Synthesis of Carbazoles and 1,2-Dihydrocarbazoles by Domino 'Twofold Heck–6π-Electrocyclization' Reactions of Di- and Tribromo-*N*-methylindoles

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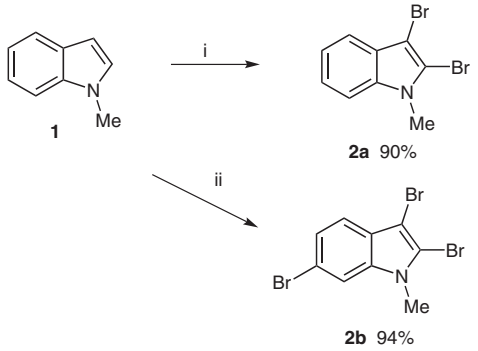
Abstract: The palladium(0)-catalyzed Heck cross-coupling reaction of 2,3-dibromo- and 2,3,6-tribromo-*N*-methylindole, using $Pd(OAc)_2$ as the catalyst and a novel biaryl monophosphine ligand developed by Buchwald and co-workers, afforded the corresponding di- and trialkenylindoles in high yields. The formation of 1,2-dihydrocarbazoles by a domino 'twofold Heck–6π-electrocyclization' was observed when the reaction was carried out at 120 °C rather than 90 °C.

Key Words: cross-coupling, electrocyclic reactions, nitrogen heterocycles, Heck reaction, palladium

Carbazoles are of considerable pharmacological relevance (antifungal, antibiotic, and antitumor activity) and occur in a variety of natural products.[1,2] Knölker and co-workers reported elegant syntheses of carbazoles based on (stoichiometric) iron-mediated cyclizations[1d] and on Buchwald–Hartwig reaction of aryl halides with anilines and subsequent oxidative cyclization.[3] Ackermann and co-workers have recently reported an efficient synthesis of indoles and carbazoles by a new palladium-catalyzed domino 'NH–CH activation' reaction of anilines with 1,2-dihaloalkenes.[4] Carbazoles have been prepared also by Diels–Alder reactions of 2- or 3-vinylindoles.[5] Kano and co-workers were the first to report the synthesis of carbazoles by 6π-electrocyclization of 2,3-di(alkenyl)indoles.[6] Later, this approach has been also studied by Pindur and Adam.[7] However, the synthesis of the starting materials was not straightforward and required many steps which is a severe drawback of this method. 2,3-Di(alkenyl)indoles were prepared by Pd(II)-catalyzed reaction of carbon atom C-3 of 2-formylindoles with alkenes to give 2-formyl-3-vinylindoles which were transformed into the desired products by Wittig reaction. However, this approach is not general. The alternative strategy, based on the double Wittig reaction of (unstable) 2,3-diformyl-*N*-methylindole, has been reported to proceed in low yield.

In recent years, it has been shown that polyhalogenated heterocycles can undergo site-selective palladium(0)-catalyzed cross-coupling reactions by selective activation of a single halogen atom. The site selectivity is controlled by electronic and steric parameters.[8] Recently, we have reported the synthesis of aryl-substituted thiophenes,[9] pyrroles,[10] and selenophenes,[11] by site-selective Suzuki reactions of tetrabromothiophene, tetrabromo-*N*-methylpyrrole, and tetrabromoselenophene, respectively. Gribble and Liu reported the synthesis of 2,3-diarylindoles by twofold Suzuki reactions of 2,3-dihalo-*N*-(phenylsulfonyl)indoles.[12] Other palladium(0)-catalyzed cross-coupling reactions of 2,3-dihaloindoles have, to the best of our knowledge, not been reported to date. De Meijere and co-workers reported twofold Heck reactions of 1,2-dibromocycloalk-1-enes and related substrates and subsequent 6π-electrocyclization.[13] It occurred to us that domino 'twofold Heck–6π-electrocyclization' might provide a useful method for the direct and convenient synthesis of dihydrocarbazoles and carbazoles. Herein, we report preliminary results of these studies.

