Synthesis of New 2-Benzazepino[4,5-*a*]naphthalene Derivatives via 1,7-Electrocyclisation of Nonstabilised Azomethine Ylides

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Abstract: Novel 2-benzazepino[4,5-*a*]naphthalene derivatives were synthesised efficiently via 1,7-electrocyclisation of nonstabilised azomethine ylides derived from 1-aryl- or 1-alkenyl-naphthalene-2-carbaldehyde derivatives. In some cases, surprisingly, pyrrole derivatives were isolated. A mechanism for the formation of the pyrrole byproduct is proposed.

Key words: Azepines, electrocyclic reactions, heterocycles, tandem reactions, ylides

A number of seven-membered heterocyclic rings form part of the structures of a range of biologically active natural products and medicinally important compounds. Owing to this over the last few decades several new methodologies have been developed for the construction of such ring systems.[1,2]

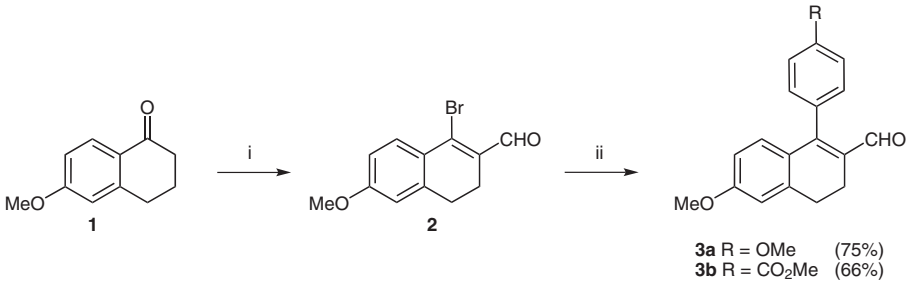
For many years 1,3-dipoles have been used extensively for the construction of five-membered heterocyclic rings via their cycloadditions with suitable dipolarophiles[3,4] and by the 1,5-electrocyclisation reactions of α,β-unsaturated 1,3-dipoles.[5,6] More recently, the electrocyclisation of diene-conjugated 1,3-dipolar intermediates has provided a powerful general synthetic route to seven-membered heterocyclic ring systems.[7–19] The investigation of such reactions of azomethine ylides resulted in the development of a new approach to azepine derivatives.[20]

As a continuation of these studies our aim was to show the generality of these methods as useful tools for the annelation of a benzazepine ring to different naphthalene derivatives in a single step. In this paper we describe the synthesis of some hitherto unknown 2-benzazepino[4,5-*a*]naphthalene derivatives. The starting material 3,4-dihydro-aryl-naphthalenes **3a** and **3b** were prepared by the method of De Koning[21] in two steps starting from the corresponding α-tetralone **1** (Scheme 1).

Our initial studies applied the generation of nonstabilised azomethine ylides[16] **4** by the decarboxylation method, involving the condensation of N-monosubstituted α-amino acids with 1-aryl-3,4-dihydro-naphthalene-2-carbaldehydes **3a** and **3b**. In the first set of experiments a mixture of **3a** or **3b** and sarcosine was refluxed for three hours in *p*-xylene, and after the workup the expected benzazepine derivatives **6a** and **6b** were obtained in good yield. No reaction occurred at lower temperature, for example, in refluxing toluene, nor did the microwave irradiation facilitate the reaction. The obtained products arise from a 1,7-electrocyclisation of the conjugated azomethine ylide **4** formed by the condensation of aldehydes **3** and sarcosine, to give the intermediate **5**, followed by a [1,5]-hydrogen shift, resulting in the rearomatisation of the benzene ring (Scheme 2).

The same reaction was observed with *N*-benzylglycine **8** and the electron-withdrawing or electron-donating nature of the substituent of the participating aromatic ring did not affect the reaction course.

