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Aza-Nazarov cyclization cascades

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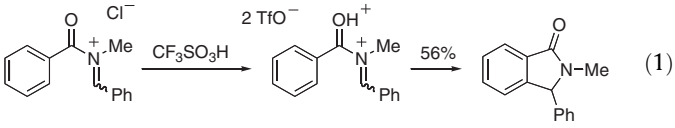
ABSTRACT

Benzamides with tethered acetal groups undergo reactions in CF_3SO_3H to give ring-fused isoindolinones by a cyclization cascade. The reaction initially forms an *N*-acyliminium ion which then gives the isoindolinone by the aza-Nazarov reaction. An unusual variant also cyclizes at the allylic position.

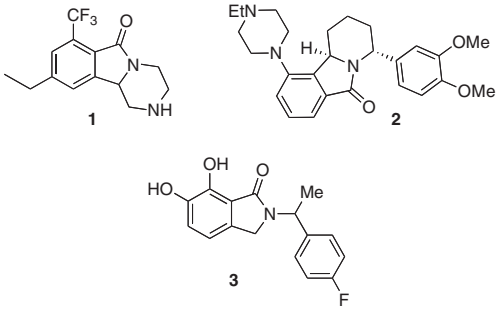
The Nazarov reaction is an acid-catalyzed cyclization involving the divinyl ketones and related compounds.[1] This reaction has been useful in carbocyclic synthesis, including utilization in natural products and pharmaceutical agent syntheses. The mechanism of this conversion generally involves a concerted, 4π-electron electrocyclization. Recently, there have been several reports of aza-Nazarov reactions in which the nitrogen atoms have been incorporated into the new ring.[2] Our own studies showed that *N*-acyliminium ions may undergo cyclization in the presence of superacidic CF_3SO_3H to give nitrogen heterocycles (Eq. 1).[2d] We proposed the involvement of superelectrophilic, dicationic species in these conversions. In these studies, the requisite *N*-acyliminium ions were prepared by the direct acylation of imines using carboxylic acid chlorides.



(1)

The products from our reactions were derivatives of isoindolinones. This class of compounds is well known for a variety of biological activities. The 5-HT2c agonist (**1**),[3] urotensin-II receptor antagonist (**2**),[4] and HIV-1 integrase inhibitor (**3**)[5] are representative examples of the biologically active isoindolinones (Scheme 1).

N-Acyliminium ions may be generated by a number of methods.[6] For example, King and coworkers prepared pyrrolo-tetrahydroisoquinolinones via *N*-acyliminium ions by the acid-catalyzed reactions of phenylacetamides having tethered acetal groups.[7] Another recent report described an *N*-acyliminium ion cyclization cascade done with a ketoamide.[8] In the following Letter, we report a new route to the ring-fused aza-Nazarov products. This chemistry utilizes acid-promoted reactions of acetals, aldehydes and enamides to generate the intermediate *N*-acyliminium ions. Subsequent cyclizations then give the ring-fused aza-Nazarov products.



Scheme 1.

Our studies began with the syntheses of a series of acetal derivatives (**4**–**9**, Table 1). The compounds were prepared from the corresponding carboxylic acid chlorides and 4,4-diethoxy-1-butanamine. In reactions with CF_3SO_3H, the heterocyclic products were obtained in fair to good yields (entries 1–4). In an effort to cyclize into olefinic sites, indene and dihydronaphthalene derivatives (**8**–**9**) were also reacted in superacid. However, products (**19**–**20**) were obtained from cyclization at the methyl carbon. We also explored the option of cyclizing alcohol substrates (entries 7–11).

