Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3913–3917

Serendipitous synthesis of 2-amino-2,3-dihydrobenzofuran derivatives starting from Baylis–Hillman adducts

Ka Young Lee,[a] Joobeom Seo[b] and Jae Nyoung Kim[a,*]

[a]*Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea*
[b]*Department of Chemistry and Research Institute of Natural Sciences, Gyeongsang National University, Jinju 660-701, Republic of Korea*

Received 22 February 2006; revised 22 March 2006; accepted 24 March 2006
Available online 21 April 2006

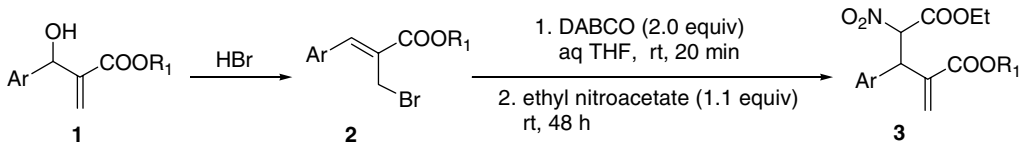
Abstract—Serendipitous synthesis of 2-amino-2,3-dihydrobenzofuran derivatives **4a**–**g** was achieved starting from the Baylis–Hillman adducts. In the reaction sequence, intramolecular oxygen atom transfer from nitrogen atom to arene moiety was observed.

The Baylis–Hillman reaction is a carbon–carbon bond-forming reaction between activated vinyls and electrophiles like aldehydes and imines with the aid of tertiary amine or phosphine.[1] The Baylis–Hillman adducts have versatile functionality and, as a result, the chemical transformations using the Baylis–Hillman adducts have been investigated extensively by us and other groups.[1–3]

Cyclic α,α-disubstituted α-amino acids represent a unique class of sterically constrained amino acids, which have been used to modify the conformation and/or stability of a biologically active peptide.[4] In these respects, the synthesis of highly sterically constrained amino acids has been studied extensively.[4] However, there have been reported only a few examples of cyclic α-amino acid precursors having heteroatom-containing substituent as one of the α-substituents.[5]

Regioselective introduction of various nucleophiles at the secondary position of the Baylis–Hillman adducts can be carried out easily.[3] During the studies on the chemical transformations of the Baylis–Hillman adducts,[2,3] we introduced ethyl nitroacetate at the secondary position of Baylis–Hillman adduct to prepare **3** (Scheme 1). We thought that **3** could be used for the synthesis of naphthalene derivative (Scheme 2), which might be produced by the sequential intermolecular Friedel–Crafts reaction, intramolecular Friedel–Crafts type cyclization,[6] and the following aromatization process.

The starting material **3a** was synthesized as a diastereomeric mixture (*syn*/*anti*, 1:1) from the reaction of cinnamyl bromide derivative **2** and ethyl nitroacetate in the presence of DABCO in aq THF in 75% yield as reported.[3] With this compound **3a** in our hands, we examined the reaction of **3a** in benzene under a variety of conditions. Among them the use of H_2SO_4/CF_3COOH in benzene at 60–70 °C gave **4a** in 55% isolated yield unexpectedly. The mechanism for the formation of **4a** could be proposed tentatively as follows