2,3-Dibromo-*N*-methylindole (**2a**) has been recently prepared in 64% yield by reaction of *N*-methylindole (**1**) with copper(II) bromide.[14] We have found that the reaction of *N*-methylindole (**1**) with NBS (2.1 equiv) in THF (–78 °C, 4 h) resulted in selective formation of 2,3-dibromo-*N*-methylindole (**2a**) in 90% yield (Scheme 1).[15] In addition, we have prepared 2,3,6-tribromo-*N*-methylindole (**2b**) in 94% yield by reaction of **1** with NBS (3.1 equiv) in THF (–78 °C, 4 h).



Scheme 1 Bromination of *N*-methylindole (**1**). *Reagents and conditions*: *i*, NBS (2.1 equiv), THF, –78 °C, 4 h; *ii*, NBS (3.1 equiv), THF, –78 °C, 4 h, then 20 °C, 14 h.

The Heck reaction of **2a** with acrylates **3c**–**g** afforded the 2,3-di(alkenyl)indoles **4c**–**g** in good yields (Scheme 2, Table 1). The best yields were obtained when the reactions were carried out using $Pd(OAc)_2$ (5 mol%) and the biaryl monophosphine ligand **L** (10 mol%, Figure 1) which has been recently developed by Buchwald and co-

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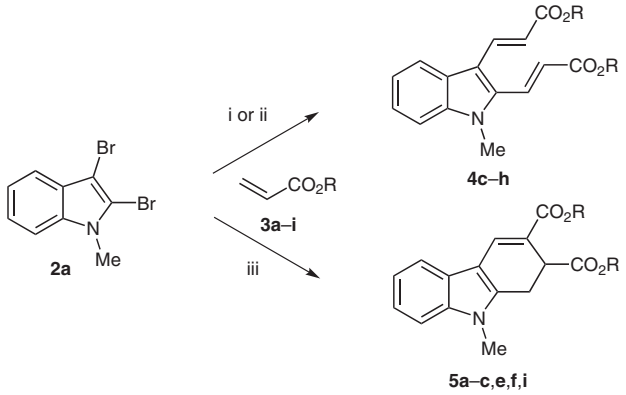
workers.[16] The reactions were carried out in DMF at 90 °C for 36 hours. The employment of $Pd(PPh_3)_4$ was less successful in terms of yield. Recently, Li and Wang reported[17] that triethanolamine represents an efficient and reusable combined base, ligand, and solvent for palladium(0)-catalyzed Heck reactions. The application of these conditions to the reaction of **2a** with acrylate **3h** proved to be successful and resulted in the formation of **4h** in 74% yield.

The $Pd(OAc)_2$/**L**-catalyzed reaction of **2a** with acrylates **3a–c,e,f,i**, carried out at 120 °C rather than 90 °C, afforded the 1,2-dihydrocarbazoles **5a–c,e,f,i** in good yields.[18] The formation of these products can be explained by a domino 'twofold Heck–6π-electrocyclization' cyclization and subsequent double-bond migration. The initially formed 2,3-dihydrocarbazoles undergo a rearrangement into the more stable 1,2-dihydrocarbazoles. For the electrocyclization, a thermally induced process appears to be more likely as the product distribution (formation of **4** or **5**) depends on the temperature. In addition, heating of **4f** (120 °C) results in formation of **5f** in good yield.



Scheme 2 Synthesis of **4c–h** and **5a–c,e,f,i**. *Reagents and conditions*: *i*, for **4c–g**: $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N, DMF, 90 °C, 36 h; *ii*, for **4h**: $Pd(OAc)_2$ (5 mol%), $N(CH_2CH_2OH)_3$ (3 mL), 90 °C, 36 h; *iii*, $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N (8.0 equiv), DMF, 120 °C, 48 h.