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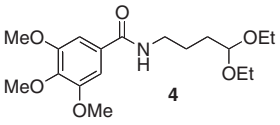
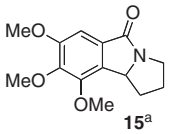
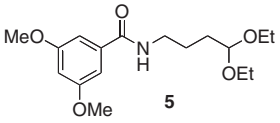
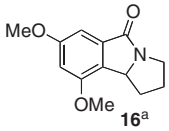
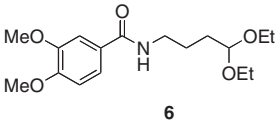
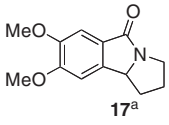
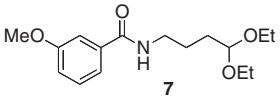
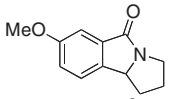
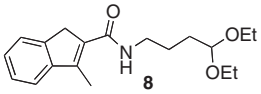
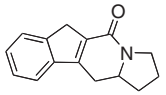
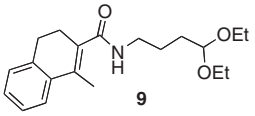
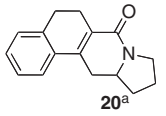
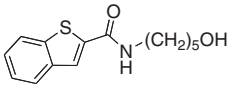
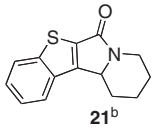
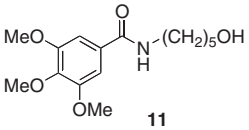
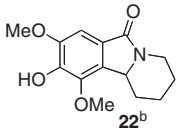
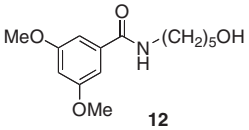
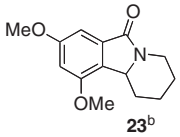
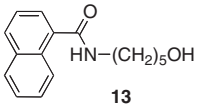
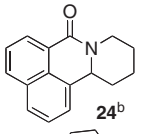
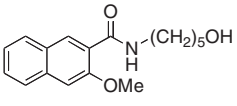
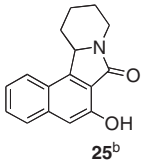
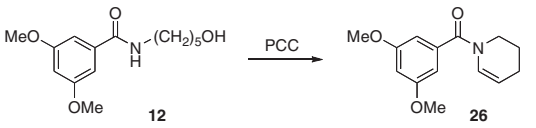
Table 1
Products and yields from cyclization cascades

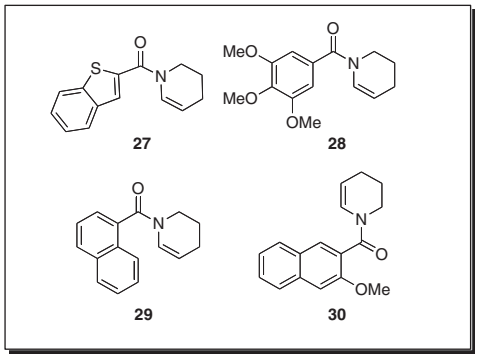
Entry	Substrate	Product	Yield (%)
(1)	 **4**	 **15**[a]	69
(2)	 **5**	 **16**[a]	76
(3)	 **6**	 **17**[a]	71
(4)	 **7**	 **18**[a]	66
(5)	 **8**	 **19**[a]	63
(6)	 **9**	 **20**[a]	64
(7)	 **10**	 **21**[b]	40[c]
(8)	 **11**	 **22**[b]	43
(9)	 **12**	 **23**[b]	81
(10)	 **13**	 **24**[b]	53
(11)	 **14**	 **25**[b]	45

[a] Product from CF_3SO_3H.
[b] Product from PCC oxidation, followed by reaction with CF_3SO_3H.
[c] Isolated yields, calculated from conversions of enamides to final products.

