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Tetrahedron: *Asymmetry* 17 (2006) 1985–1989

1,3-Dipolar cycloadditions of azomethine ylides with chiral acrylates derived from methyl (*S*)- and (*R*)-lactate: diastereo- and enantioselective synthesis of polysubstituted prolines

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Received 2 June 2006; accepted 6 July 2006
Available online 27 July 2006

Abstract—The 1,3-dipolar cycloaddition of acrylates derived from methyl (*R*)- and (*S*)-lactate, as chiral dipolarophiles, with glycine and alanine derived azomethine ylides is described for the first time. By using the corresponding silver metallo-azomethine ylides polysubstituted *endo*-prolines were obtained with high diastereo- and enantioselectivity. The process occurs at room temperature in toluene with 10 mol % of AgOAc by using either KOH or Et_3N as bases, also in substoichiometric amounts. Under these mild reaction conditions, enantiomerically enriched polysubstituted prolines resulting from an *endo* approach were obtained in general in high yields and de (86–99%). The absolute configuration of the resulting prolinates can be determined on the basis of X-ray diffraction analysis.

1. Introduction

The enormous demand for enantiomerically enriched molecules has no limits and asymmetric synthesis[1] is continuously developing new methodologies in order to cover this urgency. The main challenge in this area is to create the maximum number of stereogenic centres in only one reaction step employing the minimum amounts of reagents. From this point of view, asymmetric cycloaddition reactions[2] are very interesting because the absolute configuration of four stereocentres can be controlled simultaneously. This control is more secure and reliable when very low to ambient temperatures are employed.

The 1,3-dipolar cycloaddition reaction of azomethine ylides[3] and alkenes was revealed to be an appropriate strategy to develop this multiple stereocontrol (including the regiochemistry of the process), especially in the metal-assisted generation of the corresponding azomethine ylides.[3e] If we evaluate all of the possible ways to generate the title azomethine ylides,[3d] we observe that the *N*-metallation route, where a *N*-metallo imine, direct precursor of the metallo-dipoles, allows the cycloaddition with alkenes to proceed under very mild reaction conditions. In fact, the most important and attractive asymmetric 1,3-dipolar cycloadditions have been optimized using the combination of *N*-metallo dipole/base, with the chiral information being placed at either the dipole, the alkene (diastereoselective processes)[3c] or more recently, by using a chiral ligand–transition metal complex as catalyst (enantioselective processes).[3a,b] There has been high interest since 2002 regarding the use of substoichiometric chiral metal complexes as catalysts or even organocatalysts.[3a,b,4] Although all these contributions are good pieces of successful chemistry, they cannot be extensively applied to a very wide number of substrates because the enantiodiscrimination exhibited by these catalysts are very sensitive to structural changes in both dipole and dipolarophile components. In this sense, a diastereoselective route using metallo-azomethine ylides seems to be more tolerant versus these structural modifications, especially when the chiral information is bonded either to the acrylate moiety[3d] or to the dipole.[5]

The most relevant recent contributions dealing with this type of transformation employed chiral acrylamides,[6] including the Oppolzer sultam-derived acrylamide used in the total synthesis of (−)-lemonomycin,[6c] chiral enones

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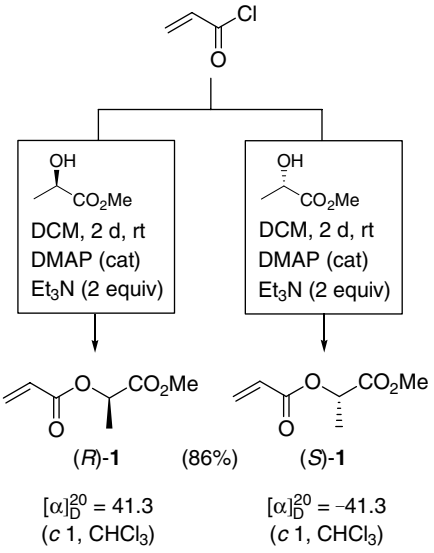
doi:10.1016/j.tetasy.2006.07.006

