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Synthesis of Cyclobutane Serine Analogues

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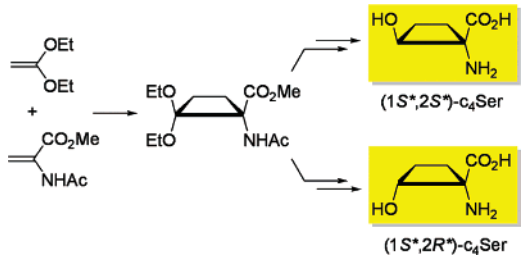

In this paper, we describe a thermal [2 + 2] cycloaddition involving 2-acylaminoacrylates as electron-poor acceptor alkenes, a reaction that involves a Michael−Dieckmann-type process. The reaction gives rise to a new substituted cyclobutane skeleton that can be transformed into amino acid derivatives. For example, a number of transformations were carried out to give the two pairs of stereoisomers of the 2-hydroxycyclobutane-α-amino acid serine analogue (c_4Ser); compounds **22** and **23**. This synthesis covers a gap in knowledge in the broad field of restricted amino acids.

The introduction of small-ring systems, especially cyclobutane derivatives, as molecular building blocks has recently gained increasing significance.[1] However, amino acids from the cyclobutane series have been investigated very little.[2] Prior to 1980, these amino acids were almost the only type of amino acids that had not been detected in natural sources.[3] The biological significance of 1-aminocyclobutanecarboxylic acid derivatives has been well-documented in several publications that provide evidence of their extremely high activity as *N*-methyl-D-aspartate (NMDA) receptor agonists or antagonists attending the substitution.[4]

In recent years, extraordinary advances in the synthesis of new nonproteinogenic α,α-disubstituted amino acids[5] has allowed the development of peptidomimetics and pseudopeptides. In this sense, substituted 1-aminocycloalkanecarboxylic acids have been the focus of many researchers, although the synthesis of substituted 1-aminocyclobutanecarboxylic acids has not received the same level of attention.[6] Despite this, conformational studies on model peptides with 1-aminocyclobutanecarboxylic acid residues have been published, indicating that this type of amino acid derivative can be accommodated in folded motifs commonly found in proteins and peptides.[7] Given these results, it appears likely that cyclobutane-α-amino acids could be used for the design of conformationally restricted peptides and peptidomimetics.

A few methods for the synthesis of 2-substituted 1-aminocyclobutanecarboxylic acids have been described in the last year.[8] However, serine analogues that incorporate the cyclobutane skeleton (c_4Ser) have not been synthesized to date. Taking into account that numerous analogues of serine have been synthesized as acyclic and cyclic compounds, filling this gap in our knowledge is an attractive goal. We report here the first synthesis of both two pairs of stereoisomers of c_4Ser.

In an effort to achieve the goal outlined above, we envisioned that the reaction between 2-acylaminoacrylates and electron-rich donor alkenes could furnish the desired four-ring system with oxygen substitution in the 2-position. The important role played by 2-amidoacrylates in the field of novel amino acids has made these compounds the subject of several synthetic studies.[9] However, these compounds have never been investigated in terms of [2 + 2] reactions, although methyl acrylate, an olefin acceptor, has been widely used as a starting material in [2 + 2] cycloadditions.[10]

Thermal (nonphotochemical) reactions of electron-rich donor alkenes with electron-poor acceptor alkenes usually lead to cyclobutanes via zwitterionic intermediates,[11] and in some cases, these intermediates could incorporate another alkene—electron-poor or electron-rich—to furnish a cyclohexane ring.[12] Vinyl ethers and the most effective ketene diethyl acetal have been used as electron-rich olefins. As electron-poor olefins, the whole range of tri- and tetrasubstituted ethylenes containing combinations of ester (weak acceptor) and cyano (strong acceptor)