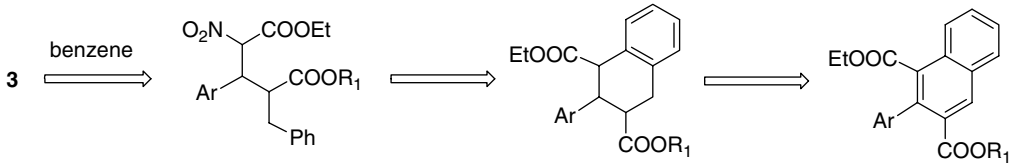


1 2 3

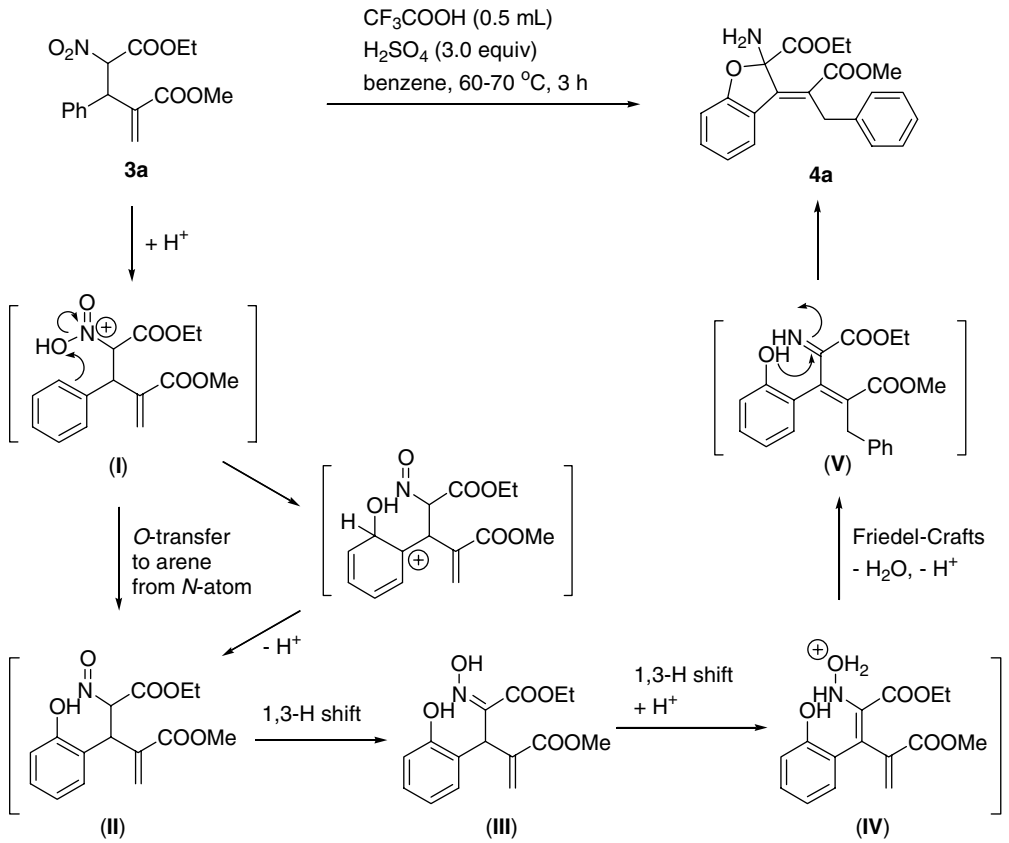
Scheme 1.

Keywords: 2-Amino-2,3-dihydrobenzofurans; Baylis–Hillman adducts; Oxygen atom transfer; α-Amino acids.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.167



Scheme 2.



Scheme 3.

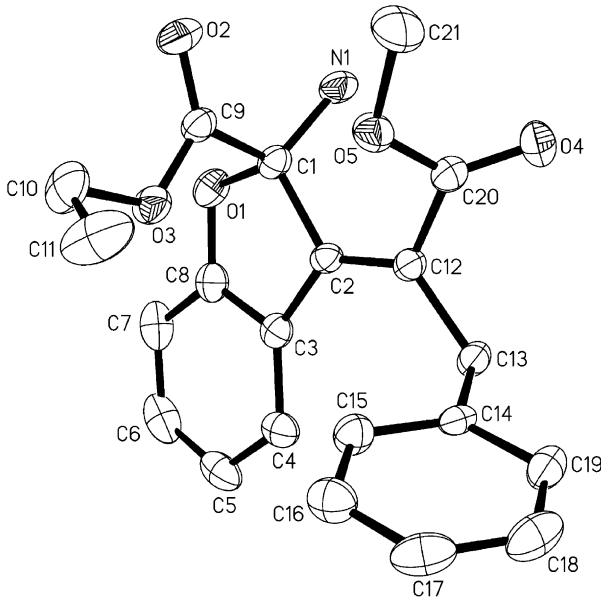


Figure 1. ORTEP drawing of compound **4a**.