derived from carbohydrates,[7] a chiral α-sulfinylcyclopentenone,[8] a chiral Fischer alkenyl carbene,[9] and chiral nitroalkenes used in the preparation of inhibitors of $\alpha_4\beta_1$-integrin-mediated hepatic melanome metastasis.[10] Many of these chiral auxiliaries are very sophisticated or not very easily accessible molecules, so in the search of the most simple and readily available chiral acrylate, we focussed our attention on a very inexpensive, small and nontoxic methyl (*S*)-lactate as chiral auxiliary.[11] In this communication, we report the use for the first time of methyl (*S*)- and (*R*)-lactate acrylates as dipolarophiles in the 1,3-dipolar cycloaddition reaction with silver azomethine ylides for the synthesis of polysubstituted prolines.

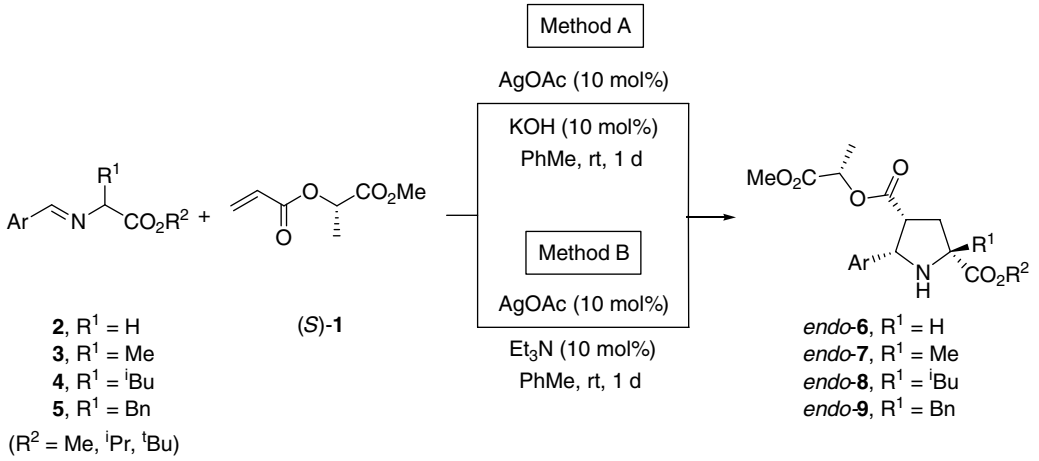
2. Results and discussion

Enantiomerically enriched acrylates (*R*)- and (*S*)-**1** were easily obtained in 86% isolated yield, starting from acryloyl chloride and the corresponding methyl (*R*)- or (*S*)-lactate using triethylamine and a small amount of *N*,*N*-dimethylaminopyridine (DMAP) as bases in dichloromethane for 2 days at room temperature (Scheme 1).[16] This process represents an advantageous alternative to the previously reported synthesis employing acryloyl chloride and the corresponding methyl lactates in refluxing carbon tetrachloride (very toxic and no more commercially available) for 4 days.[12a]



Scheme 1. Synthesis of chiral acrylates **1**.

Following with our previous studies analyzing the effects of the amounts of silver salts, bases and the introduction of PTC agents in the 1,3-dipolar cycloaddition reactions of azomethine ylides and alkenes,[17] we selected two methods to run the diastereoselective cycloaddition reaction between the enantiomerically pure alkenes **1** with several imino esters **2**–**5**. Both methods (A and B) operated with the same amount of silver acetate (10 mol %), in toluene employing either KOH (10 mol %) (Method A) or triethylamine (10 mol %) (Method B) (Scheme 2 and Table 1). When alkylidene glycinates **2** were allowed to react with acrylate (*S*)-**1** under Methods A and B reaction conditions, the corresponding *endo*-**6** products were mainly obtained as pure crude compounds. The initial experiment using Method A, between benzaldiminine glycinate methyl ester **2aa** and (*S*)-lactate acrylate **1** gave *endo*-**6aa** proline derivative in 98% yield and 93% de (Table 1, entry 1). When the same reaction was performed with the (*R*)-lactate acrylate compound **6aa** was obtained with the same but opposite specific rotation and by chiral HPLC analysis of the crude reaction mixture (Chiralcel OD-H) (Table 1, entry 2). The influence of the steric effect caused by the ester group was evaluated using methyl **2aa**, isopropyl **2ab** and *tert*-butyl **2ac** glycinates, obtaining similar diastereoselection (92–94% de) for the methyl and isopropyl esters and a 99% de for the *tert*-butyl ester (Table 1, entries 1, 3 and 5). According to the quantitative yields obtained in the reaction of the methyl ester **2aa** under Method A conditions, it can be concluded that potassium hydroxide did not hydrolyze the ester group, which represented an advantage because methyl esters are commercially more available and inexpensive. Both effects (the ester influence and its hydrolysis by the base) were also confirmed by comparison between the crude reaction products obtained from methyl