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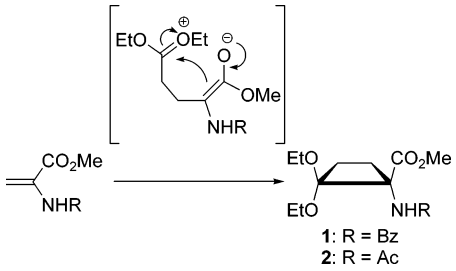
TABLE 1. Reactivity of Electron-Poor Acceptor Alkenes $H_2C{=}CR_1R_2$ and Ketene Diethyl Acetal

entry	R_1	R_2	equiv	solvent	product	yield[a] (%)
1	CN	H	2	^{t}BuOH	cyclobutane	62,[b] 27[c]
2	CO_2Me	H	1	CH_3CN	cyclobutane	44,[b] 60,[c] 63[d]
3	CN	CN	5.5	CH_2Cl_2	cyclohexane	47[e]
4	CN	CO_2Me	1	CH_3CN	cyclohexane	85[f]
5	CO_2H	NHAc	2 + 8	^{t}BuOH		
6	$CONH^iPr$	NHAc	2 + 8	^{t}BuOH		
7	CO_2Me	NHAc	10	^{t}BuOH	cyclobutane	11
8	CO_2Me	NHAc	5 + 5	^{t}BuOH	cyclobutane	25
9	CO_2Me	NHAc	5 + 5	Bu_2O	cyclobutane	9
10	CO_2Me	NHBz	2 + 8[g]	^{t}BuOH	cyclobutane (**1**)	51
11	CO_2Me	NHAc	2 + 8[g]	^{t}BuOH	cyclobutane (**2**)	64

[a] Yield after column chromatography. [b] See ref 10c. [c] See ref 10b. [d] See ref 10a. [e] See ref 15. [f] See ref 12. [g] The last 8 equiv were added as a solution in ^{t}BuOH by syringe pump over 90 min.

SCHEME 1. Thermal [2 + 2] Cycloaddition of Methyl 2-Acylaminoacrylate and Ketene Diethyl Acetal



groups have been used. When monosubstituted acceptor alkenes are used, the donor alkene must be highly reactive.[12b] Acrylonitrile and methyl acrylate do not react with vinyl ethers under these conditions but do react with ketene diethyl acetal to form cyclobutanes, as recently shown by Hall, Jr., and co-workers, to give 62% and 44% yield, respectively (Table 1, entries 1 and 2).[10c]

Bearing in mind the information outlined above, we recently reported a communication about the reaction between 2-acylaminoacrylates and ketene diethyl acetal.[13] Several sets of conditions were applied to this reaction (Table 1) following previous work on thermal [2 + 2] cycloadditions by Huisgen,[11] Scheeren[14] and Hall, Jr.[12]

The mechanism proposed for the thermal [2 + 2] cycloaddition between acrylates and ketene diethyl acetal involves zwitterionic intermediates, so that we attempted the reaction in two solvents (^{t}BuOH and Bu_2O), obtaining better yields when a polar solvent was used (entries 8 and 9, Table 1). Reaction did not occur for entries 5 and 6 in Table 1 (R_1 = CO_2H or $CONH^iPr$ and R_2 = NHAc). When the ketene diethyl acetal was added in one portion the best result afforded only 11% yield of compound **2** (Scheme 1). The use of inhibitors[10c] such as DABCO and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (SULFIDE) furnished similar yields. Nevertheless, when the ketene diethyl acetal was added in two portions the yield increased to 25%. Unexpectedly, when the addition was

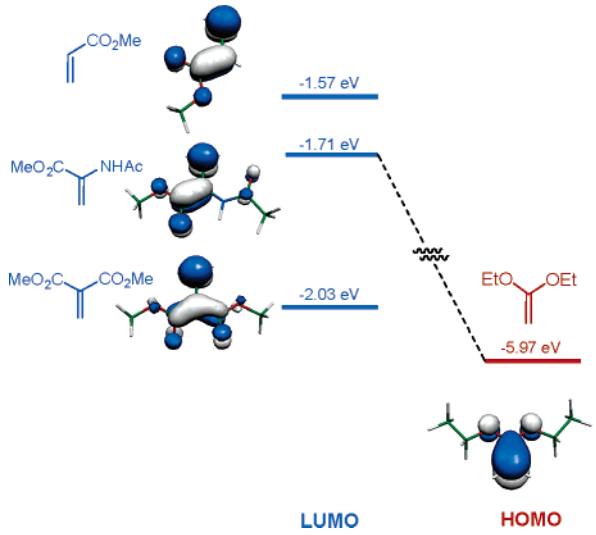


FIGURE 1. Evaluation of LUMO energies for various acceptor olefins and HOMO energy of ketene diethyl acetal.

completed by syringe pump (8 equivalents dissolved in ^{t}BuOH added over 90 min) the yield reached 64%, a better result than in the cases of acrylonitrile and methyl acrylate.