We next chose to form the azomethine ylides from the 1-aryl-3,4-dihydronaphthalene-2-carbaldehydes **3a** and **3b** and some cyclic secondary α-amino acids, such as pipecolinic acid (**10**), proline (**12**), 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**16**), and 4-thiazolidinecarboxylic acid (**14**), allowing the formation of various new penta- and hexacyclic ring systems **9a,b**, **11a,b**, **13a,b**, and **15a**, respectively, in a single step, in good yields (Scheme 3).[22] The intermediacy of an azomethine ylide in this processes was proved by trapping an ylide **4**



Scheme 1 *Reagents and conditions*: *i*. DMF, PBr_3; *ii*. $ArB(OH)_2$, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Na_2CO_3.

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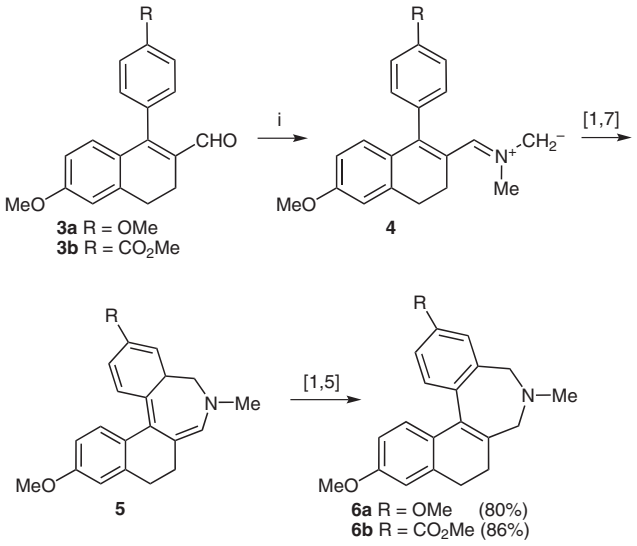
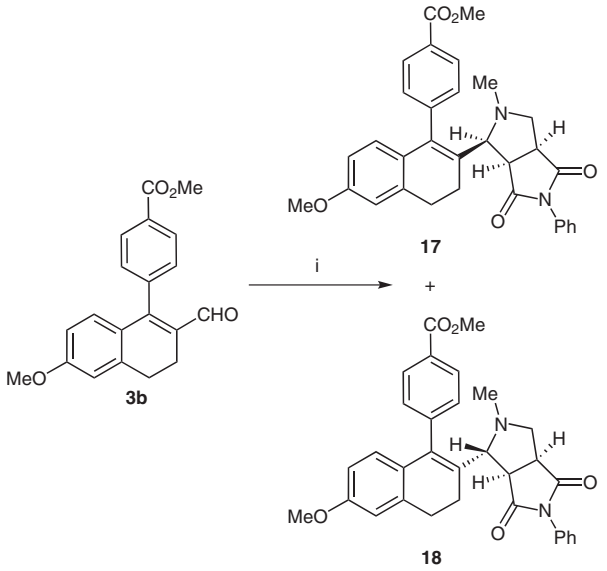


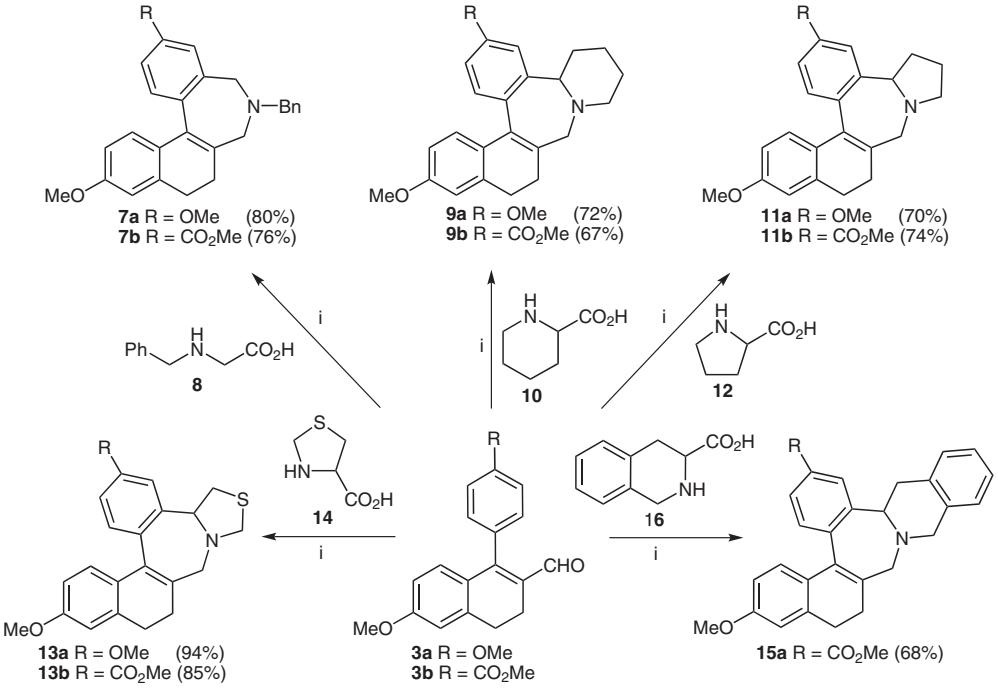
Scheme 2 *Reagents and conditions*: *i.* sarcosine, xylene, reflux.



