**5a**	*n*Bu	Et	Ph	**10a**	94
2	**5b**	*n*Bu	Et	4-ClC_6H_4	**10b**	73[a]
3	**5c**	*n*Bu	*t*Bu	Ph	**10c**	71[a]
4	**5d**	*n*Bu	*t*Bu	4-ClC_6H_4	**10d**	73[a]
5	**5e**	*n*C_6H_{13}	Et	Ph	**10e**	75[a]
6	**5f**	*n*C_7H_{15}	Et	Ph	**10f**	76[a]
7	**5g**	*n*C_6H_{13}	Et	4-ClC_6H_4	**10g**	84[a]
8	**5h**	*n*C_7H_{15}	Et	4-ClC_6H_4	**10h**	81[a]
9	**9a**	H	Et	Ph	**10i**	95
10	**9b**	H	Et	4-ClC_6H_4	**10j**	94
11	**9c**	H	*t*Bu	Ph	**10k**	95
12	**9d**	H	*t*Bu	4-ClC_6H_4	**10l**	93

[a] In these cases, compounds **10** were accompanied by small amounts of side products containing a C_3=C_4 double bond, presumably arising from elimination of a molecule of water from **10**.

constant studies, which are summarized in Scheme 4 for the case of compound **10d**. The conformation proposed for compounds **10** is probably stabilized by an intramolecular hydrogen bond between the axial hydroxy and alkylamino substituents.

The diastereoselectivity observed in the reduction step can be explained by the mechanism proposed in Scheme 5. As

Scheme 5. Mechanistic Proposal for the Diastereoselectivity Observed in the Reduction of Compounds **5** and **9** to **10**



described in the literature for a related reduction,[17] coordination to boron should take place on the enol tautomer of the starting material, leading to **11**, and the first hydride transfer step can be expected to take place from the face opposite to the hydroxyl group, as this would allow an intramolecular hydrogen bond to develop in the transition state **12**. Protonation of the enol moiety in **13** would then take place from the face opposite to the amino and hydroxyl substituents, leading to the observed stereochemistry for compounds **10**.

In summary, we have developed an experimentally convenient, user- and environmentally friendly two-step protocol that requires simple, inexpensive, and readily available starting materials, reagents, and catalysts and allows the efficient and completely diastereoselective synthesis of tetrasubstituted cyclohexane frameworks bearing four functional groups, including a *cis*-β-aminoester moiety and containing four stereocenters, three of which are adjacent and a fourth which is quaternary.

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Supporting Information Available: Representative experimental procedures, characterization data for compounds **5**, **9**, and **10**, X-ray data and cif file for **5c**, and spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In most reactions, compounds **5** were accompanied by small amounts (5−10%) of the corresponding 1,3-cyclohexadiene derivatives, arising from elimination of a molecule of water.

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(15) Although the reaction described here is unprecedented, there is a literature report of the preparation of 1-acetyl-2-alkylamino-1,3-cyclohexadiene derivatives in 0−74% yield from β-enaminones and chalcones generated in situ from aryl bromides and propargyl alcohols. See: Schramm, O. G.; Müller, T. J. J. *Synlett* **2006**, 1841.

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