This reaction represents the first time that alkyl 2-acylaminoacrylates have been reacted with an electron-rich olefin to afford the cyclobutane ring in a good yield. In an effort to explain this reactivity of methyl 2-acetamidoacrylate, and taking into account that the reaction is driven by HOMO-donor olefin and LUMO-aceptor olefin,[12c,14a] we compared the LUMO energies for several acceptor olefins at the B3LYP/6-31+G(d) theory level for optimized geometries using the Gaussian 98 package.[16] The value for the LUMO energy of methyl 2-acetamidoacrylate is −1.71 eV, for methyl acrylate (monoactivated olefin) it is −1.57 eV and for dimethyl 2-methylenemalonate (diactivated olefin) the LUMO energy is −2.03 eV. The difference $E_{HOMO} - E_{LUMO}$ for methyl 2-acetamidoacrylate (4.26 eV) is located between the monoactivated (4.40 eV) and diactivated (3.94 eV) olefins and it appears reasonable to believe that the reactivity of methyl 2-acetamidoacrylate will be similar or superior to that of methyl acrylate. Moreover, the formation of the cyclohexane derivatives, as occur in entries 3 and 4 in Table 1, was not observed (Figure 1).

With the aim of obtaining both pairs of stereoisomers of c_4Ser, we attempted the transformation of the diethyl acetal group of compound **2** into the corresponding ketone. However, all attempts to remove the protecting group, including treatment with formic acid, were unsuc-

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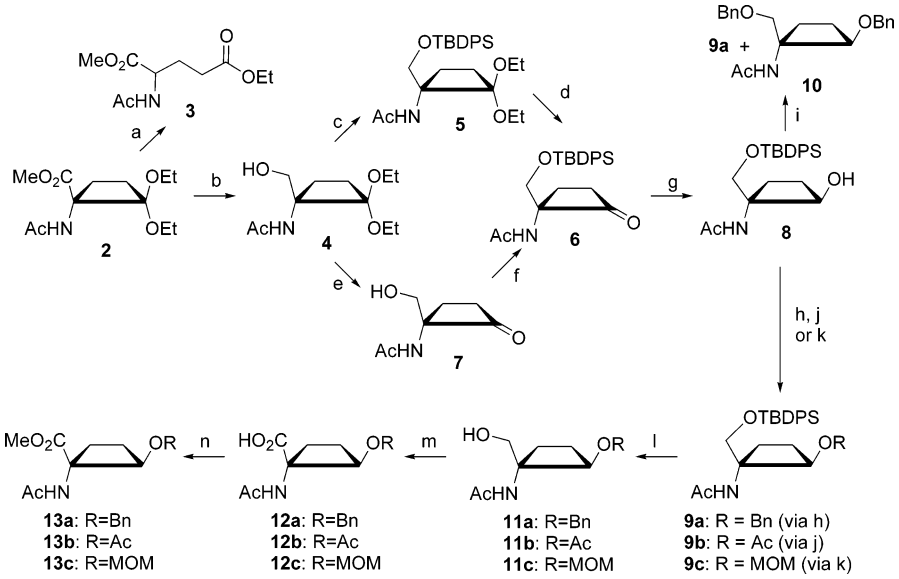
SCHEME 2[a]



[a] Key: (a) formic acid 88%, 35 °C, 65%; (b) $LiBH_4$, Et_2O, 0 °C to rt, 90%; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, 86%; (d) 0.5 N HCl, THF, rt, 35%; (e) 0.5 N HCl, THF, rt, 90%; (f) TBDPSCl, imidazole, DMF, 50 °C, 97%; (g) $NaBH_4$, EtOH/THF, 0 °C, 91%; (h) benzyl 2,2,2-trichloroacetimidate, triflic acid, Et_2O, 0 °C to rt, 40%; (i) NaH, BnBr, Bu_4NI, THF, rt, 20% of **10** and 16% of **9a**; (j) acetic anhydride, DMAP, pyridine, rt, 96%; (k) MOMCl, DIEA, 0 °C to rt, 60%; (l) TBAF, THF, 0 °C to rt, 72% of **11a**, 30% of **11b** and 60% of **11c**; (m) Jones reagent, acetone, 0 °C, 70% of **12a**, 72% of **12b** and 80% of **12c**; (n) CH_2N_2, Et_2O, rt, 95% of **13a**, 93% of **13b**, and 73% of **13c**.

cessful (Scheme 2). The electron-withdrawing character of the carboxylate group facilitates the stabilization of the carbanion to force the retro-Dieckmann-type reaction. This process led to the acyclic product, a new glutamic acid derivative (**3**) whose structure was unambiguously determined by X-ray diffraction. In these cases, the usual procedure to avoid this opening reaction involves reduction of the methyl ester group to a primary alcohol. Therefore, compound **2** was reduced using $LiBH_4$ in Et_2O to give the corresponding cyclobutylmethanol **4** (Scheme 2).