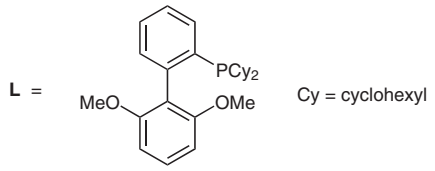


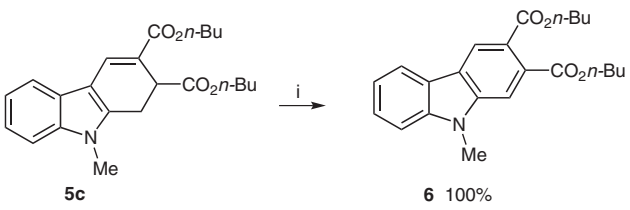
Figure 1 Biaryl monophosphine ligand developed by Buchwald and co-workers (ref. 16)

Heating of a dioxane solution of 1,2-dihydrocarbazole **5c** in the presence of DDQ resulted in the formation of carbazole **6**, albeit in only 20% yield. Pindur reported the DDQ-mediated formation of 2,3-di(methoxycarbonyl)-*N*-phenylsulfonylcarbazole from the corresponding 1,2-dihydrocarbazole in equally low yield (18%). We have found that a dramatic increase of the yield (100%) can be achieved when the reaction is carried out using Pd/C (10 mol%) in refluxing xylene (Scheme 3).[19]

Table 1 Synthesis of **4c–h** and **5a–c,e,f,i**

Compd **4**, **5**	R	Yield of **4** (%)[a]	Yield of **5** (%)[a]
4a, **5a**	Me	–[b]	77
4b, **5b**	Et	–[b]	93
4c, **5c**	*n*-Bu	72	77
4d, **5d**	*i*-Bu	69	–[b]
4e, **5e**	*n*-Hex	77	81
4f, **5f**	*t*-Bu	78	85
4g, **5g**	*i*-Oct	76	–[b]
4h, **5h**	$CH_2CH(Et)Bu$	74	–[b]
4i, **5i**	$(CH_2)_2NMe_2$	–[b]	79

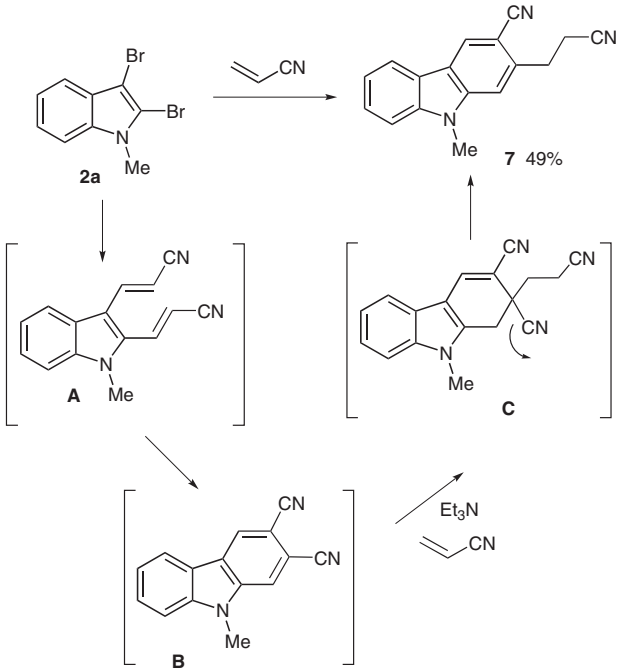
[a] Yields of isolated products based on **2a**.
[b] Experiment was not carried out.



Scheme 3 Synthesis of carbazole **6**. *Reagents and conditions*: *i*, Pd/C (10 mol%), xylene, reflux, 48 h.

