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The Ritter Reaction of Terpenes. Part 3. Investigation of Carvone and Related Compounds

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The Ritter reaction of (*R*)-carvone (**1**), *cis*-carveol (**2**) and carvyl ethers **3** and **4** was investigated. For ketone **1** formation of 8-amido-6-p-menthen-2-ones (**7–12**) in moderate yields was observed. Alcohol **2** gave, depending on the reaction conditions, 2-amido-6,8(9)-p-menthadienes, 2-amido-4(8),6-p-menthadienes and/or 2,8-diamido-6-p-menthenes. Ethers **3** and **4** underwent cleavage to almost the same amides as it was observed for *cis*-carveol (**2**). Additionally, tertiary phenylcarveol (**5**) under similar conditions furnished 6-acetamido-2-phenyl-1,8(9)-p-menthadiene (**28**) as a result of dehydration, followed by migration of a double bond. The proposed mechanisms of the reactions are presented.

Key words: terpenes, p-menthadienyl system, Ritter reaction, rearrangements

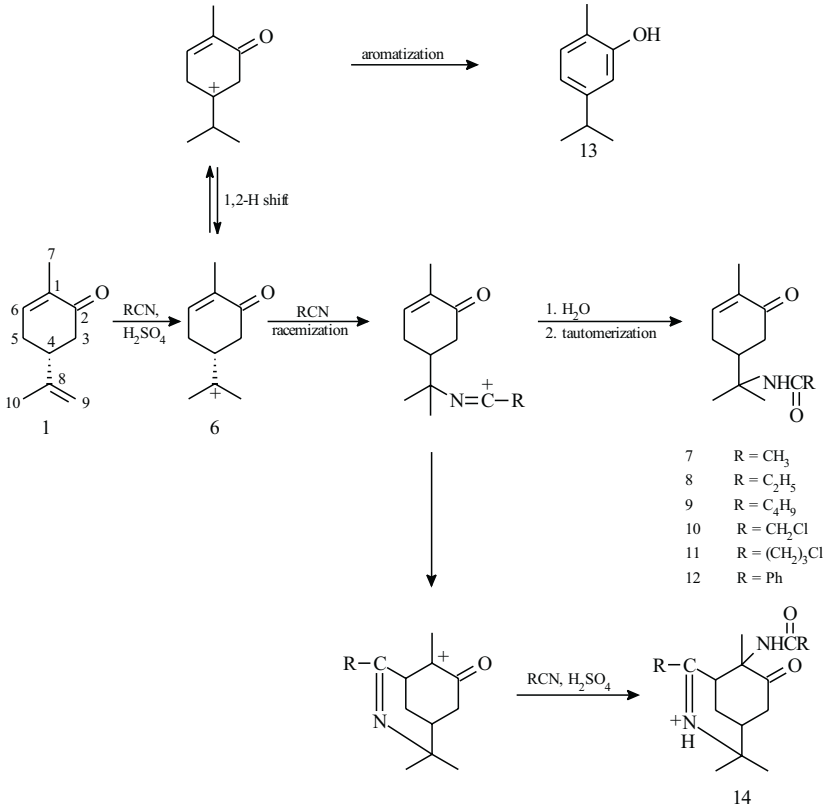
Previously [1,2] we have described the Ritter reaction of tri- and bicyclic terpenes leading to a variety of new N-terpene substituted amides. Such compounds can serve as precursors of terpene amines exhibiting pharmacological activity [3–6]. In addition, application of the title reaction to terpenes makes possible investigations of cationic rearrangements in these systems [1,2,7–10].

In this paper we report on a continuation of our studies [1,2] on (*R*)-carvone (**1**) and some related compounds **2–5** (Schemes 1–3) containing the monocyclic p-menthadienyl skeleton. One might expect that for carvone (**1**) the first stage of the Ritter reaction should involve a formation of a tertiary carbonium ion **6**. This ion may react with nitriles to give the corresponding substituted amides **7–12**. Simultaneously, a possibility of expelling of H^+ and isomerization of the produced ion to carvacrol (**13**) as a result of the 1,2-hydrogen shift must be taken into consideration. Cyclization leading to iminium salts **14**, as it was observed for (*R*)-limonene and other terpenes [11,12], is the another hypothetical course of the reaction under investigation. It is, however, less probable because of a decreased electron density at the C-6 position due to an electron-withdrawing effect of the conjugated carbonyl group.

