Easy access to various substituted 4-aminocyclopentenes by rearrangement of 2-ethenyl-substituted cyclopropylamines

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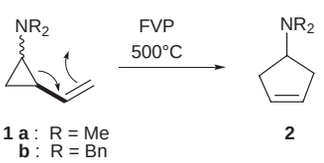
A variety of 2-ethenyl-substituted cyclopropylamines upon flash vacuum pyrolysis or under silver nitrate catalysis cleanly undergo ring enlargement and afford high yields (up to 95%) of 4-aminocyclopent-1-enes, some of which have unprecedented substitution patterns.

Introduction

A few biologically active compounds contain the 4-aminocyclopent-1-ene fragment,[1] yet the latter have gained real importance as precursors to nucleoside analogues with carbocyclic desoxypentose moieties.[2] The known synthetic routes to 4-aminocyclopent-1-enes are somewhat limited in regard to functionalisation[3] and the little progress that has been made within the last decades has been centered around the parent 4-aminocyclopent-1-ene.[1e,2b]

The well known vinylcyclopropane to cyclopentene rearrangement is one of the established routes to cyclopentenes (Scheme 1).[4] Therefore our recently developed synthesis of



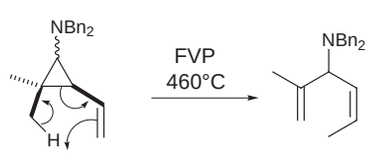
Scheme 1

(2-ethenylcyclopropyl)amines from *N*,*N*-dialkylcarboxamides *via* ligand exchanged titanium-alkadiene intermediates[5] should provide a new access to 4-aminocyclopent-1-enes especially since a dimethylamino group is known to facilitate the vinylcyclopropane rearrangement dramatically.[6] In fact, upon attempted purification of some new *N*,*N*-dialkylamino-2-ethenylcyclopropanes[5] partial rearrangement to the corresponding *N*,*N*-dialkylaminocyclopentenes was observed. As the previous study by Richey *et al.*[6] was purely kinetic, and no yields were quoted, we looked into the possibility to make this rearrangement synthetically viable and applicable for substituted 4-(*N*,*N*-dialkylamino)cyclopent-1-enes as well.

Results and discussion

Since the dimethylamino group cannot be deprotected to a primary amino group, but benzyl groups can be removed under a variety of conditions, the 1-(*N*,*N*-dibenzylamino)-2-ethenyl-2-methylcyclopropane **3** (Table 1, entry 3) was investigated to insure the same rearrangement occurs with both different substituents on the amino group and the three membered ring. Initially vacuum distillation (160–170 °C/10^{-2} Torr) gave only partial conversion to the expected aminocyclopentene **4** although at slightly higher temperatures and a higher pressure (170–180 °C/2–3 Torr) total conversion was achieved, and compound **4** was obtained in 60–70% yield. However, when **3** was subjected to flash vacuum pyrolysis (FVP), the product **4** was isolated in 90% yield. In view of this success the unsubstituted 1-(*N*,*N*-dialkylamino)-2-ethenylcyclopropanes **1a**,**b** (entries 1,2) were also subjected to flash vacuum pyrolysis conditions. Initially this was somewhat problematic with the dimethylamino derivative **1a** due to the higher volatility of the substrate, however when the pressure was increased (10^{-2} Torr) and the rate of evaporation of the substrate **1a** dramatically decreased, the aminocyclopentene **2a** was obtained in 90% yield. The yield is essentially quantitative, yet due to the volatility of the product **2a**, losses occurred upon small scale operation. The *N*,*N*-dibenzylamino derivative **1b** under the same conditions gave **2b** in 95% isolated yield (entry 2).

The rearrangement of the 1-(*N*,*N*-dibenzylamino)-2-ethenyl-2-(4′-methylpent-3′-enyl)cyclopropane **5** could be carried out at 400 °C, but was less efficient and gave the 1-substituted 4-dibenzylaminocyclopentene **6** only in 54% yield. With additional substituents around the three-membered ring, the rearrangement apparently tends to lead to more side products or even take a different route. For example, 1-(*N*,*N*-dibenzylamino)-3,3-dimethyl-2-ethenylcyclopropane **7** (entry 5), rearranged only at slightly higher temperatures (460 °C)[7] and led to two products along with starting material. Only the minor product (6%) was the expected aminocyclopentene **8** while the major product (36%) was *cis*-3-(*N*,*N*-dibenzylamino)-2-methylhexa-1,4-diene **9** derived from **7** by a homo-1,5-hydrogen shift[8] (Scheme 2). Difficulties were also encountered