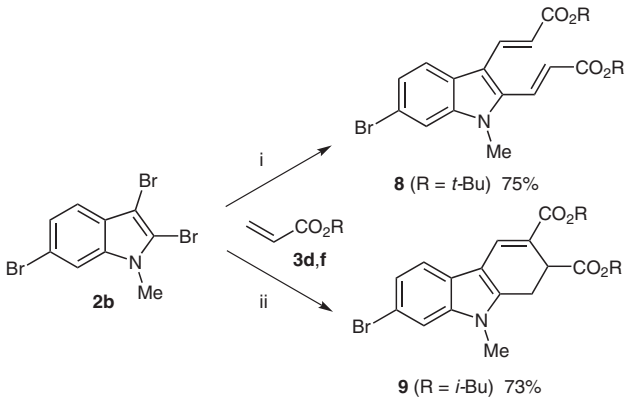
The $Pd(OAc)_2$/**L**-catalyzed reaction of **2a** with acryl nitrile (120 °C, 48 h) afforded the unexpected carbazole **7** in 49% yield (Scheme 4). The formation of **7** can be explained by twofold Heck reaction of **2a** to give intermediate **A**, electrocyclization (intermediate **B**), base-mediated conjugate addition to give intermediate **C**, and subsequent aromatization by elimination of HCN. This process was not observed for the reaction of **2a** with acrylates. This might be explained by the assumption that the Michael reaction is reversible. In case of the reaction of **2a** with acryl nitrile the Michael reaction may become irreversible by the subsequent elimination of cyanide and aromatization.

The $Pd(OAc)_2$/**L**-catalyzed reaction of 2,3,6-tribromo-*N*-methylindole (**2b**) with acrylate **3f** (90 °C, 36 h) afforded the di(alkenyl)indole **8** in 75% yield (Scheme 5). The site-selective formation of **8** is worth to be noted because Ohta and co-workers reported[20] that the site selectivity of the Suzuki reaction of 3,6-dibromo-*N*-TBDS-indole was in favor of carbon atom C-6. Our result can be explained by the assumption that the first Heck reaction of **2b** occurs at carbon C-2, which is most electron deficient, to give intermediate **D** (Figure 2). Due to the electron-withdrawing character of the 2-(*tert*-butoxycarbonyl)alkenyl substitu-



Scheme 4 Possible mechanism of the formation of **7**. *Reagents and conditions*: *i*, $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N, DMF, 120 °C, 48 h.

ent, carbon C-3 becomes more electron deficient and, thus, more reactive than C-6. Alternatively, the site selectivity might be due to a proximity effect, wherein a labile coordination between the newly installed alkene and Pd(0) favors the second oxidative addition on the neighboring bromine atom. This might also explain the observation that the reaction of 2,3-dibromoindole (**2a**) with only one equivalent of acrylate mainly results in the formation of 2,3-di[2-(alkoxycarbonyl)ethenyl]indole **4** and starting material. The $Pd(OAc)_2$/**L**-catalyzed reaction of **2b** with acrylate **3d**, carried out at 120 °C rather than 90 °C, afforded the 1,2-dihydrocarbazole **9** in 73% yield (Scheme 5).



Scheme 5 Synthesis of **8** and **9**. *Reagents and conditions*: *i*, $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N, DMF, 90 °C, 24 h; *ii*, $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N, DMF, 120 °C, 48 h.

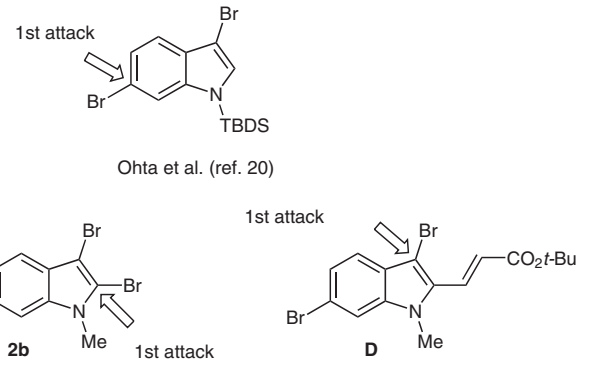
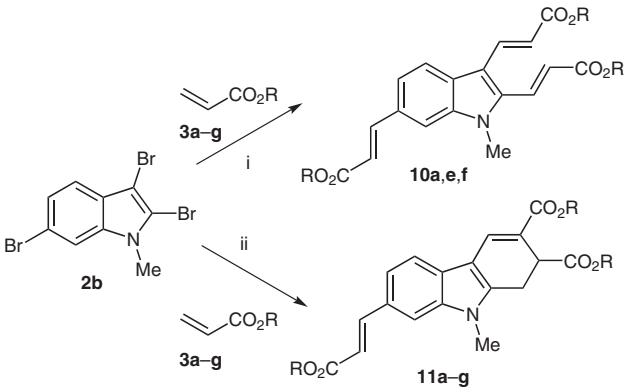