Scheme 2. 1,3-Dipolar cycloaddition reactions.

Table 1. Diastereoselective 1,3-dipolar cycloaddition reactions of compounds **2**–**5** with chiral alkenes **1**[18]

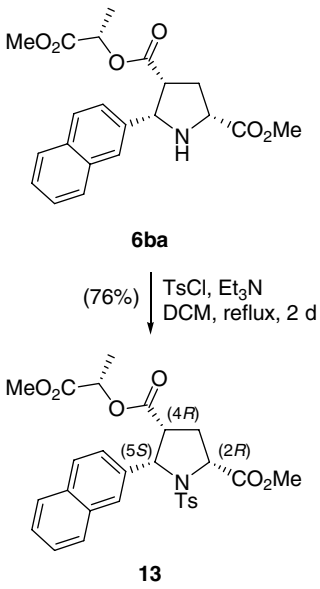
Entry	Compounds **2**–**5**				Method	Crude *endo*-**6**–**9**			Purified *endo*-**6**–**9**		
	No.	Ar	R^1	R^2		No.	Yield[a] (%)	de[b] (%)	Yield[c] (%)	de[b] (%)	$[\alpha]_D$ (20 °C) in $CHCl_3$
1	**2aa**	Ph	H	Me	A	**6aa**	98	93	64	94	−82.6 (*c* 1)
2	**2aa**	Ph	H	Me	A[d]	**6aa**	98	93	65	94	+82.6 (*c* 1)
3	**2ab**	Ph	H	^{i}Pr	A	**6ab**	98	92	63	92	−63.0 (*c* 1)
4	**2ab**	Ph	H	^{i}Pr	B	**6ab**	97	92	64	92	−63.0 (*c* 1)
5	**2ac**	Ph	H	^{t}Bu	A	**6ac**	99	95	73	99	−59.8 (*c* 1)
6	**2ba**	2-Naphthyl	H	Me	A	**6ba**	99	88	60	90	−63.9 (*c* 1.2)
7	**2ba**	2-Naphthyl	H	Me	B	**6ba**	99	88	60	90	−63.9 (*c* 1.2)
8	**2bc**	2-Naphthyl	H	^{t}Bu	A	**6bc**	98	90	70	99	−57.0 (*c* 1)
9	**2bc**	2-Naphthyl	H	^{t}Bu	B	**6bc**	90[e]	91	63	99	−57.0 (*c* 1)
10	**3aa**	Ph	Me	Me	A	**7aa**	99	90–92	65	88–90	−66.3 (*c* 1.2)
11	**3aa**	Ph	Me	Me	B	**7aa**	99	91	64	88–90	−66.3 (*c* 1.2)
12	**3ac**	Ph	Me	^{t}Bu	A	**7ac**	97	88	70	92	−57.4 (*c* 1)
13	**4aa**	Ph	^{i}Bu	Me	A	**8aa**	45	90	32	90	−44.0 (*c* 1.2)
14	**5aa**	Ph	Bn	Me	A	**9aa**	97–98	83	67	86	−45.3 (*c* 1)

[a] Isolated crude yield after work-up.
[b] Determined by chiral HPLC (Chiralcel OD-H).
[c] Isolated yield after purification by flash chromatography.
[d] The reaction was carried out with acrylate derived from methyl (*R*)-lactate.
[e] Unpurified reaction crude.

and *tert*-butyl naphthaldehyde-imine glycinates **2ba** and **2bc**, respectively (Table 1, entries 6 and 8).