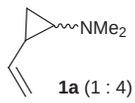
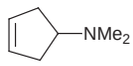
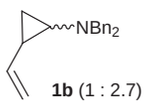
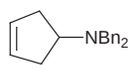
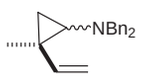
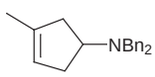
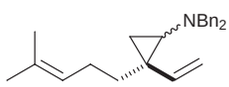
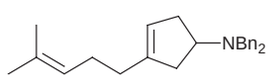
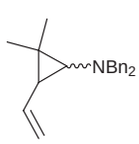
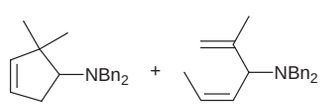
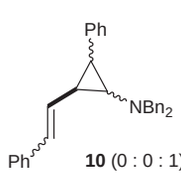
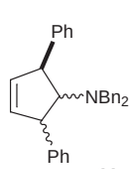
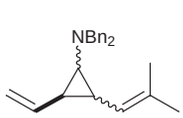
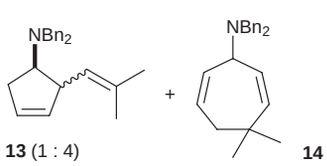
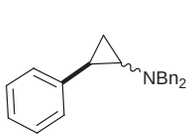
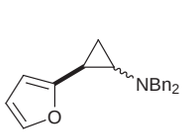
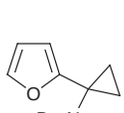


Scheme 2

with 1-(*N*,*N*-dibenzylamino)-2-phenyl-3-(2-phenylethenyl)-cyclopropane **10** (entry 6). Due to the higher molecular mass relatively high sublimation temperatures (250 °C) were needed to introduce the material into the hot tube. This apparently led to side reactions and resulted in lower yields of product (27%). Surprisingly, the same rearrangement was induced when **10** was passed through a plug of silver nitrate-impregnated silica, to give the same aminocyclopentene **11** in slightly better yield (30%).

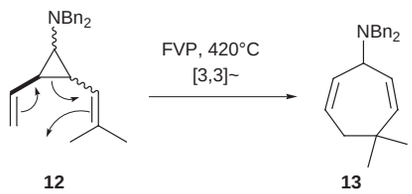
In order to test whether an amino group would facilitate the vinylcyclopropane to cyclopentene rearrangement rather than a Cope rearrangement, 1-(*N*,*N*-dibenzylamino)-2-ethenyl-3-(2-methylpropenyl)cyclopropane **12** (entry 7) was pyrolysed at

Table 1 Flash vacuum pyrolysis of various 2-ethenylcyclopropylamines to yield 4-aminocyclopent-1-enes

Entry	Starting Material (*cis* : *trans*)	Product	Yield (%)	*T*/°C	*P*/Torr
1	 **1a** (1 : 4)	 **2a**	90	500	10^{-2}
2	 **1b** (1 : 2.7)	 **2b**	95	500	$>10^{-5}$
3	 **3** (> 2 : 98)	 **4**	90	400	$>10^{-5}$
4	 **5** (> 2 : 98)	 **6**	54	400	$>10^{-5}$
5	 **7** (1 : 5.3)	 **8** **9**	6 + 36	460	$>10^{-5}$
6	 **10** (0 : 0 : 1)	 **11**	27 (30)[a]	500	$>10^{-5}$
7	 **12** (1 : 2 : 2)	 **13** (1 : 4) **14**	5 + 61	420	$>10^{-5}$
8	 **15** (0 : 1)	_[b]	0	400–650	$>10^{-5}$
9	 **16** (1 : 4)	_[b]	0	400–650	$>10^{-5}$
10	 **17**	_[b]	0	400–650	$>10^{-5}$

[a] Yield in parentheses obtained at ambient temperature under silver nitrate catalysis. [b] Starting material was recovered at 400 °C, however, increased decomposition was observed with increased temperature.