Figure 2 Possible explanation for the site-selective formation of **8** and **9**

The $Pd(OAc)_2$/**L**-catalyzed reaction of **2b** with an excess of acrylates **3a**,**e**,**f** (90 °C, 36 h) afforded the 2,3,6-tris(alkenyl)indoles **10a**,**e**,**f** in good yields (Scheme 6, Table 2). The cross-coupling reactions of **2b** with **3a**–**g**, carried out at 120 °C rather than 90 °C, gave the 7-alkenyl-1,2-dihydrocarbazoles **11a**–**g**.



Scheme 6 Synthesis of **10a**,**e**,**f** and **11a**–**g**. *Reagents and conditions*: *i*, $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N, DMF, 90 °C, 36 h; *ii*, $Pd(OAc)_2$ (5 mol%), **L** (10 mol%), Et_3N, DMF, 120 °C, 48 h.

Table 2 Synthesis of **10a**,**e**,**f** and **11a**–**g**

Compd **10**, **11**	R	Yield of **10** (%)[a]	Yield of **11** (%)[a]
10a, **11a**	Me	69	79
10b, **11b**	Et	–[b]	67
10c, **11c**	*n*-Bu	–[b]	95
10d, **11d**	*i*-Bu	–[b]	72
10e, **11e**	*n*-Hex	74	74
10f, **11f**	*t*-Bu	76	79
10g, **11g**	*i*-Oct	–[b]	74

[a] Yields of isolated products based on **2b**.
[b] Experiment was not carried out.

In conclusion, we have reported the synthesis of di- and trialkenylindoles by palladium(0)-catalyzed Heck cross-

coupling reactions of di- and tribromo-*N*-methylindoles. The reactions were carried out at 90 °C using a novel biaryl monophosphine ligand developed by Buchwald and co-workers. 1,2-Dihydrocarbazoles were formed by a domino 'twofold Heck–6π-electrocyclization' when the reaction was carried out at 120 °C rather than 90 °C. The site selectivity of the Heck reaction of 2,3,6-tribromo-*N*-methylindoles was in favor of carbon atoms C-2 and C-3. Some of the 1,2-dihydrocarbazoles prepared were transformed, by Pd/C-catalyzed dehydrogenation, into the corresponding carbazoles in high yield.

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(15) **Synthesis of 2,3-Dibromo-*N*-methylindole (2a)**
To a THF solution (20 mL) of *N*-methylindole (**1**, 1.0 mL, 8.0 mmol) was added portionwise NBS (3.30 g, 18.4 mmol) at –78 °C, and the soln was stirred at this temperature for 4 h. To the soln was added water (25 mL). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with a saturated aqueous soln of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash silica column chromatography (pure heptanes) to yield **2a** as a colorless solid (1.83 g, 90%).