RESULTS AND DISCUSSION

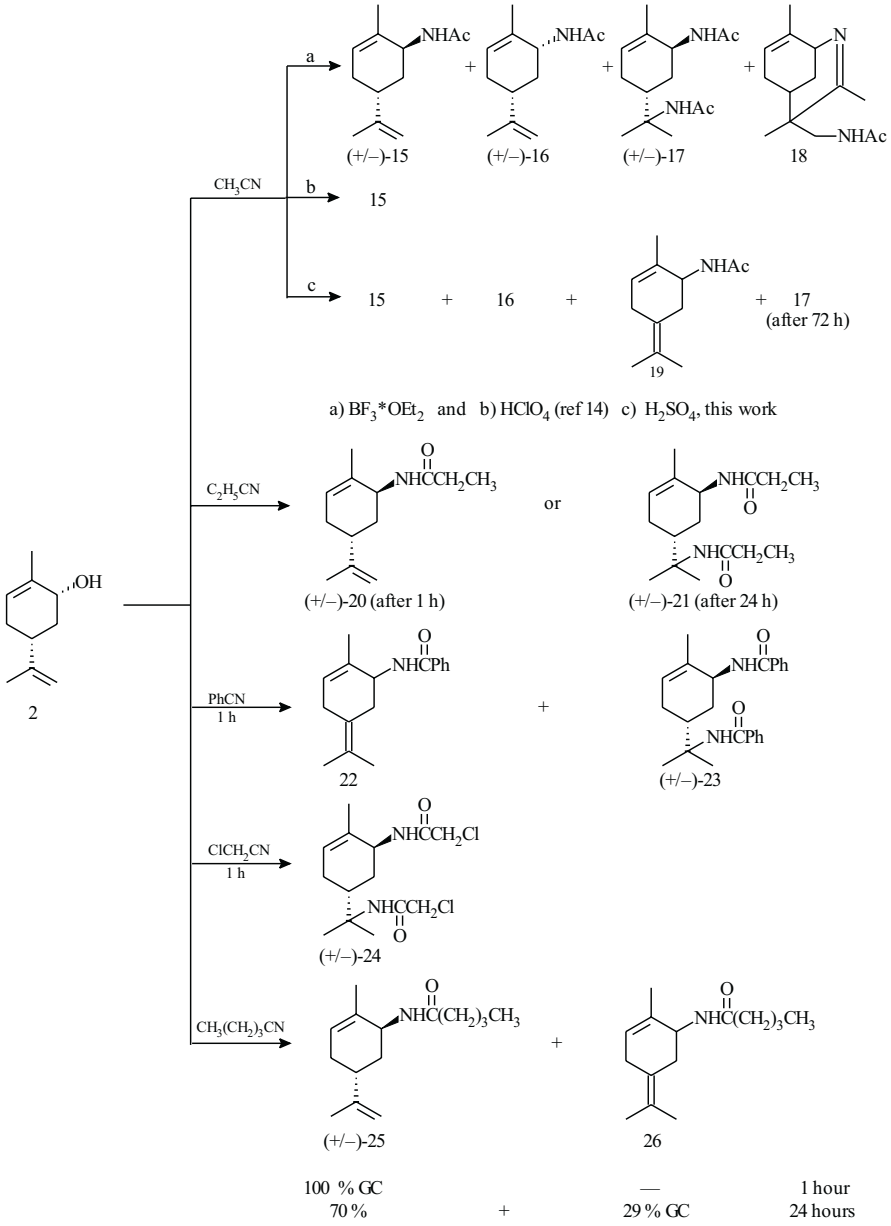
(*R*)-Carvone (**1**) was subjected to the Ritter reaction with various nitriles in the presence of concentrated sulphuric acid. As expected, amides **7–12** were obtained in moderate yields (Scheme 1). Their structures were determined by spectroscopic