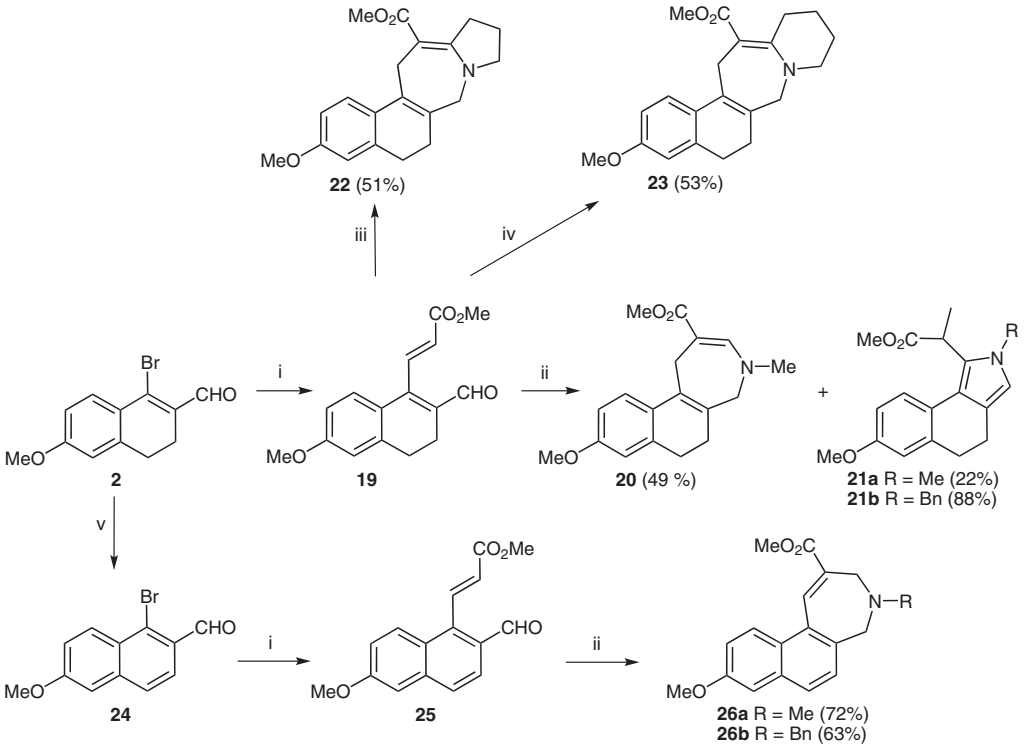
Scheme 4 *Reagents and conditions*: *i. N*-phenylmaleimide, sarcosine, xylene, reflux, 61%.

($R = CO_2Me$) with *N*-phenylmaleimide to give the two isomeric cycloadducts **17** and **18** (*exo*/*endo* ratio = 1:1) which were separated by column chromatography and characterised by NMR methods (Scheme 4).