Methods A and B provided identical results in the transformations starting from glycinate Schiff bases derived from benzaldehyde **2ab** and naphthaldehyde **2ba** (Table 1, compare entries 3 with 4 and 6 with 7, respectively). However, the reaction, when using imino ester **2bc** in the presence of triethylamine, yielded (in 90% and with a 91% de) a crude product with significant unidentified impurities (approximately 3%) of the crude product, whilst the reaction performed with KOH gave a 98% crude yield and 93% de (Table 1, entries 8 and 9). The absolute configuration of these three newly created stereogenic centres was determined by X-ray diffraction analysis of the *N*-(*p*-toluenesulfonyl) derivative **13**,[19] obtained from the corresponding compound **6ba**[20] by treatment with *p*-toluenesulfonyl chloride and triethylamine in refluxing DCM for 2 days (Scheme 3 and Fig. 1). It can be deduced that (*S*)-lactate acrylate gave (2*R*,4*R*,5*S*)-prolinates and the enantiomeric (*R*)-lactate acrylate (2*S*,4*S*,5*R*)-prolinates.

Next, the effect of the α-substituent on the dipole was studied. As a result, the 1,3-dipolar cycloaddition reactions with azomethine ylides derived from benzaldimines of alanine, leucine and phenyl alanine **3**, **4** and **5**, respectively, were performed employing both methods. Thus, the alanine derived Schiff base **3aa** gave almost pure compound **7aa** (99% crude yield and 90–92 de), independent of the method used for the cycloaddition reaction (Table 1, entries 10 and 11). Apparently, some difference can be observed between the methyl and *tert*-butyl imino esters **3aa** and **3ac** generating the cycloadducts **7** in 99% crude



Scheme 3. Derivatization of compound **6ba**.

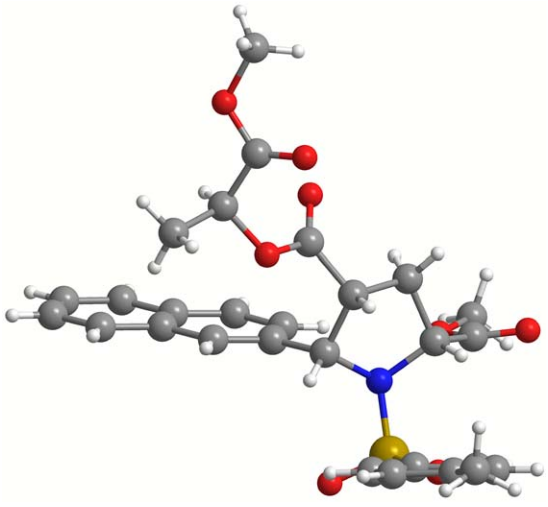
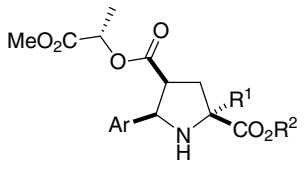


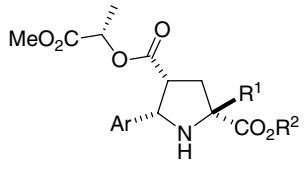
Figure 1. X-ray structure of Proline **13**.[19]

and 88–91% de yield (Table 1, entries 10 and 12). A bulkier group such as ^{t}Bu at the α-position of the azomethine ylide, as occurred in the example of imino ester **4**, had a dramatic influence over the reaction course, obtaining very low conversions (45%) and poor isolated yields of the cycloadduct **8aa** (Table 1, entry 13). In contrast, the phenylalanine derived imino ester **5aa** did not seem to be influenced so dramatically by the bulkiness of its α-substituent in the reaction to proceed in 97–98% yield and 86% de (Table 1, entry 14). In general, yields and conversions were similar to those obtained for the examples described with glycine but with slightly lower diastereoselection (from 90–93% to 83–92%).