420 °C. The expected aminocyclopentene **13** was obtained in only 5% yield, the major product was 3-(*N*,*N*-dibenzylamino)-6,6-dimethylcyclohepta-1,4-diene **14** (61%). The structure of **14** was established on the basis of 2D NOESY and long range HMBC NMR spectra. Apparently, the [3,3]-sigmatropic (Cope) rearrangement of **12**, at least of its *cis*-2,3-dialkenyl diastereomers is faster than the vinylcyclopropane to cyclopentene rearrangement in spite of the two terminal methyl substituents in **12** (Scheme 3), and *trans–cis* isomerisation especially



12 **13**

Scheme 3

of donor-substituted ethenylcyclopropanes is known to be faster than their ring enlargement to cyclopentenes.[6,9]

The (arylcyclopropyl)amines 1-(*N*,*N*-dibenzylamino)-2-phenylcyclopropane **15**, 1-(*N*,*N*-dibenzylamino)-2-(2-furyl)-cyclopropane **16**, and 1-(*N*,*N*-dibenzylamino)-1-(2-furyl)-cyclopropane **17** (entries 8–10) did not undergo the expected ring-enlarging rearrangement in a temperature range of 400–650 °C; they were either recovered intact at lower or fully decomposed at higher temperatures. If 1,3-diradicals are initially formed by homolytic ring opening of cyclopropyl groups in compounds of types **15**–**17**, they apparently have little tendency to undergo five-membered ring closure by radicophilic attack on the aromatic rings.

In conclusion, several 4-aminocyclopent-1-enes are now accessible in good to high yields within two steps from conjugated dienes *via* 2-alkenyl-cyclopropylamines[5a] and their thermal rearrangement.

Experimental

^{1}H (250 MHz) and ^{13}C (62.9 MHz) NMR spectra were obtained with a Bruker AM 250 nuclear magnetic resonance spectrometer in deuterochloroform with tetramethylsilane as an internal standard, coupling constants are reported in Hz. Mass spectra were recorded on a Varian MAT CH7, MAT 731 and high resolution mass spectra were recorded on a Varian MAT 311 A spectrometer with preselected molecular peak matching at $R \geqslant 10000$ to be within ±2 ppm of the exact masses. Microanalyses were performed by the Mikroanalytisches Laboratorium des Instituts für Organische Chemie der Georg-August-Universität Göttingen. Melting points were determined on a Büchi 510 and are uncorrected. Flash vacuum pyrolysis experiments were conducted using a hollow ceramic electric tube furnace containing a quartz tube (71.5 cm × 2.5 cm) placed horizontally in the centre with a flask connected at one end for sublimation of the starting material. The other end was connected to a vacuum system where the products were collected either in the exit tube or the liquid nitrogen cold trap. Pyrolysis conditions are quoted in parenthesis (sublimation oven temperature/thermolysis oven temperature/pressure). Radial chromatography was performed on a Chromatotron, Model 7924T using silica gel PF-254 with $CaSO_4 \cdot 0.5\ H_2O$ type 60 for TLC, Merck 7749.

4-(*N*,*N*-Dimethylamino)cyclopent-1-ene 2a

1-(*N*,*N*-Dimethylamino)-2-ethenylcyclopropane (491 mg, 4.42 mmol) was subjected to flash vacuum pyrolysis (ambient temp./500 °C/10^{-2} Torr) with slow evaporation. The condensed product was a colourless oil (450 mg, 90%), and it was shown by ^{1}H NMR spectroscopy to be 99% pure, however no further purification was attempted due to the high volatility of the product (Found: M^+ 111.1047. Calc. for $C_7H_{13}N$, M 111.1047). δ_H 2.13–2.33 [2 H, m, 3(5)-H], 2.21 (6 H, s, NCH_3), 2.33–2.48 [2 H, m, 3(5)-H], 2.91 (1 H, quintet, *J* 7.7, 4-H), 5.62 [2 H, s, 1(2)-H]; δ_C 36.48 (2 × t), 43.41 (2 × q), 66.40 (d), 129.13 (2 × d); *m*/*z* 111 (M^+, 100%), 96 (38), 85 (54), 82 (47), 70 (42), 67 (29), 58 (21), 55 (15), 53 (9).

