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Synthesis and biological evaluation of new antimalarial isonitriles related to marine diterpenoids

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Abstract—By exploiting the chemistry of arene tricarbonylchromium(0) complexes, some analogues of antimalarial marine isonitrile diterpenoids were synthesized in a completely diastereoselective fashion and their activity against the malaria parasite *Plasmodium falciparum* was assessed in an in vitro assay.

Malaria is considered the world's most important tropical disease killing more people than any other communicable disease except tuberculosis and HIV/AIDS.[1] It is a public health problem in more than 90 countries inhabited by 40% of the world's population. An additional difficulty arises from the increasing resistance of the malaria parasite *Plasmodium falciparum* against chloroquine.

Therefore, the search for new antimalarial compounds represents a particularly challenging task for chemical research.[2] Some of the most promising new antimalarial compounds have recently been isolated and the chemical structure determined by König et al.[3] These natural products, for example **1**, **2** and **3** (Fig. 1) are amphilectane or cyclo-amphilectane diterpenoids possessing a characteristic isonitrile functionality.[4] Their potent activity against some clones of *P. falciparum* rivals the in vitro potency of some clinically-used antimalarial drugs.

In the course of our research program on the use of chiral arene–$Cr(CO)_3$ complexes in stereo-selective synthesis,[5] we recently showed that the SmI_2-mediated cyclization of imines of type **4** gives rise to tricyclic products of type **5** and **6** in good yield (Scheme 1).[6]

The obvious structural relationship between **5** and **6** and the bioactive isonitriles **1** and **2** prompted us to apply this chemistry for the synthesis of such compounds. In this paper we report our preliminary results on the synthesis of some racemic, structurally simplified analogues of the natural isonitriles and demonstrate their in vitro activity against *P. falciparum*.

The conversion of the cyclization products *rac*-**5a** and *rac*-**6a** (R = H)[6] into the isonitriles *rac*-**9** and *rac*-**10**, respectively, was accomplished as shown in Scheme 2. At first, the $Cr(CO)_3$ moiety was removed by oxidative decomplexation and the *N*-benzyl protecting group was

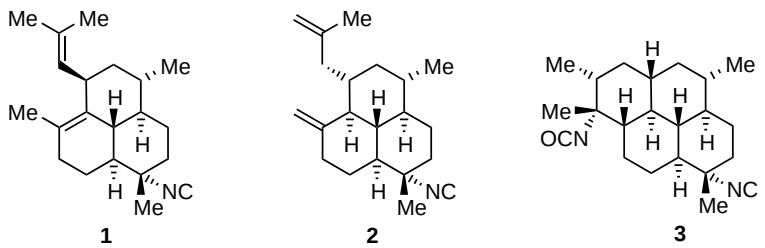

Figure 1. Some potent antimalarial diterpene isonitriles isolated from a marine sponge.[3]

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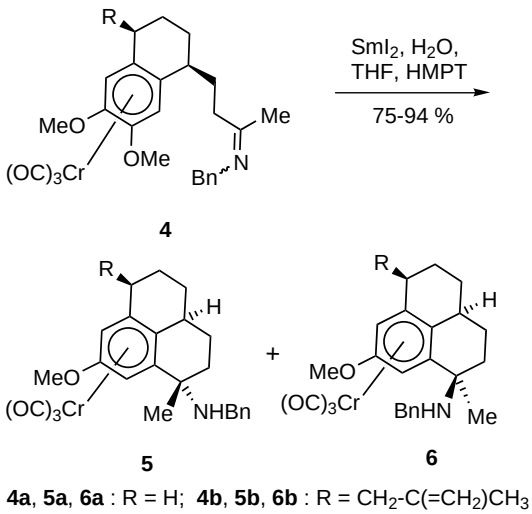
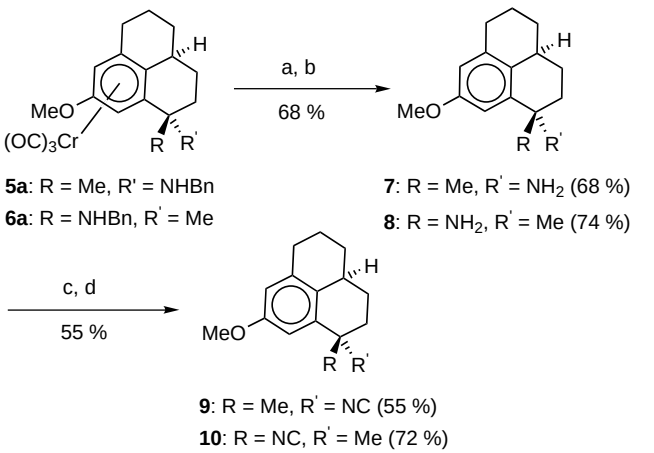