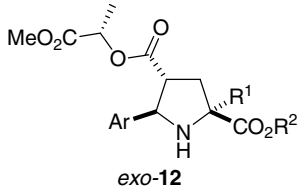
The major compounds *endo*-**6**–**9** were obtained together with the other diastereomeric *endo*-**10**. These isomers were generated in higher proportions through the thermal 1,3-dipolar cycloaddition reaction of imino esters **2**–**5** with the acrylate (*S*)-**1** and further identified by ^{1}H NMR and assigned to the peaks observed in the corresponding HPLC analysis. Moreover, the presumed *exo*-adducts *exo*-**11** and *exo*-**12** could also be detected by chiral HPLC analysis.



endo-**10**



exo-**11**



exo-**12**

In all of the examples described, a partial decomposition of the cycloadducts was observed during the flash chromatography purification and, as a consequence, a significant drop in the isolated yields occurred. However, cycloadducts **6**–**9** were isolated after flash chromatography purification in higher de than the crude products.

3. Conclusion

We can conclude that chiral acrylates derived from methyl (*R*)- and (*S*)-lactate, easily obtained in one step process from inexpensive starting materials, are excellent dipolarophiles for the diastereoselective 1,3-dipolar cycloaddition with amino esters azomethine ylides. In particular, methyl (*S*)-lactate generated a (2*R*,4*R*,5*S*)-configuration in the *endo*-**6**–**8** and (2*S*,4*R*,5*S*)-*endo*-**9** adducts with very good diastereoselectivities. Apart from glycine Schiff bases, this procedure was successfully applied to imino esters derived from α-substituted amino acids generating the three new stereogenic centres, one of which is a quaternary carbon atom. These products were cleanly obtained using potassium hydroxide rather than triethylamine. New examples for the direct application of this methodology, as well as computational studies about the influence of the chiral arrangement on the enantiodiscrimination of the process, are currently underway.

Acknowledgements

We thank the Spanish Ministerio de Educación y Cultura (M.E.C.) (CTQ2004-02375/BQU and CTQ2004-00808/BQU), Generalitat Valenciana (CTIOIB/2002/320, GRUPOS03/134 and GV05/144) and the University of Alicante for financial support.