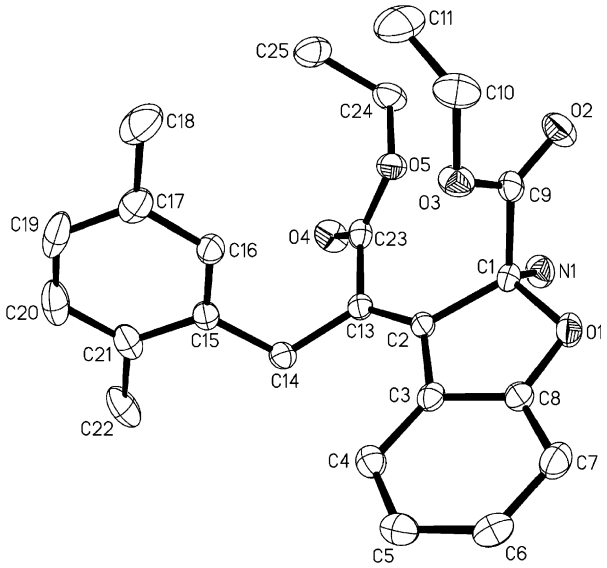
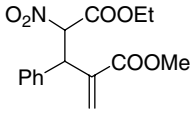
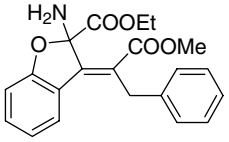
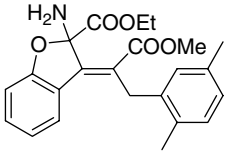
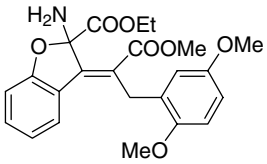
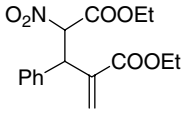
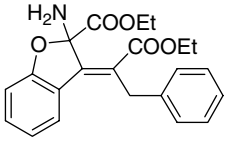
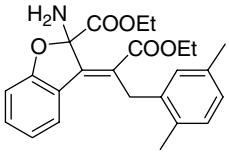
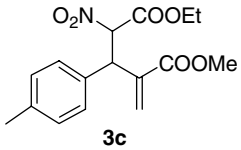
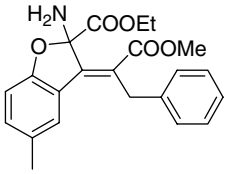
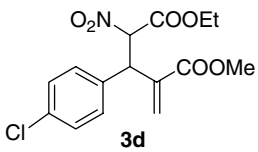
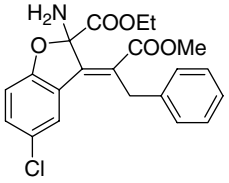


Figure 2. ORTEP drawing of compound **4e**.

as shown in Scheme 3: (i) protonation at the nitro group to give (**I**), (ii) intramolecular transfer of oxygen atom from nitrogen to carbon of benzene moiety to afford (**II**),[5a,7] (iii) successive 1,3-H shift to form the intermediate (**IV**),[6] (iv) intermolecular Friedel–Crafts type reaction with benzene, and finally (v) formation of cyclic aminal derivative **4a**.[5a] Harada and co-workers reported the synthesis of 1,3,3a,8-tetrahydro-2*H*-benzofuro[2,3-*b*]pyrrol-2-ones, which were formed by the mechanism very close to our proposed one.[5a]