Scheme 1. SmI_2-mediated cyclization of $Cr(CO)_3$-complexed imines of type **4**.[6]



Scheme 2. Synthesis of the isonitriles *rac*-**9** and *rac*-**10**. (a) Sunlight, air, Et_2O, rt; (b) H_2 (1 atm.), 10% Pd/C, EtOH, rt, 24 h; (c) AFA (excess), 3 equiv. pyridine, THF, 0°C to rt, 48 h; (d) 1.1 equiv. $POCl_3$, 2.7 equiv. NEt_3, CH_2Cl_2, 0°C to rt, 2 h.

cleaved by hydrogenolysis. The resulting amines *rac*-**7** and *rac*-**8**, respectively, were then converted into the corresponding formamides by treatment with acetic formic anhydride (AFA) and pyridine.[7] Subsequent dehydration with $POCl_3$ in the presence of NEt_3[7,8] afforded the desired isonitriles *rac*-**9** and *rac*-**10**.

The structure, especially the relative configuration of *rac*-**9**, was unequivocally confirmed by X-ray crystallography (Fig. 2).[9] It shows the isonitrile function taking a pseudo-equatorial position.

We next focused our attention on the synthesis of compounds possessing an unsaturated side-chain at C-6, as found in the natural products **1** and **2**. To avoid any undesired hydrogenation of the side-chain double bond under the conditions of the *N*-deprotection by

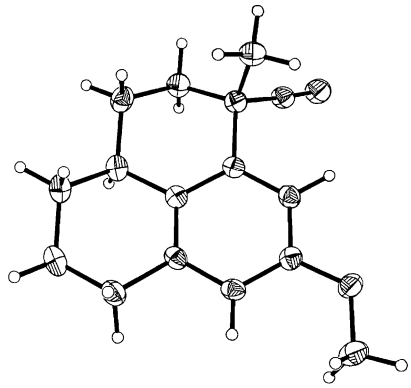


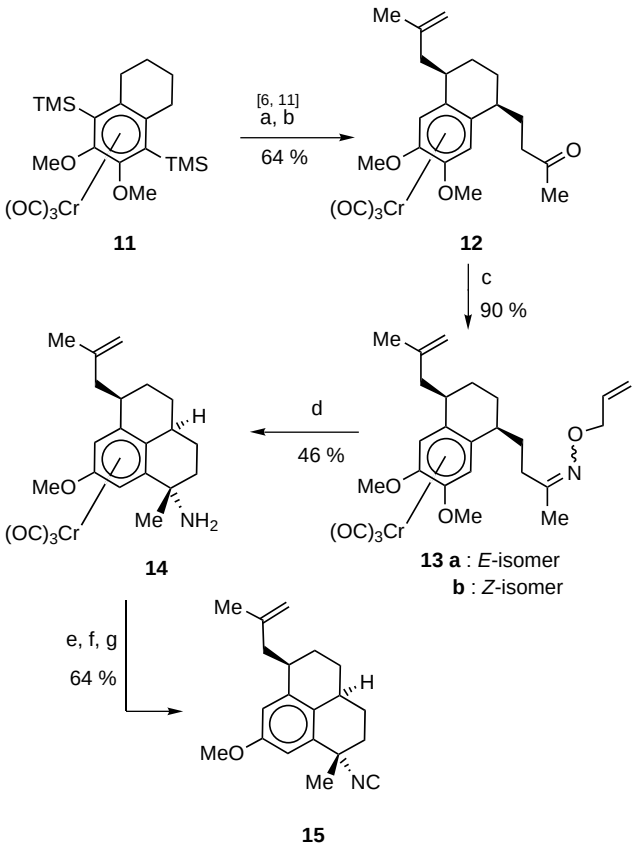
Figure 2. Structure of the isonitrile *rac*-**9** in the crystalline state.

means of hydrogenolysis as described above, we searched for a different type of imine derivative of the cyclization precursor, where the '*N*-protecting group' would directly be cleaved under the reductive cyclization conditions. Indeed, it was found that *O*-allyl oximes exhibit the desired properties. Thus, the ketone *rac*-**12**, prepared from the silylated tetraline derivative **11** via two subsequent deprotonation/alkylation steps,[5b,11] was transformed into the cyclization precursor *rac*-**13** in high yield by reaction with *O*-allylhydroxylamine under mild dehydration conditions (basic alumina in benzene).[12] The product (*rac*-**13**) was obtained as a mixture of *E*- and *Z*-isomers (Scheme 3), which, for analytical purposes, could easily be separated by chromatography.