4-(*N*,*N*-Dibenzylamino)cyclopent-1-ene 2b

1-(*N*,*N*-Dibenzylamino)-2-ethenylcyclopropane (410 mg, 1.56 mmol) was subjected to flash vacuum pyrolysis (175 °C/500 °C/ >10^{-5} Torr). The product, a pale yellow oil, was placed on a silica plug, and this was washed with copious amounts of *n*-hexane, and the product itself was eluted with *tert*-butyl methyl ether–*n*-hexane (7:93). After evaporation of the solvents, the residue was distilled in a Kugelrohr (150–170 °C/0.01 Torr) to give **2b** as a colourless oil (390 mg, 95%) (Found: M^+ 263.1673. Calc. for $C_{19}H_{21}N$, M 263.1673). δ_H 2.45 [4 H, d, *J* 6.8, 3(5)-H], 3.57 [4 H, s, $N(CH_2Ph)_2$], 3.69 (1 H, quintet, *J* 6.8, 4-H), 5.73 [2 H, s, 1(2)-H], 7.22–7.44 (10 H, m, ArH); δ_C 34.50 (2 × t), 54.16 (2 × t), 57.97 (d), 126.62 (2 × d), 128.09 (4 × d), 128.63 (4 × d), 129.57 (2 × d), 140.29 (2 × s); *m*/*z* 263 (M^+, 20%), 234 (3), 222 (4), 186 (2), 172 (39), 156 (4), 145 (4), 130 (1), 118 (9), 106 (6), 91 (100).

4-(*N*,*N*-Dibenzylamino)-1-methylcyclopent-1-ene 4

1-(*N*,*N*-Dibenzylamino)-2-ethenyl-2-methylcyclopropane (420 mg, 1.51 mmol) was subjected to flash vacuum pyrolysis (150–200 °C/400 °C/>10^{-5} Torr). The pyrolysate was subjected to radial chromatography (*tert*-butyl methyl ether–*n*-hexane, 2:98–10:90 gradient) on silica gel affording compound **4** as a colourless oil (379 mg, 90%) (Found: C, 86.5; H, 8.3%; M^+ 277.1830. Calc. for $C_{20}H_{23}N$, C, 86.6; H, 8.4%; M 277.1830). δ_H 1.71 (3 H, br s, CH_3), 2.29–2.48 [4 H, m, 3(5)-H], 3.53 [4 H, s, $N(CH_2Ph)_2$], 3.66 (1 H, quintet, *J* 6.9, 4-H), 5.28 (1 H, br s, 1(2)-H)], 7.17–7.48 (10 H, m, ArH); δ_C 16.77 (q), 34.67 (t), 38.94 (t), 54.20 (2 × t), 58.91 (d), 123.09 (d), 126.58 (2 × d), 128.05 (4 × d), 128.61 (4 × d), 138.94 (s), 140.32 (2 × s); *m*/*z* 277 (M^+, 42%), 262 (6), 249 (5), 224 (18), 222 (11), 200 (6), 186 (43), 181 (2), 159 (3), 132 (4), 117 (4), 106 (14), 91 (100).

4-(*N*,*N*-Dibenzylamino)-1-(4′-methylpent-3′-en-1′-yl)cyclopent-1-ene 6

1-(*N*,*N*-Dibenzylamino)-2-ethenyl-2-(4′-methylpent-3′-en-1′-yl)cyclopropane (562 mg, 1.63 mmol) was subjected to flash vacuum pyrolysis (150–200 °C/400 °C/>10^{-5} Torr). The pyrolysate was subjected to radial chromatography (*tert*-butyl methyl ether–*n*-hexane, 2:98–10:90 gradient) on silica gel affording **6** as a colourless oil (301 mg, 54%) (Found: C, 87.2; H, 9.2%; M^+ 345.2456. Calc. for $C_{25}H_{31}N$, C, 86.9; H, 9.0%; M 345.2456). δ_H 1.64 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 2.02–2.27 (4 H, m, CH_2CH_2), 2.30–2.54 [4 H, m, 3(5)-H], 3.58 [4 H, s, $N(CH_2Ph)_2$], 3.69 (1 H, quintet, *J* 6.9, 4-H), 5.08–5.21 (1 H, m, 2-H), 5.35 [1 H, br s, $CH{=}C(CH_3)_2$], 7.15–7.54 (10 H, m, ArH); δ_C 17.69 (q), 25.68 (q), 26.27 (t), 31.45 (t), 34.44 (t), 37.21 (t), 54.18 (2 × t), 58.46 (d), 122.14 (d), 124.31 (d), 126.59 (2 × d), 128.07 (4 × d), 128.64 (4 × d), 131.45 (s), 140.39 (2 × s), 143.26 (s); *m*/*z* 345 (M^+, 35%), 313 (1), 276 (42), 254 (8), 239 (2), 224 (27), 222 (16), 210 (17), 181 (5), 132 (2), 146 (1), 117 (4), 106 (8), 91 (100).