These substrates were prepared from the 5-amino-1-pentanol and the respective acid chlorides. The conversions were accomplished by initially oxidizing the alcohol substrates with PCC. In all cases, the intermediate enamides (**26**–**30**) were formed and could be isolated. For example, substrate **12** gives the enamide **26** by reaction with PCC (Eq. 2). Further reaction with CF_3SO_3H gives the aza-Nazarov cyclization products (**21**–**25**). In some cases, demethylation of the ether groups was also observed in the major product (entries 8

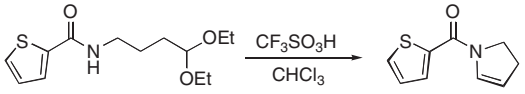
and 11). With compound **4**, demethylation of the *para*-methoxy group also occurs (similar to compound **22**), but it is a minor side reaction. Demethylation could be suppressed by carrying out the reaction with short reaction time. For the naphthyl systems (**13** and **14**), two types of cyclization were observed. Compound **13** favored the cyclization to form the six-member heterocyclic ring (**24**), while compound **14** reacted to give the aza-Nazarov product (**25**).



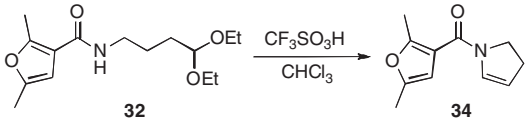


(2)

Although the conversions have not been fully optimized, reaction of compound **5** with 25 equiv of CF_3SO_3H gives a complete conversion to the heterocyclic product (**16**) in just 15 min (isolated yield 76%). Decreasing amounts of CF_3SO_3H give successively lower yields of product. With 1.0 equiv of acid, product **16** is formed in just 26% yield. Compounds **31**–**32** did not give the expected aza-Nazarov cyclization products, but the corresponding enamides **33**–**34** are major products from reactions in superacid (Eqs. 3 and 4).

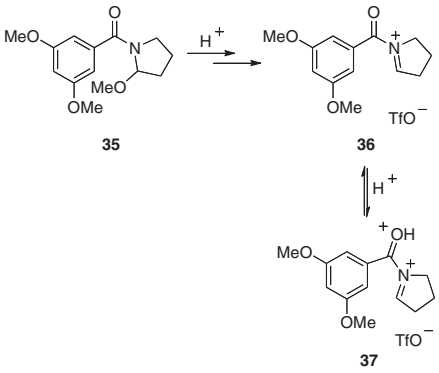


(3)



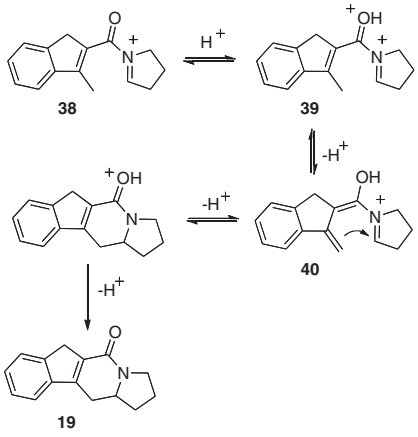
(4)

The cyclizations of the acetal derivatives (**4**–**7**) occur through the formed *N*-acyliminium ions (Eq. 5). In the case of **5**, ionization of the acetal leads to cyclization at the amide nitrogen and formation of compound **35**. Further ionization leads to the *N*-acyliminium ion **36**, where protosolvation can then lead to the superelectrophile (**37**). As shown in our previous report,[2d] formation of the superelectrophile (i.e., **37**) significantly lowers the transition state energy barrier leading to the aza-Nazarov product. It is also expected that partial protonation of the carbonyl group could help facilitate the aza-Nazarov cyclization. Analysis of some product mixtures indicated the presence of minor amounts of enamides. These are likely formed during the reaction workup from unreacted *N*-acyliminium ion. In the reactions of alcohol substrates **10**–**14**, oxidation to the aldehydes leads to the formation of the enamide-type products (i.e., **26**). Upon reaction of the superacid, the enamides are protonated and give the *N*-acyliminium ions. The resulting *N*-acyliminium ions then undergo the aza-Nazarov cyclization.