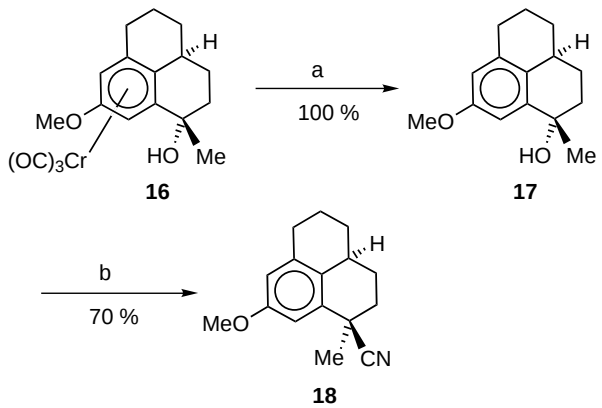
By reacting the mixture *rac*-**13a**/**b** with an excess of SmI_2 in THF/HMPA in the presence of *tert*-butanol as a proton source, both the cyclization and the *N*-deprotection proceeded in a single synthetic operation.[13] To our surprise the tricyclic amine *rac*-**14** was obtained as a pure *endo*-diastereomer (46% yield).[14] The (undesired) *exo*-diastereomer could not be detected, even in the crude product mixture. The conversion of *rac*-**14** into the isonitrile *rac*-**15** (Scheme 3) was then achieved by *N*-formylation, decomplexation and subsequent dehydration, similar to the sequence described above.

An attempt to prepare the isonitrile *rac*-**9** (or *rac*-**10**) from the tricyclic alcohol *rac*-**17** (obtained by decomplexation of *rac*-**16**[5a]) by treatment with a Lewis acid (ZnI_2) in the presence of TMSCN[15] was not successful. Instead of the desired isonitrile, the corresponding nitrile (*rac*-**18**) was formed diastereoselectively in high yield (Scheme 4).[16] This compound, however, represented an interesting compound, which was also tested against the malaria parasite (vide infra).

In order to evaluate their antimalarial potential, compounds *rac*-**9**, *rac*-**10**, *rac*-**15** and *rac*-**18** were entered into an in vitro assay. As standards, the established antimalarial compounds chloroquine and artemisinin were used. Antiplasmodial activity was determined using two strains of *P. falciparum*: NF54 (sensitive to all known drugs) and K1 (resistant to chloroquine and pyrimethamine). A modification of the [^3H]-hypoxan-



Scheme 3. Synthesis of the isonitrile *rac*-**15**.[10] (a, b) see Refs. 6 and 11; (c) 3 equiv. H_2N-*O*-CH_2-CH=CH_2, *Alox B*, benzene, rt, 72 h; (d) 8 equiv. SmI_2, THF/HMPA, *t*-BuOH, rt to 70°C, 2 h; (e) sunlight, air, Et_2O, rt; (f) AFA (excess), 3 equiv. pyridine, THF, 0°C to rt, 60 h; (g) 1.1 equiv. $POCl_3$, 2.7 equiv. NEt_3, CH_2Cl_2, 0°C to rt, 2 h.



Scheme 4. Synthesis of the nitrile *rac*-**18**.[10] (a) Sunlight, air, Et_2O, rt; (b) 3 equiv. ZnI_2, 3 equiv. TMSCN, CH_2Cl_2, 0°C to rt, 18 h.

thine incorporation assay was used.[17] Briefly, infected human red blood cells were exposed to serial drug dilutions in microtiter plates for 48 h. Viability was assessed by measuring the incorporation of [^3H]-hypoxanthine by liquid scintillation counting after an additional 24 h incubation. From the sigmoidal inhibition curves IC_{50} values were calculated. The results of the screening experiments (average values of two independent assays) are summarized in Table 1.