Scheme 1



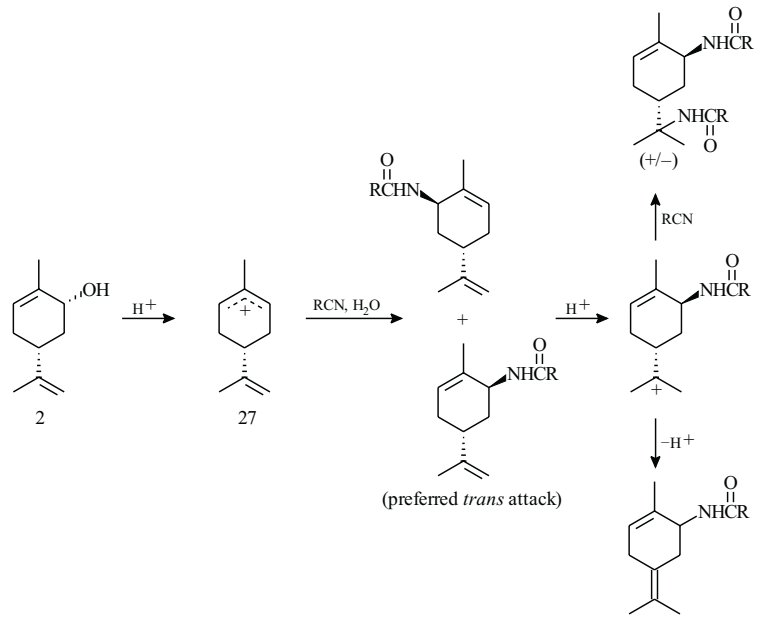
methods. Carvacrol (**13**) was a by-product of these reactions, easy to remove during an alkaline work-up. The formation of iminium salts **14** was not observed. Interestingly, all the amides obtained from (*R*)-carvone (**1**) were optically inactive. It is due to racemization on the chiral center C-4, which was presumably caused by the 1,2-hydrogen shift between the C-4 and C-8 atoms [13]. The intermediate formation of the double bond between the same positions and its further protonation from both sides may be assumed to be an alternative explanation. The Ritter reaction of *cis*-carveol (**2**) catalyzed by aqueous perchloric acid or boron trifluoride etherate investigated previously by Kabore *et al*. [14] revealed, that the composition of the products depends on the catalyst. In the former case, *trans*-2-acetamido-6,8(9)-p-menthadiene (**15**) was obtained in high yield, whereas in the latter one, a mixture of *trans*- and *cis*-acetamides **15** and **16**, diacetamide **17** and the cyclic aza derivative **18** was formed (Scheme 2). Reactions of *cis*-carveol (**2**) with various nitriles, in the presence of concentrated sulphuric acid, led to different products depending on the reaction time. Thus, in the case of acetonitrile a mixture of *trans*- and *cis*-acetamides **15, 16** and **19** was obtained after one hour. The structural elucidation of these compounds is

Scheme 2

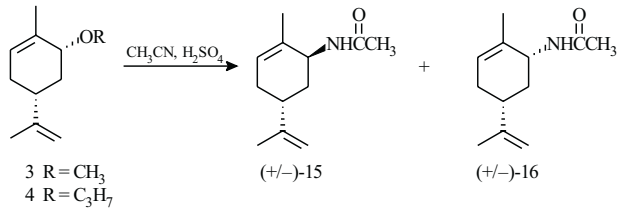


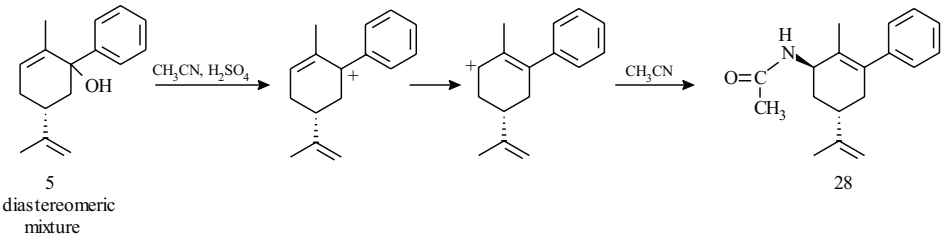
based on the analysis of ^{13}C-NMR spectra and comparison with other data reported by Kabore *et al*. [14] for amides **15** and **16**. Therefore, compared with Kabore`s products, a small amount of amide **19** was additionally obtained. It corroborates the possibility of isomerization with formation of a double bond between the C-4 and C-8 atoms. However, when the reaction was continued for 72 hours, diacetamide **17** was

Scheme 3



Mechanistic proposal for Ritter reaction of *cis*-carveol (2)





formed as an additional product. The reaction with propionitrile was more selective. After one hour compound **20** was the sole product, whereas after 24 hours only diamide **21** was obtained. In the case of benzonitrile (after 1 h) a mixture of products **22** and **23**, separable by column chromatography, was formed. Interestingly, when