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(18) **General procedure for Heck cross-coupling reactions.** In a pressure tube (glass bomb) a suspension of $Pd(OAc)_2$ (12 mg, 0.05 mmol, 1.25 mol% per Br) and dicyclohexyl (2',6'-dimethoxybiphenyl-2-yl) phosphine (**L**) (41 mg, 0.10 mmol) in DMF (5 mL) was purged with argon and stirred at 20 °C to get a yellowish or brownish transparent soln. To the stirred soln were added the brominated indole **2a,b** (1.0 mmol), Et_3N (1.1 mL, 8.0 mmol) and the acrylate (1.25 equiv. per Br). The reaction mixture was stirred at 120 °C for 48 h. The soln was cooled to 20 °C, poured into H_2O, and CH_2Cl_2 (25 mL each), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography (flash silica gel, heptanes–EtOAc).
Diethyl 9-Methyl-2,9-dihydro-1*H*-carbazole-2,3-dicarboxylate (5b)
Product **5b** was prepared starting with **2a** (367 mg, 1.0 mmol) as a yellow solid (297 mg, 93%), mp 100–103 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.30 (s, 3 H,CH_3), 2.90 (dd, 1 H_α, *J* = 8.8, 17.1 Hz, H-1), 3.50 (dd, 1 H_β, *J* = 2.6, 17.2 Hz, H-1), 3.60 (s, 3 H, NCH_3), 3.90–4.10 (m, 3 H, H_α and CH_2O), 4.20 (q, *J* = 7.1, 13.5 Hz, 2 H, CH_2O), 7.10–7.20 (m, 3 H, ArH), 7.50–7.60 (m, 1 H, ArH), 7.90 (s, 1 H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0 (CH_3), 13.5 (CH_3), 22.8 (CH_2), 28.7 (CH, C-4), 37.7 (NCH_3), 59.3 (CH_2O), 60.1 (CH_2O), 108.3 (C), 108.6 (CH), 115.4 (C), 116.9, 120.0, 120.8 (CH), 124.1(C), 131.2 (CH), 137.0, 138.6 (C), 166.3, 172.3 (CO). IR (KBr): ν = 2981, 2928, 2854(w), 1725(s), 1629, 1599(w), 1470 1454(m), 1372, 1261, 1238(s), 1109, 1079, 147(m), 787, 747, 723, 608, 561(w)cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 325(89) [M – 2]$^+$(carbazole), 280(13), 252(100), 208(07), 179(13). HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{19}NO_4$ [M – 2]$^+$(carbazole): 325.13141; found: 325.13161.

(19) **Dibutyl 9-Methyl-9*H*-carbazole-2,3-dicarboxylate (6)**
To xylene (5 mL) were added **5c** (100 mg, 0.26 mmol) and Pd/C (10 mg, 10 mol%). The soln was stirred under reflux for 48 h under argon atmosphere. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give **6** as a light yellow solid (99 mg, 100%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, *J* = 7.4 Hz, CH_3), 0.90 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.30–1.50 (m, 4 H, 2 CH_2), 1.60–1.80 (m, 4 H, 2 CH_2), 3.80 (s, 3 H, NCH_3), 4.30 (t, 2 H, *J* = 6.8 Hz, CH_2O), 4.30 (t, 2 H, *J* = 6.7 Hz, CH_2O), 7.20–7.30 (m, 1 H, ArH), 7.30–7.40 (m, 1 H, ArH), 7.40–7.50 (m, 1 H, ArH),

7.60 (s, 1 H, H-1), 8.00–8.10 (m, 1 H, ArH), 8.40 (s, 1 H, H-4). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.7, 13.8 (CH_3), 19.2, 19.3 (CH_2), 29.4 (NCH_3), 30.6, 30.8 (CH_2), 65.3, 65.7 (CH_2O), 109.0, 109.1, 120.2, 121.0 (CH), 121.7, 122.2 (C), 122.4 (CH), 123.6 (C), 127.1 (CH), 131.1, 141.5, 142,1 (C), 167.9, 169.4 (CO). IR (KBr): ν = 2956, 2931, 2871(w), 1709(s), 1464, 1387, 1362, 1340, 1325(m)1255, 1221(s), 1131, 1106, 1077, 1045(m), 950, 902, 843, 829(w), 784, 743, 721(m), 632, 608, 561(w)cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 381(56) [M^+], 308(15), 280(100), 224(87), 212(27), 206(77), 180(10), 152(11). HRMS (EI, 70 eV): *m/z* calcd for $C_{23}H_{27}NO_4$ [M^+]: 381.19401; found: 381.19422.

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