Table 1. Activities of the synthetic compounds against two strains of *Plasmodium falciparum*. All values are the mean of two independent assays run in duplicate and given in ng/mL

Substrate	IC_{50} K1	IC_{50} NF 54
rac-**9**	121	102
rac-**10**	249	169
rac-**15**	109	100
rac-**18**	>5000	>5000
Chloroquine	56	3.1
Artemisinin	2.2	4.1

Interestingly, *all of the isonitriles tested exhibited significant antimalarial activities* while the nitrile (*rac*-**18**) was virtually inactive. This immediately proved the importance of the isonitrile functionality. It seems highly probable that the antimalarial activity of the isonitriles is connected to the ability of isonitriles to bind to iron porphyrins, which play a crucial role in the metabolism of *P. falciparum*.[2]

Even the activities observed for the synthetic compounds are about one order of magnitude smaller than those of the natural products (e.g. **1**, **2**, and **3**); our results reveal the general antimalarial potential of structurally greatly simplified analogues. By comparing the activities of *rac*-**9** and *rac*-**10** it also becomes obvious that the stereochemistry influences the biological properties. The isonitrile (*rac*-**9**) with the 'natural' relative configuration is almost twice as active as its diastereomer (*rac*-**10**). The introduction of the unsaturated side-chain (*rac*-**15**), however, resulted only in a small increase of the activity.

In conclusion, we have developed a novel synthetic methodology to access structurally less complex analogues of the marine isonitriles[18] and have demonstrated that such compounds possess a general potential as antimalarial drugs. Future investigations will focus on the (enantioselective) synthesis and biological evaluation of related isonitriles with structurally diverse hydrocarbon skeletons. The good accessibility of the synthetic compounds offers a chance to investigate the pharmacological properties (including the mechanism of action) of such compounds against *P. falciparum* in greater detail.