chloroacetonitrile was used, after one hour, it resulted in diamide **24** formation. It is probably a consequence of greater nucleophilicity of this nitrile in comparison with the other nitriles used. Valeronitrile gave selectively amide **25** after one hour and a mixture of the same compound and its isomerization product **26** after 24 hours. The proposed mechanism for the Ritter reaction of *cis*-carveol (**2**) is outlined in Scheme 3. The ambident allylic cation **27**, initially formed, reacts with nitriles to give *trans*-2-amido-6,8(9)-p-menthadienes. These compounds can undergo further protonation and subsequent addition of a second molecule of nitrile to furnish the corresponding diamides. Alternatively they lose a proton to give 2-amido-4(8),6-p-menthadienes. The stereochemical analysis of this mechanism leads to the conclusion that a nucleophilic attack of the nitrile molecule can proceed at C-2 as well as C-6 in a trans- or cis-manner. However, the trans attack is strongly preferred, thereby avoiding unfavorable steric hindrance from the isopropenyl group at C-4. As a consequence none of the possible *cis*-diastereomers were detected, except for amide **16** with the smallest acyl group. A similar stereoselectivity was observed for diamides **21** and **24**, obtained earlier from sobrelol by Kozlov *et al*. [15]. The other fragment of the present work deals with the Ritter reaction of carvyl ethers **3** and **4** synthesized by the Williamson reaction of carveol (**2**) with corresponding iodides. After one hour almost the same composition of products, as in the case of *cis*-carveol (**2**), except compound **19**, was observed. It indicates that these reactions must proceed *via* the same intermediate allylic carbonium ion **27**. The tertiary alcohol **5** resulted as a diastereomeric mixture in the Grignard reaction of (*R*)-(–)-carvone (**1**) with phenylmagnesium bromide was the last of the compound examined. The Ritter reaction of this derivative under conditions described above, but for three hours, gave amide **28**. Such an isomerization is facilitated by the presence of an aromatic ring connected with the tertiary carbocationic center initially formed.

EXPERIMENTAL

Melting points were measured on a Boetius apparatus and were uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solutions with a Varian Gemini 200 spectrometer. Ratios and purity of the obtained products were determined by GC with a Hewlett Packard 5890 chromatograph (capillary column HP-1-phase) and Chrom-5 apparatus (Chromosorb W AWDMCS, 60-100 mesh with OV-17 (3%) phase). IR absorption spectra were taken with Spectrum 2000 Perkin-Elmer spectrophotometer. Mass spectra were recorded with a Finningan MAT spectrometer. Optical rotation were measured with an Officine Galileo polarimeter. All the obtained amides, except amide **28,** were optically inactive. *cis*-Carveol (**2**) and its methyl ether (**3**) were prepared according to [16]. (*R*)-(–)-Carvone (**1**) was purchased from Aldrich.

*1. Ritter reaction of (R)-(–)-carvone (**1**):* Conc. H_2SO_4 (1 ml) was added dropwise to a solution of of carvone (**1**; 3 g, 20 mmol) in 75 mmol of the corresponding nitrile at –25°C. The reaction mixture attained room temperature and was stirred for 24 h, poured into water, alkalized with 25% aq. NH_3 and extracted with Et_2O (3 × 50 ml). The combined extracts were washed with H_2O and dried over $MgSO_4$. The solvent was distilled off under reduced pressure to give amides **7–12** crystallized from EtOH or purified by means of column chromatography (CC) on SiO_2 (60–100 mesh) and acetone as an eluent. The following compounds were obtained:

a) *8-Acetamido-6-p-menthen-2-one* (**7**): 1.60 g (38% yield after CC), m.p. 97–99°C; ^{1}H-NMR, δ: 1.29 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.02–2.58 (m., 4H, 2 CH_2), 2.95 (m., 1H, CH), 5.21 (bs, 1H, NH), 6.75 (d, 1H, J = 5.5 Hz, =CH); ^{13}C-NMR, δ: 15.52 (CH_3), 24.08 (CH_3), 24.44 (2 CH_3), 27.61 (CH_2), 39.74 (CH_2), 41.10 (CH), 55.51 (C), 135.29 (C), 144. 87 (CH), 169.47 (C), 199.68 (C); IR (nujol, cm^{-1}): 3340, 1720, 1660, 1550. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.67. Found C, 68.73; H, 9.18; N, 6.80.

b) *8-Propioamido-6-p-menthen-2-one* (**8**): 1.56 g (34% yield after CC), m.p. 72–74°C; ^{1}H-NMR, δ: 1.08 (t, 3H, J = 8.0 Hz, CH_3), 1.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.95–2.52 (m., 6H, 3 CH_2), 2.90 (m., 1H, CH), 5.34 (bs, 1H, NH), 6.72 (d, 1H, J = 6.0 Hz, =CH_2); ^{13}C-NMR, δ: 9.73 (CH_3), 15.13 (CH_3), 24.35 (CH_3), 24.63 (CH_3), 27.69 (CH_2), 30.55 (CH_2), 39.86 (CH_2), 42.08 (CH), 55.38 (C), 135.50 (C), 144.14 (CH), 172.99 (C), 204.60 (C); IR (nujol, cm^{-1}): 3340, 1730, 1660, 1540. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found C, 69.86; H, 9.42; N, 6.32.