We were also interested in determining the reactivity of azomethine ylides derived from conjugated aldehyde **19**[23] in similar electrocyclisation processes. In the reaction of **19** with sarcosine under the same conditions which were used in the previous experiments we obtained a byproduct **21a** which was isolated in addition to the expected azepine derivative **20** (ratio = 2:1 in favour of **20**). In addition, the position of the double bond in the obtained azepine derivative **20** was different to that in the previous examples. By adding an excess of triethylamine base to the reaction mixture the ratio of the formed products was reversed (ratio 2:1 in favour of **21a**). In the presence of DBN (a strong base) only the formation of **21a** was observed. Applying *N*-benzylglycine **8** instead of sarcosine in the reaction with **19** the pyrrole derivative **21b** was the sole product isolated from the reaction mixture without the presence of extra base. The reactions of **19** with cyclic amino acids as well as naphthalene aldehyde with sarcosine or *N*-benzylglycine proceeded again only on the normal 1,7-electrocyclisation pathway resulting in the formation of the expected azepine derivatives, and no pyrrole or other byproduct formation was observed (Scheme 5).



Scheme 3 *Reagents and conditions*: *i.* xylene, reflux.

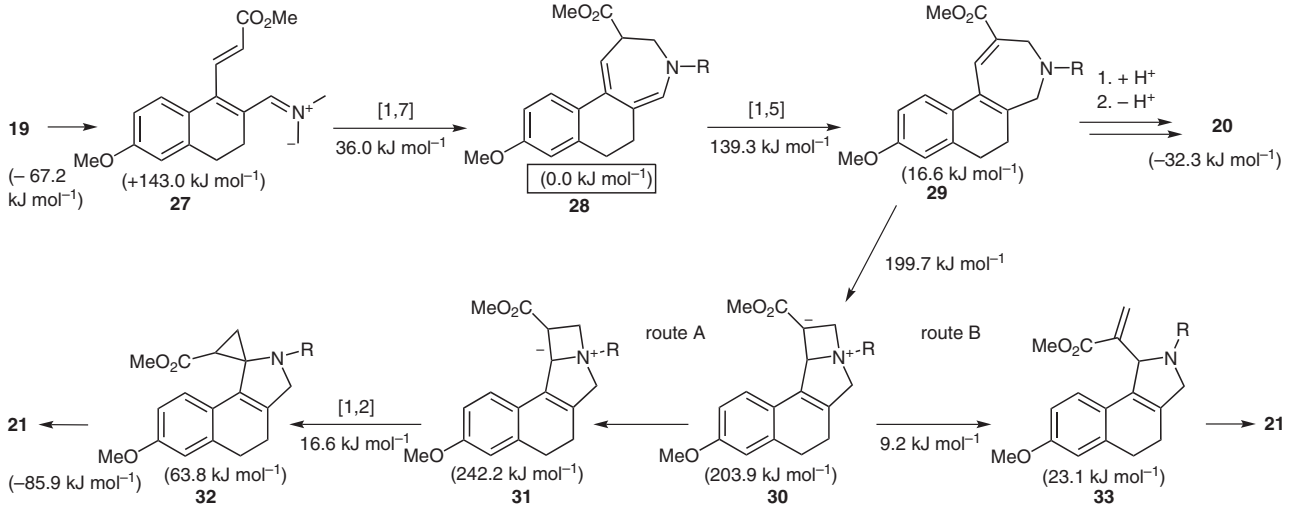


Scheme 5 *Reagents and conditions*: *i*. CH_2=$CHCO_2Me$, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, DMA,120 °C, 3 h (82%); *ii*. sarcosine (R = Me) or *N*-benzylglycine (R = Bn), xylene, reflux; *iii*. **12**, xylene, reflux; *iv*. **10**, xylene, reflux; *v*. DDQ, $CHCl_3$, 60 °C, 48 h (65%).

A possible mechanism for the pyrrole formation, drawn in Scheme 6 was investigated by computational methods.[24,25] After the expected 1,7-electrocyclisation of azomethine ylide **27** followed by the 1,5-sigmatropic rearrangement of azepine intermediate **28** the formed **29** could be stabilised in two possible ways. The simple migration of one of the double bond resulting in the formation of the more stable azepine derivative **20** via a solvent-mediated proton-transfer reaction, driven by the increasing olefinicity value[25] (33.3% → 54.7%) during the rearrangement.