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11. Enantiomerically enriched acrylates (*R*)- and (*S*)-**1** are known compounds, which have been employed: (a) in diastereoselective Diels–Alder reactions using an in situ thermal generation of α-hydroxy-*o*-quinodimethane,[12] in the preparation of the optically active podophyllotoxin analogues[13] and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN);[14] and (b) in 1,3-dipolar cycloaddition reaction between an alkene (*S*)-**1** and *N*-benzyl-3-hydroxypyridinium chloride for the synthesis of the alkaloid Bao Gong Teng A.[15]
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16. In spite of the fact that crude product **1** could be used directly, without any further purification, in the 1,3-dipolar cycloaddition reaction with silver azomethine ylides, it was purified by flash chromatography in order to determine exactly the stoichiometric amount needed for these processes. These chiral acrylates **1** were immediately used because some decomposition was observed upon standing for three weeks at −20 °C.
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18. Typical procedure: To a suspension of the iminoester **2**–**5** (0.25 mmol), chiral alkene **1** (0.3 mmol, 47 mg), silver acetate (0.025 mmol, 4 mg) in toluene (3 ml) potassium hydroxide (0.025 mmol, 2 mg for method A) or triethylamine (0.025 mmol, 7 μL for method B) was added and the resulting mixture was stirred vigorously for 1 d at room temperature. The solvent was evaporated under vacuo (15 Torr), ethyl acetate was added and the mixture percolated through a Celite path eluting with ethyl acetate. The solvent was evaporated (15 Torr) obtaining prolinates **6**–**9** in yields and dr as shown in Table 1. The crude product was next purified by flash chromatography eluting with mixtures of hexanes/ethyl acetate.
19. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 608938. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Compound **13**: Colourless solid; mp 142–144 °C (*n*-hexane/Et_2O); $[\alpha]_D^{25} = -112$ (*c* 1.2; $CHCl_3$), 99% de by HPLC, Chiralcel AD, 1 mL/min, *n*-hexane/*i*-PrOH: 80/20, λ 225 nm, $t_R =$ 32.65 min; R_f: 0.24 (*n*-hexane/ethyl acetate, 3/2); IR (KBr) *v*: 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.10 (d, $J = 7.2$ Hz, 3H, $CHCH_3$), 2.16 (s, 3H, $PhCH_3$), 2.43–2.54 (m, 1H, CH_2), 2.65–2.76 (m, 1H, CH_2), 3.45–3.52 (m, 1H, NafCHC*H*), 3.55 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.40 (q, $J = 7.0$ Hz, 1H, $CHCH_3$), 4.59 (dd, $J = 9.7$ and 7.0 Hz, 1H, $NHCHCH_2$), 5.36 (d, $J = 9.0$ Hz, 1H, NaphC*H*), 6.98 (d, $J = 8.0$ Hz, 2H, ArH), 7.41–7.48 (m, 3H, ArH), 7.55–7.73 (m, 6H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 16.5 ($CHCH_3$), 21.3 ($PhCH_3$), 30.9 (CH_2), 48.9 (NaphCH*C*H), 52.2 (OCH_3), 52.7 (OCH_3), 60.9 ($NHCCH_2$), 64.7 (PhCH), 68.8 ($CHCH_3$), 125.3, 125.9, 126.0, 127.4, 127.7, 128.0, 129.0 (ArCH), 132.7, 132.9, 134.8, 143.8 (ArC), 168.3, 170.6, 172.0 (C*C*OO); MS (IE) *m*/*z* (%): 539 (M^+, 33%), 482 (10), 481 (30), 480 (100), 385 (14), 384 (60), 383 (10), 376 (14), 348 (30), 325 (15), 222 (10), 221 (34), 220 (41), 205 (18), 195 (13), 194 (74), 193 (38), 192 (11), 167 (44), 166 (24), 165 (20), 155 (31), 154 (10), 140 (14), 139 (13), 91 (53); HRMS calcd for $C_{28}H_{29}NO_8S$: 539.1614; found: 539.1618. Microanalysis calcd for $C_{28}H_{29}NO_8S$: C 62.3, H 5.4, N 2.6, S 5.9; found: C 62.6, H 5.53, N 2.6, S 5.9.
20. Compound **6ba**: Pale yellow oil; $[\alpha]_D^{25} = -63.9$ (*c* 1.2; $CHCl_3$), 90% by HPLC, Chiralcel OD-H, 1 mL/min, *n*-hexane/*i*-PrOH, 80/20, λ 220 nm, $t_R = 33.72$ min, $t_R = 23.05$ min; R_f: 0.12 (*n*-hexane/ethyl acetate, 3/2); IR (neat) *v*: 3358, 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.70 (d, $J = 7.1$ Hz, 3H, $CHCH_3$), 2.50–2.54 (m, 2H, CH_2), 2.70 (br s, 1H, NH), 3.47–3.52 (m, 1H, NaphCHC*H*), 3.57 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.03–4.07 (m, 1H, $NHCHCH_2$), 4.40 (q, $J = 7.1$ Hz, 1H, $CHCH_3$), 4.71 (d, $J = 7.6$ Hz, 1H, NaphCH), 7.43–7.49 (m, 3H, ArH), 7.78–7.84 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 16.1 ($CHCH_3$), 33.5 (CH_2), 49.0 (NaphCH*C*H), 52.1 (OCH_3), 52.3 (OCH_3), 59.7 ($NHCCH_2$), 66.10 (NaphCH), 68.2 ($CHCH_3$), 125.2, 125.4, 125.9, 126.2, 127.5, 127.7, 127.9 (ArCH), 132.8, 133.0, 136.0 (ArC), 170.9, 172.1, 173.6 (C*C*OO); MS (IE) *m*/*z* (%): 385 (M^+, 25%), 327 (11), 326 (45), 298 (13), 282 (21), 228 (10), 227 (60), 222 (21), 196 (46), 195 (19), 194 (48), 193 (11), 167 (100), 166 (12), 165 (15), 152 (13), 140 (11); HRMS calcd for $C_{21}H_{23}NO_6$: 385.1525; found: 385.1529.