c) *8-Valeramido-6-p-menthen-2-one* (**9**): 2.68 g (53% yield) m.p. 80–83°C (EtOH); ^{1}H-NMR, δ: 0.89 (t, 3H, J = 6.0 Hz, CH_3), 1.29 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.20–1.60 (m, 6H), 1.73 (s, 3H, CH_3), 2.00–2.55 (m, 4H), 2.90 (m, 1H, CH), 5.22 (bs, 1H, NH), 6.72 (d, 1H, J = 5.5 Hz, =CH); ^{13}C-NMR, δ: 13.66 (CH_3), 15.36 (2 CH_3), 22.22 (CH_3), 24.22 (CH_2), 24.32 (CH_2), 27.44 (CH_2), 27.75 (CH_2), 37.02 (CH_2), 41.01 (CH), 55.15 (C), 135.07 (C), 145.10 (CH), 172.72 (C), 199.79 (C); IR (nujol, cm^{-1}): 3340, 1720, 1660, 1550. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.68; H, 10.02; N, 5.57. Found C, 71.83; H,10.08; N, 5.71.

d) *8-Chloroacetamido-6-p-menthen-2-one* (**10**): 3.32 g (68% yield), m.p. 111–113°C (EtOH); ^{1}H-NMR, δ: 1.33 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.02–2.48 (m, 4H, 2 CH_2), 2.85 (m, 1H, CH), 3.95 (s, 2H, CH_2), 6.30 (bs, 1H, NH), 6.72 (d, 1H, J = 6.0, Hz =CH); ^{13}C-NMR, δ: 15.43 (CH_3), 23.79 (CH_3), 23.95 (CH_3), 27.34 (CH_2), 39.48 (CH_2), 41.28 (CH), 42.81 (CH_2), 56.01 (C), 135.38 (C), 144.54 (CH), 172.80 (C), 200.20 (C); IR (nujol, cm^{-1}): 3350, 1730, 1680, 1550. Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.14; H, 7.44; Cl, 14.55; N, 5.75. Found C, 59.22; H, 7.48; Cl, 14.65; N, 5.82.

e) *8-(4-Chlorobutyramido)-6-p-menthen-2-one* (**11**): 3.16 g (54%), m.p. 84.5–85.0°C (EtOH); ^{1}H-NMR, δ: 1.29 (s, 3H, CH_3), 1.30 (s, 3H, CH), 1.74 (s, 3H, CH_3), 1.96–2.52 (m, 8H, 4 CH_2), 2.85 (m, 1H, CH), 3.57 (t, 2H, J = 9.0 Hz, CH_2), 5.40 (bs, 1H, NH), 6.75 (d, 1H, J = 5.5 Hz, =CH); ^{13}C-NMR, δ: 17.93 (CH_3), 26.56 (CH_3), 26.83 (CH_3), 29.84 (CH_2), 30.38 (CH_2), 36.34 (CH_2), 42.15 (CH_2), 43.69 (CH), 46.95 (CH_2), 58.08 (C), 137.80 (C), 147.30 (CH), 173.53 (C), 202.13 (C); IR (nujol, cm^{-1}): 3350, 1730, 1670, 1540. Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; Cl, 13.04; N, 5.15. Found C, 62.03; H, 8.20; Cl, 13.10; N, 5.18.

f) *8-Benzamido-6-p-menthen-2-one* (**12**): 2.61 g (48% yield), m.p. 128–129°C (EtOH); ^{1}H-NMR, δ: 1.42(s, 6H, 2 CH_3), 1.71 (s, 3H, CH_3), 2.05–2.62 (m, 4H, 2 CH_2), 3.07 (m, 1H, CH), 5.82 (bs, 1H, NH), 6.72 (d, 1H, J = 5.0 Hz, =CH), 7.45 (m, 3H, 3 CH), 7.90 (m, 2H, 2 CH); ^{13}C-NMR, δ: 15.11 (CH_3), 23.85 (CH_3), 24.03 (CH_3), 27.17 (CH_2), 39.31 (CH_2), 40.78 (CH), 55.51 (C), 119.21 (C), 126.29 (2 CH), 128.15 (2 CH), 130.97 (CH), 134.96 (C), 144.52 (CH), 166.58 (C), 199.28 (C); IR (nujol, cm^{-1}): 3350, 1670, 1600, 1540. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found C, 75.32; H, 7.75; N, 5.20.