Acknowledgements

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9. X-Ray crystal structure of *rac*-**9**: Siemens SMART diffractometer, $\lambda = 0.71069$ Å; structure determination by direct methods (SHELXS). $C_{16}H_{19}NO$, triclinic, space group: *P*-1, $a = 9.3310$ (11), $b = 9.4386$ (10), $c = 15.925$ (2) Å, $\alpha = 85.713(11)$, $\beta = 85.378(11)$, $\gamma = 71.902(8)°$, $V = 1327.0$ (3) Å^3, $Z = 4$, $\delta_{calcd} = 1.208$ g/cm^3, $\mu = 0.075$ mm^{-1}, 7803 independent reflections, refinement by full-matrix least-squares on F^2. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 153962. Copies of the data may be obtained from the Director of the Cambridge Crystallographic Centre, 12 Union Road, GB-Cambridge CB2 1EZ, UK (Fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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18. Selected characteristic data: *rac*-**9**: M: 64–65°C; IR: $\tilde{\nu}$ = 2933, 2860, 2837, 2129 (N≡C), 1728, 1606, 1474; ^{1}H NMR: $\delta = 1.28$ (Ψdq, 1H, $J_d = 4.0$ Hz, $J_q = 12.0$ Hz), 1.43 (Ψdq, 1H, $J_d = 3.5$ Hz, $J_q = 13.0$ Hz), 1.73 (t, 3H, $J = 1.8$ Hz), 1.75–1.85 (m, 1H), 1.86–1.99 (m, 3H), 2.21–2.39 (m, 2H), 2.60 (Ψtt, 1H, $J_1 = 5.0$ Hz, $J_2 = 13.0$ Hz), 2.76–2.85 (m, 2H), 3.80 (s, 3H), 6.61 (d, 1H, $J = 2.5$ Hz), 6.95 (d, 1H, $J = 2.5$ Hz); ^{13}C NMR: $\delta = 22.5$ (t), 27.5 (t), 29.5 (t), 30.4 (t), 33.2 (q), 35.9 (d), 38.5 (t), 55.3 (q), 59.7 (t, $^1J_{C,N} = 5.5$ Hz), 109.5 (d), 114.2 (d), 127.9 (s), 137.8 (s), 138.3 (s), 153.4 (t, $^1J_{C,N} = 5.3$ Hz), 157.9 (s); HR-MS: calcd for $C_{16}H_{19}NO$: 241.1467, found: 241.1465. *rac*-**10**: mp: 77–78°C; IR: $\tilde{\nu}$ = 2932, 2858, 2837, 2124 (NC), 1726, 1607, 1473; ^{1}H NMR: $\delta = 1.36$ (Ψdq, 1H, $J_d = 3.0$ Hz, $J_q = 12.5$ Hz), 1.63–1.79 (m, 2H) 1.80 (Ψt, 3H, $J = 2.0$ Hz), 1.82–1.99 (m, 4H), 2.31–2.40 (m, 1H), 2.46 (Ψtt, 1H, $J_1 = 3.5$ Hz, $J_2 = 11.5$ Hz), 2.79–2.87 (m, 2H), 3.81 (s, 3H), 6.64 (d, 1H, $J = 2.5$ Hz), 6.95 (d, 1H, $J = 2.5$ Hz); ^{13}C NMR: $\delta = 22.4$ (t), 26.9 (t), 29.6 (t), 30.3 (t), 31.4 (q), 36.4 (d), 39.4 (t), 55.2 (q), 58.4 (t, $^1J_{C,N} = 5.1$ Hz, C-3), 109.9 (d), 114.2 (d), 128.9 (s), 137.2 (s), 138.4 (s), 153.2 (t, $^1J_{C,N} = 5.1$ Hz), 157.9 (s); HR-MS: calcd for $C_{16}H_{19}NO$: 241.1467, found: 241.1469. *rac*-**13a**: *E*-isomer: mp: 102°C; IR: $\tilde{\nu}$ = 2933, 2862, 1949 ($Cr(CO)_3$), 1861 ($Cr(CO)_3$); ^{1}H NMR: $\delta = 1.48$–1.60 (m, 2H), 1.62–1.98 (m, 4H), 1.80 (s, 3H), 1.91 (s, 3H), 2.12–2.39 (m, 4H), 2.59–2.69 (m, 1H), 2.72–2.82 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.56 (d, 2H, $J = 5.6$ Hz), 4.75 (s, 1H), 4.87 (s, 1H), 5.21 (dd, 1H, $J_1 = 10.4$ Hz, $J_2 = 1.5$ Hz), 5.28 (s, 1H), 5.30 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 1.5$ Hz), 5.38 (s, 1H), 5.95–6.06 (m, 1H); ^{13}C NMR: $\delta = 14.5$ (q), 22.0 (q), 24.0 (2t), 33.1 (t), 33.6 (t), 34.2 (d), 35.5 (d), 46.1 (t), 57.0 (q), 57.1 (q), 74.3 (t), 77.8 (d), 78.0 (d), 107.1 (s), 107.4 (s), 113.4 (t), 117.0 (t), 132.3 (s), 132.4 (s), 134.5 (d), 142.9 (s), 156.80 (s), 233.75 (s); HR-MS: calcd for $C_{26}H_{33}NO_6Cr$: 507.1713, found: 507.1713. *rac*-**13b**: *Z*-isomer: mp: 81°C; IR: $\tilde{\nu}$ = 3075, 2939, 2866, 1950 ($Cr(CO)_3$), 1861 ($Cr(CO)_3$); ^{1}H NMR: $\delta = 1.50$–1.66 (m, 2H), 1.66–1.88 (m, 4H), 1.81 (s, 3H), 1.91 (s, 3H), 2.18 (dd, 1H, $J_1 = 14.0$ Hz, $J_2 = 9.0$ Hz), 2.28–2.48 (m, 3H), 2.58–2.68 (m, 1H), 2.70–2.80 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.54 (d, 2H, $J = 5.8$ Hz), 4.74 (s, 1H), 4.87 (s, 1H), 5.20 (dd, 1H, $J_1 = 11.0$ Hz, $J_2 = 1.5$ Hz), 5.25 (s, 1H), 5.26 (s, 1H), 5.29 (dd, 1H, $J_1 = 16.6$ Hz, $J_2 = 1.5$ Hz), 5.92–6.04 (m, 1H); ^{13}C NMR:

$\delta = 20.2$ (q), 22.0 (q), 23.5 (t), 24.0 (t), 27.0 (t), 32.6 (t), 34.3 (d), 36.3 (d), 46.0 (t), 57.0 (q), 57.1 (q), 74.2 (t), 77.7 (d), 77.9 (d), 106.7 (s), 107.4 (s), 113.4 (t), 117.0 (t), 132.4 (2s), 134.5 (d), 142.8 (s), 157.5 (s), 233.7 (s); HR-MS: calcd for $C_{26}H_{33}NO_6Cr$: 507.1713, found: 507.1714. *rac*-**14**: IR: $\tilde{\nu} = 3076$, 2935, 2861, 1947 ($Cr(CO)_3$), 1854 ($Cr(CO)_3$); ^1H NMR: $\delta = 1.24$–1.36 (m, 1H), 1.44 (s, 3H), 1.38–1.48 (m, 1H), 1.54–1.63 (m, 1H), 1.70–1.98 (m, 6H), 1.81 (s, 3H), 1.98–2.08 (m, 1H), 2.27–2.42 (m, 2H), 2.55 (Ψtt, 1H, $J_1 = 12.4$ Hz, $J_2 = 4.5$ Hz), 2.90–2.97 (m, 1H), 3.69 (s, 3H), 4.74 (s, 1H), 4.87 (s, 1H), 5.01 (d, 1H, $J = 1.8$ Hz), 5.54 (d, 1H, $J = 1.8$ Hz); ^{13}C NMR: $\delta = 21.9$ (q), 24.6 (t), 25.2 (t), 28.5 (t), 34.4 (q), 35.7 (d), 37.5 (d), 41.0 (t), 47.3 (t), 52.0 (s), 55.5 (q), 76.4 (d), 78.2 (d), 100.9 (s), 113.4 (t), 115.9 (s), 123.1 (s), 142.1 (s), 142.9 (s), 234.5 (s); HR-MS: calcd for $C_{22}H_{27}NO_4Cr$: 421.1345, found: 421.1351. *rac*-**15**: mp: 42–44°C; IR: $\tilde{\nu} = 2935$, 2860, 2837, 2129 (NC), 1606, 1470; ^1H NMR: $\delta = 1.24$–1.40 (m, 1H), 1.45 (Ψdq, 1H, $J_d = 3.5$ Hz, $J_q = 14.0$ Hz), 1.66–1.88 (m, 3H), 1.73 (br s, 3H), 1.79 (s, 3H), 1.92–2.02 (m, 1H), 2.18–2.39 (m, 4H), 2.61 (Ψtt, 1H, $J_1 = 4.4$ Hz, $J_2 = 12.0$ Hz), 2.86–2.99 (m, 1H), 3.82 (s, 3H), 4.71 (s, 1H), 4.83 (s, 1H), 6.68 (d, 1H, $J = 2.5$ Hz), 6.97 (d, 1H, $J = 2.5$ Hz); ^{13}C NMR: $\delta = 22.0$ (q), 25.4 (t), 26.2 (t), 27.5 (t), 33.3 (q), 35.2 (d), 36.0 (d), 38.5 (t), 46.2 (t), 55.3 (q), 59.9 (t, $^1J_{C,N} = 5.5$ Hz), 109.4 (d), 112.4 (t), 114.3 (d), 127.7 (s), 137.6 (s), 142.8 (s), 143.9 (s), 153.4 (t, $^1J_{C,N} = 4.1$ Hz), 157.9 (s); HR-MS: calcd for $C_{20}H_{25}NO$: 295.1936, found: 295.1933. *rac*-**18**: mp: 70°C; IR: $\tilde{\nu} = 2932$, 2857, 2837, 2229 (CN), 1605, 1582, 1474; ^1H NMR: $\delta = 1.33$ (Ψdq, 1H, $J_d = 3.6$ Hz, $J_q = 12.0$ Hz), 1.65 (Ψq, 1H, $J = 12.2$ Hz), 1.75 (s, 3H), 1.71–1.86 (m, 2H), 1.86–2.00 (m, 3H), 2.40 (Ψdt, 1H, $J_d = 13.4$ Hz, $J_t = 3.6$ Hz), 2.50 (Ψtt, 1H, $J_1 = 4.0$ Hz, $J_2 = 12.0$ Hz), 2.76–2.86 (m, 2H), 3.80 (s, 3H), 6.61 (d, 1H, $J = 2.4$ Hz), 6.84 (d, 1H, $J = 2.4$ Hz); ^{13}C NMR: $\delta = 22.4$ (t), 28.3 (t), 28.9 (q), 29.6 (t), 30.3 (t), 36.5 (d), 37.2 (t), 55.2 (q), 71.6 (s), 110.7 (d), 113.8 (d), 125.2 (s, CN), 129.4 (s), 135.8 (s), 138.8 (s), 157.9 (s); GC–MS $C_{16}H_{19}NO$, $T = 100$°C, (70 eV): m/z (%) = 241 (55, M^+), 213 (45), 174 (100).