In the ^{1}H NMR spectrum of **4a**, broad singlet of $-NH_2$ appeared at 2.85 ppm and a singlet at 4.18 ppm corresponding to the benzyl moiety of **4a**.[8] In the IR spectrum, two N–H stretching vibrations appeared at 3417 and 3332 cm^{-1}. Mass spectra also showed the molecular weight is $m/z = 367$. However, the assignment of the structure of **4a** was insufficient. Thus, we identified the structure of **4a** unequivocally by its X-ray crystal structure (Fig. 1).[9] As shown in its X-ray structure, the geometry of the double bond is *Z*-form. The benzene ring of

Table 1. Synthesis of 2-amino-2,3-dihydrobenzofurans **4**[a]

Entry	Substrate **3**	Conditions[b]	Product **4** (%)
1	 **3a**	Benzene CF_3COOH (0.5 mL) H_2SO_4 (3.0 equiv) 60–70 °C, 3 h	 **4a** (55)
2	**3a**	*p*-Xylene CF_3COOH (0.5 mL) H_2SO_4 (3.0 equiv) 30–40 °C, 5 h	 **4b** (51)
3	**3a**	1,4-Dimethoxybenzene (2.0 equiv) CF_3COOH (0.5 mL), $ClCH_2CH_2Cl$ H_2SO_4 (3.0 equiv) 40–50 °C, 4 h	 **4c** (38)
4	 **3b**	Benzene CF_3COOH (0.5 mL) H_2SO_4 (3.0 equiv) 40–50 °C, 5 h	 **4d** (56)
5	**3b**	*p*-Xylene CF_3COOH (0.5 mL) H_2SO_4 (3.0 equiv) 40–50 °C, 4 h	 **4e** (52)
6	 **3c**	Benzene CF_3COOH (0.2 mL) H_2SO_4 (1.0 equiv) 60–70 °C, 20 h	 **4f** (39)
7	 **3d**	Benzene CF_3COOH (0.2 mL) H_2SO_4 (1.0 equiv) 60–70 °C, 24 h	 **4g** (36)

[a] The reaction was carried out with 1.0 mmol of **3**.
[b] Arene was used as solvent except for entry 3.

benzyl group and the amino group were positioned in opposite directions and this could be explained by the proposed reaction mechanism.

Without TFA the reaction showed more complex nature although we could observe the formation of **4a** in small amounts on TLC. Actually, without TFA, dark and sticky solution phase (H_2SO_4, most of the starting material, and products were dissolved in this phase) was separated out from the upper benzene phase. Such phase separation could make the reaction more complex. When we used AcOH or formic acid instead of TFA, we could obtain **4a** although in low yields (20–25%) than the standard conditions using TFA. From these observations we tentatively concluded that the use of TFA improved the miscibility of the reaction mixtures and make the reaction cleaner.

Encouraged by the results we examined the reaction of starting materials **3a**–**d** and arene nucleophiles including benzene, *p*-xylene, and 1,4-dimethoxybenzene. We obtained desired compounds **4b**–**g** similarly, although the yields were moderate (Table 1). The yields were better when we used 1.0 equiv of H_2SO_4 for the cases of **3c** and **3d**. For 1,4-dimethoxybenzene (solid) we used only 2.0 equiv of arene nucleophile for the facility of separation. In order to make the structures of **4a**–**g** more clear we solved another X-ray crystal structure with **4e** (Fig. 2).[8,10] Based on the X-ray data of **4e** it was clear that the arene moiety at the benzylic site of **4a**–**g** was derived from the external nucleophile, arene solvent.

In summary, we disclosed the first synthesis of unusual amino acid esters, 2-amino-2,3-dihydrobenzofuran derivatives, starting from the Baylis–Hillman adducts. In the reaction, unusual oxygen atom transfer process was the key step. Further studies on the reaction mechanism and synthetic applications are actively underway.

Acknowledgments

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2005-041-C00248). Spectroscopic data was obtained from the Basic Science Institute, Gwangju branch.