2. Ritter reaction of cis-carveol (2): Conc. H_2SO_4 (1 ml) was added dropwise to a solution of *cis*-carveol (**2**; 4.5 g, 30 mmol) in 10 ml of an appropriate nitrile cooled to –25°C. The reaction was continued at ambient temperature for various time (1 h, 24 h or 72 h), poured into 50 ml of ice-water, alkalized with aq. NH_3 and extracted with ether (3 × 50 ml). The etheral extracts were washed with water and dried over anhyd. $MgSO_4$. The solvent was distilled off and the residue was purified by means of column chromatography (SiO_2, Et_2O or EtOH) or by crystallization from EtOH to obtain, respectively: a) for acetonitrile (1 h and 24 h): 5.8 g of a mixture consisted of *trans*-2-acetamido-6,8(9)-p-menthadiene (**15**) (77% GC), *cis-2-acetamido-6,8(9)-p-menthadiene* (**16**) (17% GC) and 2-acetamido-4(8),6-p-menthadiene (**19**) (6 % GC). After 72 h: compounds **15** (59% GC), **16** (16% GC), **19** (5% GC) and 2,8-diacetamido-6-p-menthene (**17**). Amide **15** (after CC): m.p. 118°C (acetone) (lit. [14] m.p. 119°C (acetone)); ^{13}C-NMR, δ: 20.27 (CH_3), 20.38 (CH_3), 22.92 (CH_3), 30.28 (CH_2), 33.61 (CH_2), 35.72 (CH_2), 47.39 (CH), 108.67 (CH_2), 125.55 (CH), 132.01 (C), 148.30 (C), 169.13 (C); GC-MS (CI): 194, 170, 166, 150, 135, 119, 108, 100, 91, 83, 68. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found C, 74.66; H, 9.96; N, 7.30. Amide 16 (after CC): m.p. 138°C (acetone) (lit. [14] m.p. 138°C (acetone)); ^{13}C-NMR, δ: 19.93 (CH_3), 20.57 (CH_3), 23.04 (CH_3), 30.56 (CH_2), 35.54 (CH_2), 40.38 (CH), 49.39 (CH), 109.10 (CH_2), 124.92 (CH), 129.29 (CH), 133.82 (C), 169.91 (C). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25.