4-(*N*,*N*-Dibenzylamino)-3,3-dimethylcyclopent-1-ene 8 and *cis*-3-(*N*,*N*-dibenzylamino)-2-methylhexa-1,4-diene 9

1-(*N*,*N*-Dibenzylamino)-3,3-dimethyl-2-ethenylcyclopropane (263 mg, 0.9 mmol) was subjected to flash vacuum pyrolysis (250 °C/460 °C/>10^{-5} Torr). The pyrolysate was subjected to column chromatography (ethyl acetate–*n*-hexane, 10:90) on silver nitrate-impregnated silica gel[10] affording three fractions.

The first fraction contained *cis*-3-(*N*,*N*-dibenzylamino)-2-methylhexa-1,4-diene **9** as a colourless oil (94 mg, 36%) (Found: M^+ 291.1986. Calc. for $C_{21}H_{25}N$, M 291.1986). δ_H 1.43 (3 H, dd, *J* 6.8 and 1.6, CH_3), 1.92 (3 H, s, CH_3), 3.61 [4 H, AB, *J* 14.0, $N(CH_2Ph)_2$], 3.91 (1 H, d, *J* 9.7, 3-H), 4.83–4.98 (2 H, m, CH_2=), 5.61–5.73 (1 H, m, 5-H), 5.79–5.94 (1 H, m, 4-H), 7.18–7.60 (10 H, m, ArH); δ_C 13.29 (q), 21.12 (q), 53.57 (2 × t), 60.18 (d), 112.76 (t), 126.23 (d), 126.60 (2 × d), 128.09 (4 × d), 128.26 (d), 128.64 (4 × d), 140.25 (2 × s), 146.21 (s); *m*/*z* 291 (M^+, 6%), 250 (100), 196 (1), 182 (6), 158 (2), 118 (1), 104 (2), 95 (12), 91 (68). The second fraction contained the cyclopentene **8** as a colourless oil (15 mg, 6%) (Found: M^+ 291.1986; $C_{21}H_{25}N$ requires M 291.1986). δ_H 0.88 (3 H, s, CH_3), 1.20 (3 H, s, CH_3), 2.28–2.57 (2 H, m, 5-H), 3.09 (1 H, dd, *J* 7.5 and 5.1, 4-H), 3.63 [4 H, AB, *J* 14.4, $N(CH_2Ph)_2$], 5.51–6.66 [2 H, m, 1(2)-H], 7.18–7.47 (10 H, m, ArH); δ_C 23.37 (q), 29.39 (q), 30.02 (t), 47.40 (s), 55.64 (2 × t), 67.54 (d), 126.22 (d), 126.57 (2 × d), 128.11 (4 × d), 128.42 (4 × d), 140.62 (d), 142.02 (2 × s); *m*/*z* 291 (M^+, 39%), 276 (11), 250 (39), 222 (17), 200 (21), 174 (5), 145 (3), 132 (25), 106 (4), 95 (10), 91 (100). The third fraction contained starting material (47 mg, 18%).

4-(*N*,*N*-Dibenzylamino)-3,5-diphenylcyclopent-1-ene 11

1-(*N*,*N*-Dibenzylamino)-2-phenyl-2-(2-phenylethenyl)cyclopropane (164 mg, 0.39 mmol) was passed through a column (ethyl acetate–*n*-hexane, 1:19) of silver nitrate-impregnated silica gel[10] affording the title compound **11** as a colourless oil (50 mg, 30%) (Found: M^+ 415.2299. Calc. for $C_{31}H_{29}N$, M 415.2299). δ_H 3.47 (1 H, t, *J* 8.0, 4-H), 3.72 [4 H, s, $N(CH_2Ph)_2$], 4.13 [2 H, d, *J* 8.0, 3(5)-H], 5.82 [2 H, s, 1(2)-H], 6.90–6.95 (4 H, m, ArH), 7.05–7.15 (6 H, m, ArH), 7.18–7.37 (10 H, m, ArH); δ_C 52.19 (d), 55.01 (2 × t), 78.63 (2 × d), 126.19 (2 × d), 126.42 (2 × d), 127.79 (4 × d), 128.07 (4 × d), 128.26 (4 × d), 128.31 (4 × d), 134.19 (2 × d), 139.38 (2 × s), 144.90 (2 × s); *m*/*z* 415 (M^+, 100%), 338 (4), 324 (28), 310 (7), 298 (12), 279 (4), 246 (3), 218 (10), 206 (6), 193 (17), 167 (7), 149 (8), 117 (21), 91 (96).