(5)

The reactions of compounds **8** and **9** are quite unusual, giving products from reaction at the methyl group. It is proposed that these conversions are the result of equilibria between the *N*-acyliminium ion and an enol tautomer (Eq. 6). For example, compound **8** reacts in the superacid to give the *N*-acyliminium ion (**38**). Further reaction with the CF_3SO_3H gives the superelectrophile **39** which then gives the enol-type structure **40**. This leads to product formation, either through a concerted 6π-electron electrocyclization or a stepwise electrophilic reaction. DFT calculations at the B3LYP 6-311G (d,p) level estimate the energy of structure **40** to be about 20 kcal/mol above the *N*-acyliminium ion **38** (Fig. 1).[9] This energy difference is similar to other keto-enol tautomeric structures.[10] Regarding the role of the superelectrophile (**39**), it has been shown in several recent studies that formation of superelectrophiles can greatly enhance the acidities of adjacent carbon–hydrogen bonds.[11] Thus, formation of the superelectrophile may lead to a relatively low energy barrier between ions **38** and **40**.



(6)

In summary, the conversions described above demonstrate that aza-Nazarov products may be prepared by superacid-promoted reactions involving amides with tethered acetal and aldehyde groups (which convert into enamides).[12,13] These aza-Nazarov reactions are shown to produce ring-fused isoindolone derivatives. This represents a convenient route to a class of compounds known to possess a broad spectrum of biological activities.[12]

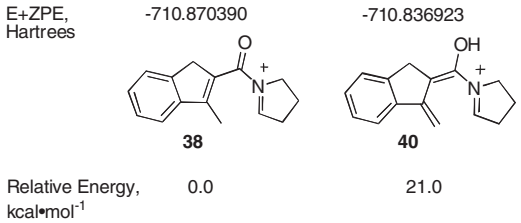


Figure 1. Relative energies of ions **38** and **40**.