Found C, 74.72; H, 9.92; N, 7.33. Amide **19** (identified from a mixture): ^{13}C-NMR, δ: 19.69 (CH_3), 20.05 (CH_3), 22.79 (CH_3), 23.76 (CH_3), 29.68 (CH_2), 33.04 (CH_2), 49.58 (CH), 109.09 (CH), 119.60 (C), 121.16 (C), 123.46 (C), 169.62 (C); diamide **17** (after CC): m.p. 218°C (acetone) (lit. [14] m.p. 218°C (acetone)); GC-MS (CI): 253, 194, 135, 119, 100, 60. Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.63; H, 9.59; N, 11.10. Found C, 66.82; H, 9.63; N, 11.20. b) for propionitrile (1 hour): *2-propioamido-6,8(9)-p-menthadiene* (**20**); 3.6 g (58% yield), m.p. 64–67°C (EtOH); ^{1}H-NMR, δ: 1.15 (t, 3H, J = 7.5 Hz, CH_3), 1.65 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.50–2.20 (m, 5H, 2 CH_2 and CH), 2.20 (q, 2H, J = 7.5 Hz, CH_2), 4.40 (m, 1H, CH), 4.70 (m, 2H,=CH_2), 5.50 (m, 1H, =CH), 5.60 (m, 1H, NH); ^{13}C-NMR, δ: 10.02 (CH_3), 20.76 (CH_3), 20.84 (CH_3), 29.95 (CH_2), 30.78 (CH_2), 34.23 (CH_2), 36.32 (CH), 47.69 (CH), 109.34 (CH), 126.02 (CH), 132.78 (C), 148.86 (C), 173.29 (C). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found C, 75.42; H, 10.28; N, 6.84; for 24 h: *2,8-dipropioamido-6-p-menthene* (**21**): 4.2 g (50% yield), m.p. 164°C (EtOH) (lit. [15] m.p. 166°C (EtOH)); ^{1}H-NMR, δ: 1.05 (t, 3H, J = 7.2, Hz CH_3), 1.10 (t, 3H, J = 7.2, Hz CH_3), 1.14 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.60-2.00 (m, 4H, 2 CH_2), 2.10 (q, 2H, J = 7.2 Hz, CH_2), 2.15 (q, 2H, J = 7.2 Hz, CH_2), 2.56 (m, 1H, CH), 4.40 (m, 1H, CH), 5.08 (m, 1H, =CH), 5.60 (m, 2H, 2 NH); GC-MS (CI): 281, 208, 135, 114, 93, 74. Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.53; H, 10.06; N, 9.99. Found C, 68.59; H, 10.12; N, 10.08; c) for benzonitrile (1 hour): *2-benzamido-4(8),6-p-menthadiene* (**22**): 2.5 g (32% yield, after CC); m.p. 115–117°C; ^{1}H-NMR, δ:1.65 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.30 (m, 1H), 2.58–3.05 (m, 3H), 4.65 (m, 1H, CH), 5.56 (m, 1H, NH), 6.00 (d, 1H, J = 8.0 Hz, =CH), 7.40 (m, 3H, CH), 7.68 (m, 2H, CH); ^{13}C-NMR, δ: 19.89 (CH_3), 20.20 (CH_3), 20.82 (CH_3), 29.86 (CH_2), 33.20 (CH_2), 49.80 (CH), 123.43 (C), 125.46 (C), 125.59 (C), 126.80 (CH), 128.44 (2 CH), 128.52 (2 CH), 131.26 (CH), 133.76 (C), 166.93 (C). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found C, 80.09; H, 8.34; N, 5.56 and *2,8-dibenzamido-6-p-menthene* (**23**): 5.1 g (27% yield after CC); m.p. 162–164°C (EtOH); ^{1}H-NMR, δ: 1.35 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.50–2.20 (m, 4H, 2 CH_2), 2.90 (m, 1H, CH), 4.65 (m, 1H, CH), 5.63 (d, 1H, J = 6 Hz, NH), 5.85 (s, 1H, NH), 6.35 (d, 1H, J = 8.0 Hz, =NH), 7.20–7.80 (m, 10H, 2 C_6H_5); ^{13}C-NMR, δ: 20.89 (CH_3), 23.83 (CH_3), 24.75 (CH_3), 27.18 (CH_2), 31.09 (CH_2), 35.03 (CH), 48.69 (CH), 56.61 (C), 126.21 (CH), 126.70 (2 CH), 127.02 (2 CH), 128.44 (4 CH), 131.25 (CH), 131.37 (CH), 133.26 (C), 134.91 (C), 135.72 (C), 167.28 (2C). Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found C, 76.43; H, 7.58; N, 7.52; d) for chloroacetonitrile (1 hour): *2,8-di(chloroacetamido)-6-p-menthene* (**24**): 5.2 g (52.2% yield); m.p. 180–181°C (EtOH) (lit. [15] m.p. 182°C (EtOH)); ^{1}H-NMR, δ: 1.25 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.35–215 (m, 4H, 2 CH_2), 2.35 (m, 1H, CH), 3.90 (s, 2H, CH_2), 4.00 (s, 2H, CH_2), 4.38 (m, 1H, CH) 5.62 (d, 1H, J = 3.5 Hz, =CH), 6.25 (bs, 1H, NH), 6.55 (m, 1H, NH); ^{13}C-NMR, δ: 20.62 (CH_3), 23.46 (CH_3), 24.11 (CH_3), 26.67 (CH_2), 30.12 (CH_2), 35.37 (CH), 42.58 (CH_2), 42.85 (CH_2), 48.78 (CH), 56.44 (C), 126.51 (CH), 132.10 (C), 164.90 (C), 165.78 (C). Anal. Calcd for $C_{14}H_{22}Cl_2N_2O_2$: C, 52.34; H, 6.90; Cl, 22.07; N, 8.72. Found C, 52.23; H, 7.13; Cl, 22.16; N, 9.03; e) for valeronitrile (1 hour): *2-valerylamido-6,8(9)-p-menthadiene* (**25**): 3.5 g (50% yield); m.p. 40–42°C (EtOH). ^{1}H-NMR, δ: 0.89 (t, 3H, J = 7.0 Hz, CH_3), 1.15–1.38 (m, 3H, CH_3), 1.53–1.70 (m, 2H), 1.67 (s, 3H, CH_3), 1.70 (s, 3H, CH_3). 1.80–1.95 (m, 2H), 2.00–2.20 (m, 3H), 3.45 (q, 1H, J = 7.0 Hz, CH_2), 4.40 (m, 1H, =CH_2), 4.70 (m, 3H, =CH_2), 5.60 (m, 1H, NH); ^{13}C-NMR, δ: 13.61 (CH_3), 20.59 (CH_3), 20.69 (CH_3), 22.20 (CH_2), 27.95 (CH_2), 30.61 (CH_2), 34.23 (CH_2), 36.17 (CH), 36.53 (CH_2), 47.61 (CH), 109.13 (CH_2), 125.82 (CH), 132.80 (C), 148.72 (C), 172.61 (C); GC-MS (EI): 236, 192, 151, 136, 119, 108, 91, 83, 77, 67. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found C, 76.63; H, 10.82; N, 5.86. After 24 h and column chromatography: 4.9 g of a mixture consisted of **25** (70.2% GC) and **26** (28.9% GC) was obtained. GC-MS (EI) for **26**: 236, 134, 119, 102, 91, 83, 77, 65.