1-(*N*,*N*-Dibenzylamino)-2-phenyl-2-(2-phenylethenyl)cyclopropane (104 mg, 0.25 mmol) was subjected to flash vacuum pyrolysis (250 °C/500 °C/>10^{-5} Torr). The pyrolysate was twice subjected to radial chromatography (*tert*-butyl methyl ether–*n*-hexane, 5:95) to give the title compound **11** (28 mg, 27%).

4-(*N*,*N*-Dibenzylamino)-3-(2-methylprop-1-enyl)cyclopent-1-ene 13 and 3-(*N*,*N*-dibenzylamino)-6,6-dimethylcyclohepta-1,4-diene 14

1-(*N*,*N*-Dibenzylamino)-2-ethenyl-3-(2-methylprop-1-enyl)-cyclopropane **12** [two major diastereomers only, however, a (1:2:2) mixture of all three gave the same result] (82 mg, 0.26 mmol) was subjected to flash vacuum pyrolysis (250 °C/420 °C/>10^{-5} Torr). The pyrolysate was subjected to column chromatography (ethyl acetate–*n*-hexane, 10:90) on silver nitrate-impregnated silica gel[10] affording two fractions. The first fraction contained 3-(*N*,*N*-dibenzylamino)-6,6-dimethylcyclohepta-1,4-diene **14** as a white solid, which was recrystallised from *n*-hexane (−23 °C), mp 72–73 °C (50 mg, 61%) (Found: M^+ 317.2143. Calc. for $C_{23}H_{27}N$, M 317.2143). δ_H 0.99 (3 H, s, CH_3), 1.02 (3 H, s, CH_3), 1.95 (1 H, dd, *J* 14.2 and 7.0, 7-H), 2.28 (1 H, dd, *J* 14.2 and 6.0, 7-H), 3.67 [4 H, AB, *J* 14.1, $N(CH_2Ph)_2$], 4.17 (1 H, br s, 3-H), 5.43–5.58 [2 H, m, 2(4)-H], 5.79–5.89 (1 H, m, 1-H), 5.99–6.05 (1 H, m, 5-H), 7.20–7.43 (10 H, m, ArH); δ_C 28.86 (q), 31.10 (q), 34.99 (s), 39.61 (t), 54.12 (2 × t), 56.53 (d), 126.71 (2 × d), 127.13 (d), 128.15 (4 × d), 128.52 (4 × d), 129.16 (d), 133.07 (d), 140.25 (d), 141.52 (2 × s); *m*/*z* 317 (M^+, 4%), 302 (6), 226 (18), 197 (11), 181 (1), 170 (3), 148 (1), 132 (1), 120 (8), 106 (11), 91 (100). The second fraction contained compound **13** (mixture of two diastereomers, ratio 4:1) as a colourless oil (4 mg, 5%) (Found: M^+ 317.2143. Calc. for $C_{23}H_{27}N$, M 317.2143). (Only the major diastereomer) δ_H 1.71 (3 H, s, CH_3), 1.77 (3 H, s, CH_3), 2.33–2.52 (2 H, m, 5-H), 3.28–3.37 (1 H, m, 4-H), 3.50–3.63 (1 H, s, 3-H), 3.59 [4 H, s, $N(CH_2Ph)_2$], 4.80–4.86 [1 H, m, C*H*C$(CH_3)_2$], 5.42–5.50 (1 H, m, 1-H), 5.62–5.79 (1 H, m, 2-H), 7.18–7.40 (10 H, m, ArH); δ_C 18.30 (q), 25.75 (q), 33.95 (t), 45.59 (d), 54.49 (2 × t), 65.72 (d), 126.59 (2 × d), 128.03 (4 × d), 128.54 (d), 128.56 (4 × d), 129.07 (d), 130.42 (s), 133.80 (d), 140.41 (2 × s); *m*/*z* 317 (M^+, 49%), 302 (8), 288 (3), 248 (4), 246 (9), 226 (11), 222 (12), 206 (2), 196 (1), 158 (6), 132 (7), 106 (6), 91 (100).

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