Acknowledgments

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12. *Typical synthetic procedure*: The 4-aminobutyraldehyde diethyl acetal (1.0 mmol) was dissolved in 10 mL of dry dichloromethane, followed by the addition of 2.0 equiv of NEt_3 at 0 °C. To this cold reaction mixture, the acid chloride (1.1 equiv dissolved in 4 mL of dry dichloromethane) was slowly added through an addition funnel. The reaction mixture was stirred for 4 h at 25 °C and then quenched using 10 g of ice. The solution was extracted twice with dichloromethane, washed twice with saturated NH_4Cl, thrice with brine solution, and then dried over anhydrous sodium sulfate. The tethered acetals were isolated by column chromatography and characterized by NMR analysis. The tethered acetal (**4**–**9**, 0.4 mmol) or the enamide (from alcohols **10**–**14**, 0.4 mmol) is dissolved in 2 mL of $CHCl_3$ to which is added triflic acid (2 mL, 22 mmol). The mixture is stirred for 5 h at 25 °C and then poured over 10 g of ice. The solution is extracted with chloroform (3 × 20 mL) and the organic solution is washed successively with water and brine. The solution is dried (Na_2SO_4) and the product is isolated using column chromatography (hexanes/Et_2O).
13. *Analytical data*: Compound **15**, mp 119–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.08 (s, 1H), 4.64 (q, 1H, J = 5 Hz), 3.96 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.66 (q, 1H, J = 8 Hz), 3.39 (t, 1H, J = 9 Hz), 2.39–2.30 (mult, 3H), 1.26–1.15 (mult, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 171.4, 155.2, 148.4, 144.1, 143.6, 131.8, 129.0, 102.0, 62.6, 61.0, 56.3, 41.8, 29.8, 29.6. Low-resolution mass spectra, EI: 263 (M^+), 235, 220, 192. Compound **16**, mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 6.57 (s, 1H), 4.60 (q, 1H, J = 5 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.66 (q, 1H, J = 8 Hz), 3.40 (t, 1H, J = 7 Hz), 2.37–2.29 (mult, 3H), 1.18–1.14 (mult, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 171.6, 161.9, 155.5, 135.9, 127.6, 102.5, 97.9, 62.7, 55.8, 55.5, 41.7, 29.7, 29.4; Low-resolution mass spectra, EI: 233 (M^+), 205, 190, 162. Compound **17**, mp 141–143 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.88 (s, 1H), 6.57 (s, 1H), 4.60 (q, 1H, J = 5 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.66 (q, 1H, J = 8 Hz), 3.40 (t, 1H, J = 7 Hz), 2.37–2.29 (mult, 3H), 1.18–1.14 (mult, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 171.6, 161.9, 155.5, 135.9, 127.6, 102.5, 97.9, 62.7, 55.8, 55.5, 41.7, 29.7, 29.4; Low-resolution mass spectra, EI: 233 (M^+), 205, 190, 162. Compound **18**, mp 120–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, 1H, J = 8 Hz), 7.20 (s, 1H), 7.02 (d, 1H, J = 8 Hz), 4.56 (q, 1H, J = 5 Hz), 3.75 (s, 3H), 3.64 (q, 1H, J = 8 Hz), 3.35 (t, 1H, J = 6 Hz), 2.32–2.19 (mult, 3H), 1.20–1.11 (mult, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 171.6, 160.1, 138.7, 134.9, 123.4, 119.7, 106.7, 64.2, 55.5, 41.9, 29.6, 29.2; Low-resolution mass spectra, EI: 203 (M^+), 175, 147, 132. Compound **19**, mp 104–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (d, 1H, J = 7 Hz), 7.40–7.35 (mult, 1H), 7.36–7.29 (mult, 2H), 3.94–3.92 (mult, 1H), 3.78–3.72 (mult, 2H), 3.63–3.56 (mult, 2H), 3.06 (dd, 1H, J = 12 Hz), 2.54–2.46 (mult, 1H), 2.34–2.29 (mult, 1H), 2.11–2.07 (mult, 1H), 1.89–1.85 (mult, 1H), 1.83–1.77 (mult, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 163.2, 148.6, 145.1, 142.3, 135.7, 127.2, 126.6, 124.6, 120.4, 58.2, 43.8, 35.7, 33.4, 29.6, 23.4; Low-resolution mass spectra, EI: 225 (M+), 156, 128, 70. Compound **20**, ^{1}H NMR (300 MHz): δ 1.70–1.95 (m, 2H), 2.05–2.15 (m, 1H), 2.27–2.36 (m, 1H), 2.41–2.57 (m, 2H), 