3. Propyl ether of cis-carveol (4): cis-Carveol (**2**; 13.09 g, 85 mmol) was added dropwise to a suspension of NaH (2.6 g, 50% in mineral oil rinsed with hexane) in 100 ml of anhydrous THF. After 15 min, isopropyl iodide (41 ml, 420 mmol) was added and the reaction mixture was the reaction mixture was heated for 4 h. The excess of NaH was decomposed by MeOH, washed with water and dried over anhyd. $MgSO_4$. The residue after the solvent removal was distilled under reduced pressure to give propyl ether of *cis*-carveol (**4**): 10.9 g (70%), b.p. 86–88°C/6 mm Hg, $[\alpha]_D^{20} = -78.9°$ (7.1, EtOH). ^{1}H-NMR, δ: 0.94 (3H, t, J = 7.0 Hz, CH_3), 1.30–1.50 (1H, dt), 1.63 (2H, q, J = 7.0 Hz, CH_2), 1.72–1.74 (m, 6H, 2 CH_3), 1.85–2.40 (4H, m), 3.34 (1H, m, OCH_2), 3.56 (1H, m, OCH_2), 3.88 (1H, m, HCO), 4.72 (2H, m, =CH_2), 5.50 (1H, m, =CH). ^{13}C-NMR, δ: 10.55 (CH_3), 18.79 (CH_3), 20.42 (CH_3), 23.31 (CH_2), 30.90 (CH_2), 34.16 (CH_2), 40.38 (CH), 70.70 (CH_2), 78.14 (CH), 109.03 (CH_2), 123.69 (CH), 136.27 (C), 148.91 (C).

*4. Ritter reaction of ethers **3** and **4**:* The reactions were carried out as in Experiment 3 using 50 mmol of the corresponding ether but for 1 h to give 5.4 g of a mixture consisted of *trans*-2-acetamido-6,8(9)-menthadiene (**15**) (83%GC) and *cis*-2-acetamido-6,8(9)-menthadiene (**16**) (17% GC) for ether **3** and 5.8 g of the same mixture in 85 : 15 GC ratio for ether **4**. Spectroscopic data as in Experiment 3 a.

*5. 2-Phenylcarveol (**5**):* (*R*)-Carvone (**1**; 15.0 g, 100 mmol) was added slowly to the solution of phenylmagnesium bromide prepared from Mg turnings (5.0 g, 210 mmol) and bromobenzene (33.8 g, 210 mmol) in 100 ml of Et_2O. The reaction was continued for 24 h at ambient temperature, cooled to 0°C and then saturated solution of NH_4Cl was dropped slowly until the precipitate of magnesium salt was dissolved. The organic layer was separated and the layer was extracted with Et_2O. The combined extracts were washed with water and dried over anhyd. $MgSO_4$. The solvent was distilled off and the residue was fractionated under reduced pressure to give 8.4 g (37%) of compound **5**. B.p. 124–126°C/15 mm Hg. ^{1}H-NMR, δ: 1.62 (s, 3H, CH_3), 1.64 (d, 3H, J = 2.0 Hz, CH_3), 1.80–2.30 (m, 6H, 2 CH_2, CH, and OH), 4.64 (d, 2H, J = 7.0 Hz, =CH_2), 5.80 (m, 1H, =CH), 7.30 (m, 3H, CH), 7.46 (m, 2H, CH).

*6. 6-Acetamido-2-phenyl-1,8(9)-p-menthadiene (**28**):* Conc. H_2SO_4 (0.5 ml) was added to alcohol **5** (3.0 g, 13 mmol) in 10 ml of acetonitrile cooled to –20°C. The reaction mixture was stirred at room temperature for 3 h and after standard work-up as in previous experiments crude product was obtained. After crystallization from EtOH 1.5 g (43%) of compound **28** was obtained. M.p. 161°C, $[\alpha]_D^{20}$ = 11.9 (2.3, EtOH). ^{1}H-NMR, δ: 1.60 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.90–2.45 (m, 5H, 2 CH_2 and CH), 4.58 (m, 1H, CH), 4.76 (s, 2H, =CH_2), 5.65 (d, 1H, J = 6.0 Hz, NH), 7.12 (m, 2H, CH), 7.27 (m, 3H, CH). ^{13}C-NMR, δ: 17.43 (CH_3), 20.28 (CH_3), 22.99 (CH_3), 33.60 (CH_2), 36.66 (CH), 37.05 (CH_2), 48.70 (C), 109.05 (CH_2), 126.22 (CH), 127.40 (2 CH), 127.63 (2 CH), 127.81 (CH), 136.77 (C), 142.44 (C), 144.05 (C), 169.15 (C). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found C, 80.31; H, 8.58; N, 5.28.

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