An attempt at direct oxidation of the alcohol group and hydrolysis of the ketal group by treatment with Jones reagent furnished a complex mixture of compounds.[10b] Protection of the alcohol group with *tert*-butyldiphenylsilyl chloride (TBDPSCl) gave compound **5** in good yield. This compound was subsequently hydrolyzed to ketone **6** by treatment with HCl in THF. A better yield was obtained when this process was inverted, i.e., first the hydrolysis to obtain the keto alcohol **7** and then the protection with *tert*-butyldiphenylsilyl chloride (Scheme 2).

The reduction of the ketone group of compound **6** on the opposite side to the silyl group, due to the spatial requirement of this group, gave alcohol **8** as a single stereoisomer. The stereochemistry of this compound was assigned unambiguously by NOE experiments and X-ray diffraction (Scheme 2).

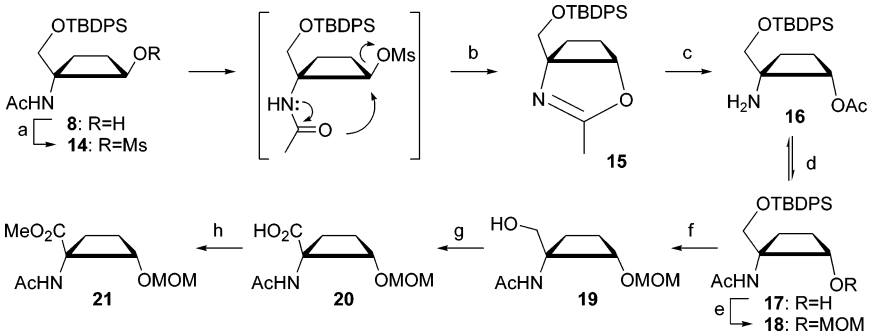
Protection of the secondary alcohol with BnI in the presence of NaH gave benzylated alcohol **9a** in low yield and furnished compound **10** from deprotection of silyl group and benzylation of the primary alcohol. The use of benzyl 2,2,2-trichloroacetimidate (BTCA)[17] as the protecting reagent led to a better yield of the required compound **9a**. An attempt to improve the yield of the protection step was made by testing two additional protecting groups. Acetylation of the alcohol in the presence of acetic anhydride and DMAP in pyridine provided the acetylated compound **9b** in 96% yield. The use of the MOMCl as the protecting agent in diisopropylethylamine (DIEA) gave compound **9c** in 60% yield (Scheme 2).

The next reaction sequence on the three protected alcohols (benzyl, acetyl, and methoxymethyl derivatives **9a**, **9b**, and **9c**, respectively) involved cleavage of the silyl group with TBAF, oxidation in the presence of Jones reagent and isolation of the target compounds—the desired carboxylic acid derivatives **12a**, **12b**, and **12c**. Deprotection of the silyl group gave moderate yields in the cases of benzyl and methoxymethyl derivatives. However, difficulties were encountered in obtaining the alcohol from the acetyl compound. In this case, the acetyl group underwent multiple transacetylations to give several acetylated derivatives. This phenomenon could be favored by the short distance between the hydroxyl and amino groups. The oxidation stage gave moderate yields in all cases. In the last step, purification of the target compounds was achieved through esterification with diazomethane to obtain, after column chromatography, the pure (1*R**,2*R**)-Ac-c_4Ser(OR)-OMe derivatives **13a**, **13b**, and **13c**. The best yield was obtained for the methoxymethyl derivative, with (1*R**,2*R**)-Ac-c_4Ser-(OMOM)-OMe (**13c**) isolated in a 9% overall yield from methyl 2-acetamidoacrylate (Scheme 2).