2.67–2.97 (m, 4H), 3.51–3.62 (m, 1H), 3.67–3.85 (m, 2H), 7.20–7.32 (m, 4H); ^{13}C NMR (DEPT results in parentheses; 300 MHz, $CDCl_3$): δ 21.6 (CH_2), 23.1 (CH_2), 28.0 (CH_2), 31.1 (CH_2), 33.7 (CH_2), 44.4 (CH_2), 55.9 (CH), 123.3 (CH), 126.5 (CH), 127.8 (CH), 128.6 (CH), 129.1 (C), 133.8 (C), 137.5 (C), 138.6 (C), 164.6 (C); Low-resolution mass spectrum, EI: 239 [M^+], 238, 170, 141, 115. HRMS $C_{16}H_{16}ON$ ($M-H$) calcd, 238.12319, found 238.12258. Compound **21**, MP 119–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44–1.57 (m, 1H), 1.62–1.78 (m, 2H), 1.81–1.90 (m, 1H), 1.98–2.08 (m, 1H), 2.53–2.59 (m, 1H), 3.00–3.10 (m, 1H), 4.43–4.50 (m, 2H), 7.42–7.48 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 23.4, 25.8, 31.8, 40.3, 58.2, 122.2, 124.5, 125.0, 126.0, 132.4, 146.1, 150.2, 162.9; Low-resolution mass spectrum, EI: 243 [M^+], 214, 186, 160. HRMS $C_{14}H_{13}ONS$ calcd, 243.07179, found 243.07083. Compound **22**, mp 171–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ, 1.07 (m, 1H), 1.36–1.44 (m, 1H), 1.64–1.67 (m, 1H), 1.75–1.84 (m, 1H), 1.92–2.03 (m, 1H), 2.51–2.58 (m, 1H), 2.96 (dt, J = 13, 3.5 Hz, 1H), 3.93 (s, 3H), 3.98 (s, 3H), 4.28–4.32 (m, 1H), 4.43–4.46 (m, 1H), 7.14 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ, 23.7, 25.4, 31.4, 39.9, 56.6, 57.7, 60.4, 100.9, 123.7, 131.3, 141.3, 141.8, 148.5, 166.2; Low-resolution mass spectrum, EI: 263 [M^+], 262, 232, 206, 165. HRMS $C_{14}H_{17}O_4N$ calcd, 263.11576, found 263.11501. Compound **23**, mp 121–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ, 6.71 (s, 1H), 6.33 (s, 1H), 4.24 (d, 1H, J = 10 Hz), 3.99 (d, 1H, J = 10 Hz), 3.63 (s, 3H), 3.59 (s, 3H), 2.75 (t, 1H, J = 10 Hz), 2.36 (d, 1H, J = 10 Hz), 1.73 (d, 1H, J = 12 Hz), 1.59 (d, 1H, J = 12 Hz), 1.42 (q, 1H, J = 13 Hz), 1.15 (q, 1H, J = 10 Hz), 0.78 (q, 1H, J = 10 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ, 165.6, 161.4, 155.3, 134.6, 126.3, 101.7, 97.9, 57.4, 55.5, 55.1, 39.5, 30.9, 25.4, 23.3; Low-resolution mass spectra (EI): 247 (M^+), 216, 191, 114. Compound **24**, ^{1}H NMR (300 MHz, $CDCl_3$): δ, 1.58–1.72 (m, 2H), 1.72–1.86 (m, 2H), 1.93–2.14 (m, 2H), 2.71 (dt, J = 12.6, 2.7 Hz, 1H), 4.84 (d, J = 11.7 Hz, 1H), 5.07–5.12 (m, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.45–7.59 (m, 2H), 7.74–7.77 (d, J = 8.4 Hz, 1H), 7.91–7.94 (m, 1H), 8.35 (dd, J = 7.2, 0.9 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ, 25.6, 25.9, 39.2, 44.0, 61.2, 122.8, 124.3, 126.0, 126.1, 126.3, 126.3, 127.3, 131.2, 132.4, 133.0, 161.4; Low-resolution mass spectrum, EI: 237 [M^+], 236, 208, 182, 153. HRMS $C_{16}H_{15}ON$ calcd, 237.11537, found 237.11414. Compound **25**, mp 149–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ, 1.54–1.61 (m, 1H), 1.84–1.92 (m, 2H), 1.97–2.20 (m, 1H), 2.28–2.34 (m, 1H), 2.87 (dt, J = 13.5, 4.0 Hz, 1H), 3.95–3.98 (m, 1H), 4.61–4.64 (m, 1H), 5.30 (dd, J = 10, 4 Hz, 1H), 7.30 (s, 1H), 7.40–7.43 (m, 1H), 7.52–7.55 (m, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5, 1H), 8.57 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ, 21.4, 23.7, 31.7, 41.6, 85.9, 111.4, 118.2, 124.8, 126.7, 128.5, 129.2, 129.5, 129.8, 136.6, 152.7, 163.1; Low-resolution mass spectrum, EI: 253 [M^+], 170, 142, 114, 83. HRMS $C_{16}H_{15}O_2N$ calcd, 253.11028, found 253.10933. Compound **26**, mp 166–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.00 (s, 1H), 4.61 (q, 1H, J = 10 Hz), 3.89 (s, 3H), 3.79 (s, 3H), 3.56 (q, 1H, J = 8 Hz), 3.31 (t, 1H, J = 9 Hz), 2.32–2.22 (mult, 3H), 1.19–1.12 (mult, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 172.0, 149.0, 141.9, 132.2, 124.4, 62.7, 60.3, 56.5, 41.8, 29.8, 29.5, 29.1; Low-resolution mass spectra, EI: 249 (M^+), 221, 206, 178.