References and notes

1. General review article of B–H reaction, (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201–350; (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (d) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481, and further references cited therein.
2. For our recent chemical transformations of Baylis–Hillman adducts, see: (a) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977; (b) Lee, M. J.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1355; (c) Lee, M. J.; Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1833; (d) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799; (e) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859; (f) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387; (g) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493.
3. For the introduction of nucleophiles at the secondary position of Baylis–Hillman adducts by using the DABCO salt concept, see: (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2000**, 173; (b) Gong, J. H.; Kim, H. R.; Ryu, E. K.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 789; (c) Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2004**, *25*, 328; (d) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, *42*, 9023.
4. For the synthesis and applications of unusual α-amino acid derivatives, see: (a) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342; (b) Mendel, D.; Ellman, J.; Schultz, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 4359; (c) Ellis, T. K.; Hochla, V. M.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 4973; (d) Belokon, Y. N.; Bespalova, N. B.; Churkina, T. D.; Cisarova, I.; Ezernitskaya, M. G.; Harutyunyan, S. R.; Hrdina, R.; Kagan, H. B.; Kocovsky, P.; Kochetkov, K. A.; Larionov, O. V.; Lyssenko, K. A.; North, M.; Polasek, M.; Peregudov, A. S.; Prisyazhnyuk, V. V.; Vyskocil, S. *J. Am. Chem. Soc.* **2003**, *125*, 12860; (e) Jorgensen, M. R.; Olsen, C. A.; Mellor, I. R.; Usherwood, P. N. R.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *J. Med. Chem.* **2005**, *48*, 56.
5. For the only example of cyclic α-oxyamino acid derivative, see: (a) Harada, K.; Kaji, E.; Takahashi, K.; Zen, S. *Chem. Pharm. Bull.* **1994**, *42*, 1562; (b) Kaji, E.; Takahashi, K.; Kitazawa, M.; Zen, S. *Chem. Pharm. Bull.* **1987**, *35*, 3062; (c) Ueda, S.; Naruto, S.; Yoshida, T.; Sawayama, T.; Uno, H. *J. Chem. Soc., Chem. Commun.* **1985**, 218; (d) Ueda, S.; Naruto, S.; Yoshida, T.; Sawayama, T.; Uno, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1013.
6. The reactions of nitro compounds including ethyl nitroacetate under strongly acidic conditions, see: (a) Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364; (b) Coustard, J.-M.; Jacquesy, J.-C.; Violeau, B. *Tetrahedron Lett.* **1991**, *32*, 3075; (c) Coustard, J.-M.; Jacquesy, J.-C.; Violeau, B. *Tetrahedron Lett.* **1992**, *33*, 8085; (d) Sartori, G.; Bigi, F.; Maggi, R.; Tomasini, F. *Tetrahedron Lett.* **1994**, *35*, 2393; (e) Berrier, C.; Brahmi, R.; Carreyre, H.; Coustard, J.-M.; Jacquesy, J.-C. *Tetrahedron Lett.* **1989**, *30*, 5763; (f) Ohta, T.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1984**, *25*, 325; (g) Miyake, S.; Sasaki, A.; Ohta, T.; Shudo, K. *Tetrahedron Lett.* **1985**, *26*, 5815.
7. For the examples of oxygen atom transfer, see: (a) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 5282; (b) Collado, D.; Perez-Inestrosa, E.; Suau, R. *J. Org. Chem.* **2003**, *68*, 3574; (c) Li, X.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 3066; (d) Terrier, F.; Beaufour, M.; Halle, J.-C.; Cherton, J.-C.; Buncel, E. *Tetrahedron Lett.* **2001**, *42*, 4499; (e) Kaplan, L. A.; Angres, I. A.; Shipp, K. G. *J. Org. Chem.* **1977**, *42*, 1262; (f) Madhusudanan, K. P.; Bajpai, L. K.; Bhaduri, A. P. *Rapid Commun. Mass Spectrom.* **1997**, *11*, 1263; (g) Wakamatsu, K.; Kouda, M.; Shimaoka, K.; Yamada, H. *Tetrahedron Lett.* **2004**, *45*, 6395; (h) Tovrog, B. S.; Mares, F.; Diamond, S. E. *J. Am. Chem. Soc.* **1980**, *102*, 6616; (i) Topiwala, U. P.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1994**, 2443.
8. Spectroscopic data of **4a** and **4e** are as follows.
Compound **4a**: 55%; white solid, mp 120–121 °C; IR (KBr) 3417, 3332, 1751, 1716, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, $J = 7.2$ Hz, 3H), 2.85 (br s, 2H), 3.63 (s, 3H), 4.06–4.15 (m, 1H), 4.18 (s, 2H), 4.31–4.42 (m, 1H), 6.08–6.87 (m, 2H), 7.18–7.30 (m, 6H), 7.38