It was desirable to obtain the other stereoisomer of (1*R**,2*R**)-c_4Ser; protected (1*R**,2*S**)-c_4Ser in which the hydroxyl group is located cis with respect to the amino group. It was envisioned that this goal could be achieved by activating the alcohol group of compound **8** to give

(17) *Handbook of Reagents for Organic Synthesis. Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. J., Eds.; John Wiley & Sons: 1999.

SCHEME 3[a]



[a] Key: (a) MsCl, DIEA, CH_2Cl_2, 0−40 °C, 95%; (b) Et_3N, DMF, 130 °C, 99%; (c) 0.1 N HCl, THF, rt, 98%; (d) silica gel, CH_2Cl_2, rt, 76%; (e) MOMCl, DIEA, 0 °C to rt, 82%; (f) TBAF, THF, 0 °C to rt, 60%; (g) Jones reagent, acetone, 0 °C, 80%; (h) CH_2N_2, Et_2O, rt, 60%.

compound **14**, and then carrying out the nucleophilic displacement with an oxygen nucleophile. On the basis of our experience with similar cyclic compounds, we ruled out the use of the typical Mitsunobu reaction. As an alternative, the mesylated compound **14** was obtained with MsCl and DIEA in CH_2Cl_2, and an S_N2 reaction was attempted with ammonium benzoate ($BzONH_4$) in DMF. This gave a mixture of two compounds corresponding to the inverted alcohol and oxazoline **15**, both in a low yield, but did not give any benzoate derivative. In view of this fact, and in order to generate the intramolecular displacement of the oxygen from the acetamide group, we carried out the reaction in DMF and in the presence of Et_3N, which gave oxazoline **15** as the only product (Scheme 3).[18]

Compound **15** is extremely unstable, and purification proved impossible. Hydrolysis of **15** was therefore performed in the presence of 0.1 N HCl to give compound **16**, in which the amine group is free and the alcohol is acetylated. With the aim of following a similar synthetic pathway to that described for compound **13c**, it was necessary to obtain the corresponding compound in which the alcohol was free and the amino group acetylated. The equilibrium of the transacetylation reaction was displaced to the desired compound (**17**) by treatment with silica gel. The structure of this compound was unambiguously determined by X-ray diffraction (Scheme 3).

The protection of alcohol **17** with MOMCl in the presence of DIEA furnished compound **18** in 82% yield—higher than the yield obtained for the protection of alcohol **8**, which had a trans disposition with respect to the amino group. The route described to obtain methyl ester **13c** from compound **9c** was also employed for obtaining methyl ester **21** from compound **18**, i.e., deprotection of the silyl group, Jones oxidation, and treatment with diazomethane to furnish the (1*R**,2*S**)-Ac-c_4Ser-(OMOM)-OMe (**21**) in 8% overall yield from methyl 2-acetamidoacrylate (Scheme 3).

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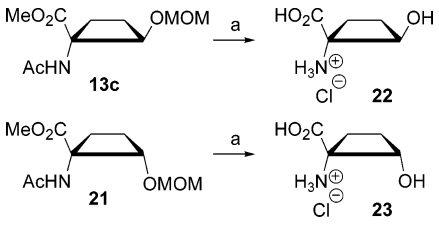
SCHEME 4[a]



[a] Key: (a) 3 N HCl, 60 °C, 47% of **22** and 59% of **23**.

Finally, we explored the possibility of removing the protecting groups without damaging the cyclobutane structure. Therefore, after several conditions tested, we obtained the corresponding cyclobutane amino acids **22** and **23** from **13c** and **21**, respectively, as hydrochloride derivatives using controlled acid hydrolysis (Scheme 4).

In conclusion, we have developed a thermal [2 + 2] cycloaddition on dehydroamino acid derivatives that involves a Michael−Dieckmann-type reaction. The special reactivity has been discussed in terms of frontier orbital theory. The result of the reaction is a new cyclobutane skeleton that can be incorporated into amino acid derivatives. As an example of this application, the two pairs of stereoisomers of the amino acid c_4Ser were obtained so much as protected derivatives (compounds **13c** and **21**) as well as hydrochloride forms (compounds **22** and **23**).

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Supporting Information Available: Experimental procedures for all compounds, copies of ^1H and ^{13}C NMR spectra and $^1H-^1H$ and $^1H-^{13}C$ correlations for most of the compounds obtained, and NOE data for compound **8**. X-ray data for compounds **3**, **8**, and **17** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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