On the other hand, competing with the previous route, **21** may form in two possible routes (A and B). Under basic conditions **29** could form an ammonium ylide **31**, through a very strained intermediate **30**, which possibly transforms to cyclopropyl derivative **32** in a Stevens [1,2] rearrangement (route A).[26–29] Alternative, **30** could undergo a ring-opening retro-Michael reaction, yielding a dihydro pyrrole derivative **33** (route B). Under the applied harsh reaction conditions the formation of **21** is facilitated by the aromatisation of the pyrrole ring in both cases of **32** and **33** (Scheme 6).

In conclusion we have developed an easy protocol for the formation of new fused benzazepine and pyrrole derivatives from simple starting materials via the 8π-electro-



Scheme 6 The possible mechanisms for the formation **20** and **21**. The computed Gibbs free energies (in kJ mol^{-1}) of intermediates and transition states are indicated below the structures and the arrows, respectively.

cyclisation process of nonstabilised azomethine ylides, followed by a sigmatropic 1,5-hydrogen shift.

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(22) **Experimental Procedure for 1,7-Electrocyclisation Reactions**
The aldehyde (**3** or **19**, 1.0 mmol) was dissolved in xylene (50 mL), and the corresponding amino acid (2.0 mmol) was added. The reaction mixture was refluxed under Dean–Stark conditions and further portions of the amino acid (1.0 mmol) were added every 2 h until the starting aldehyde completely disappeared (2–6 h) judged by TLC. All the solvent was removed in vacuo, and the residue was purified by column chromatography (eluent: heptane–EtOAc).
Selected Data of Representative Examples
Compound **6a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, 1 H, J = 8.0 Hz, H-13), 6.97 (d, 1 H, J = 8.4 Hz, H-1), 6.92 (d, 1 H, J = 2.0 Hz, H-10), 6.90 (dd, 1 H, J = 8.0, 2.0 Hz, H-12), 6.78 (d, 1 H, J = 2.8 Hz, H-4), 6.65 (d, 1 H, J = 8.4, 2.8 Hz, H-2), 3.86 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 3.45 (br m, 1 H, H-5), 3.40 (br m, 1 H, H-5), 3.03 (br m, 1 H, H-7), 2.97 (br m, 2 H, H-7 and H-9), 2.76 (br m, 2 H, H-8 and H-9), 2.42 (br m, 1 H, H-8), 2.41 (s, 3 H, NMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3 (q), 138.5 (2 × q), 137.9 (q), 134.9 (q), 131.5 (q), 130.6 (q), 129.6 (CH), 127.7 (q), 127.1 (CH), 114.7 (CH), 113.8 (CH), 112.9 (CH), 110.8 (CH), 58.1 (CH_2), 57.8 (CH_2), 55.4 (2 × CH_3), 43.8 (CH_3), 31.3 (CH_2), 29.1 (CH_2). IR (KBr): 2935, 1605, 1251 cm^{-1}.