(d, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.16, 35.74, 51.79, 62.06, 98.50, 111.09, 121.61, 124.14, 125.79, 126.28, 126.72, 128.08, 128.86, 132.48, 137.17, 145.26, 161.29, 167.46, 169.48; Mass (70 eV) m/z (rel intensity) 77 (49), 91 (100), 234 (97), 262 (63), 276 (38), 294 (80), 350 (M^+-17, 3), no M^+; ESIMS 368 (M^++H). Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.72; H, 5.83; N, 3.70. Compound **4e**: 52%; white solid, mp 175–176 °C; IR (KBr) 3421, 3336, 1751, 1712, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 2.21 (s, 3H), 2.34 (s, 3H), 2.88 (br s, 2H), 3.98 (d, $J = 16.2$ Hz, 1H), 3.95–4.07 (m, 1H), 4.08 (d, $J = 16.2$ Hz, 1H), 4.14–4.26 (m, 2H), 4.28–4.41 (m, 1H), 6.78–7.28 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.74, 14.06, 19.20, 21.13, 33.70, 60.87, 61.78, 98.21, 110.72, 121.33, 124.11, 125.55, 126.66, 127.10, 127.40, 130.03, 131.97, 133.25, 135.10, 135.36, 144.35, 160.98, 167.50, 168.75; ESIMS 410 (M^++H). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.49; H, 6.71; N, 3.39.

9. Crystal data of compound **4a**: solvent of crystal growth (hexanes/CH_2Cl_2, 95:5); empirical formula $C_{21}H_{21}NO_5$, $Fw = 367.39$, crystal dimensions $0.30 \times 0.20 \times 0.10$ mm^3, triclinic, space group P-1, $a = 9.0560(5)$ Å, $b = 10.2779(6)$ Å, $c = 11.1313(7)$ Å, $\alpha = 78.6020(10)°$, $\beta = 66.5910(10)°$, $\gamma = 79.6730(10)°$, $V = 926.17(9)$ Å^3, $Z = 2$, $D_{calcd} = 1.317$ mg/m^3. $F_{000} = 388$, Mo Kα ($\lambda = 0.71073$ Å), $R_1 = 0.0522$, w$R_2 = 0.1217$ ($I > 2\sigma(I)$). We omitted hydrogen atoms for clarity (Fig. 1). The X-ray data has been deposited in CCDC with number 295991.
10. Crystal data of compound **4e**: solvent of crystal growth (hexanes/CH_2Cl_2, 95:5); empirical formula $C_{24}H_{27}NO_5$, $Fw = 409.47$, crystal dimensions $0.30 \times 0.20 \times 0.20$ mm^3, monoclinic, space group $P2(1)/c$, $a = 12.0151(9)$ Å, $b = 11.4533(8)$ Å, $c = 15.4885(11)$ Å, $\alpha = 90°$, $\beta = 98.4690(10)°$, $\gamma = 90°$, $V = 2108.2(3)$ Å^3, $Z = 4$, $D_{calcd} = 1.290$ mg/m^3. $F_{000} = 872$, Mo Kα ($\lambda = 0.71073$ Å), $R_1 = 0.0613$, w$R_2 = 0.1413$ ($I > 2\sigma(I)$). We omitted hydrogen atoms for clarity (Fig. 2). The X-ray data has been deposited in CCDC with number 295992.