Compound **13b**: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.06 (s, 1 H, H-12), 7.96 (d, 1 H, J = 8.0 Hz, H-14), 7.36 (d, 1 H, J = 8.0 Hz, H-15), 6.84 (d, 1 H, J = 1.9 Hz, H-4), 6.76 (d, 1 H, J = 8.5 Hz, H-1), 6.70 (dd, 1 H, J = 1.9, 8.5 Hz, H-2), 4.45 (d, 1 H, J = 10.2 Hz, H-9), 4.32 (d, 1 H, J = 10.2 Hz, H-9), 4.31 (t, 1 H, J = 8.8 Hz, H-11a), 3.88 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.39 (d, 1 H, J = 15.0 Hz, H-7), 3.21 (d, 1 H, J = 15.0 Hz, H-7), 2.93 (m, 1 H, H-6), 2.89 (t, 1 H, J = 8.8 Hz, H-11), 2.86 (m, 1 H, H-6), 2.70 (m, 2 H, H-5), 2.60 (t, 1 H, J = 8.8 Hz, H-11). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.3 (q),158.8 (q), 143.4 (q), 140.0 (q), 139.0 (q), 138.3 (q), 132.9 (q), 131.8 (CH), 130.4 (CH), 128.9 (q), 128.7 (CH), 127.4 (q), 126.3 (CH), 114.2 (CH), 111.7 (CH), 70.9 (CH), 62.8 (CH_2), 56.4 (CH_2), 55.5 (CH_3), 52.6 (CH_3), 38.6 (CH_2), 30.5 (CH_2), 28.5 (CH_2). IR (KBr): 2931, 1717, 1606, 1252, 1111 cm^{-1}.
Compound **15a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, 1 H, J = 1.0 Hz, H-15), 7.96 (dd, 1 H, J = 8.0, 1.0 Hz, H-17), 7.36 (d, 1 H, J = 8.0 Hz, H-18), 7.20 (d, 1 H, J = 8.5 Hz, H-13), 7.11 (m, 2 H, H-11 and H-12), 7.04 (d, 1 H, J = 8.5 Hz, H-10), 6.87 (d, 1 H, J = 2.5 Hz, H-4), 6.81 (d, 1 H, J = 8.5 Hz, H-1), 6.68 (dd, 1 H, J = 2.5, 8.5 Hz, H-2), 3.90 (s, 3 H, OMe), 3.88 (d, 1 H, J = 17.8 Hz, H-9), 3.83 (d, 1 H, J = 17.8 Hz, H-9), 3.74 (s, 3 H, OMe), 3.52 (t, 1 H, J = 13.0 Hz, H-14), 3.19 (d, 1 H, J = 14.7 Hz, H-7), 3.15 (d, 1 H, J = 14.7 Hz, H-7), 3.15 (t, 1 H, J = 13.0 Hz, H-14a), 2.96 (d, 1 H, J = 13.0 Hz, H-14), 2.81 (m, 2 H, H-5), 2.66 (m, 1 H, H-6), 2.51 (m, 1 H, H-6). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6 (q), 158.8 (q), 145.5 (q), 140.6 (q), 138.6 (q), 135.3 (q), 134.6 (q), 133.6 (q), 129.1 (CH), 128.8 (CH), 128.7 (q), 128.2 (CH), 127.0 (CH), 126.9 (q), 126.4 (2 × CH), 126.3 (CH), 126.1 (CH), 114.2 (CH), 111.6 (CH), 58.2 (CH), 57.1 (CH_2), 56.7 (CH_2), 55.6 (CH_3), 52.7 (CH_3), 32.7 (CH_2), 32.6 (CH_2), 28.8 (CH_2). IR (KBr): 2928, 1717, 1606, 1251, 1109 cm^{-1}.
Compound **21b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, 1 H, J = 8.4 Hz, H-9), 7.35 (t, 2 H, J = 8.4 Hz, Ph-3′ and 5′H), 7.29 (t, 1 H, J = 8.4 Hz, Ph-4′H), 7.06 (d, 2 H, J = 8.4 Hz, Ph-2′ and 6′H), 6.87 (d, 1 H, J = 3.6 Hz, H-6), 6.83 (dd, 1 H, J = 8.4, 3.6 Hz, H-8), 6.43 (s, 1 H, H-3), 5.19 (d, 1 H, J = 16.8 Hz, CH_2Ph), 5.11 (d, 1 H, J = 16.8 Hz, CH_2Ph), 4.31 (q, 1 H, J = 7.6 Hz, $CHCH_3$), 3.85 (s, 3 H, OMe), 3.51 (s, 3 H, CO_2Me), 2.86 (m, 2 H, H_2-4), 2.68 (m, 2 H, H_2-5), 1.50 (d, 3 H, J = 7.6 Hz, $CHCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2 (q), 157.0 (q), 138.9 (q), 138.6 (q), 128.6 (2 × CH), 127.3 (2 × CH), 126.4 (CH), 125.8 (q), 125.2 (q), 124.9 (CH), 120.5 (q), 118.6 (q), 117.2 (CH), 114.6 (CH), 111.5 (CH), 55.3 (CH_3), 52.1 (CH_3), 50.7 (CH_2), 36.9 (CH), 32.0 (CH_2), 21.2 (CH_2), 16.1 (CH_3). IR (KBr): 2938, 1722, 1612, 1253, 1108 cm^{-1}.
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