

Tetrahedron 54 (1998) 13079-13086

TETRAHEDRON

Synthesis of Biaryls via Nickel-Catalyzed Cross-Coupling Reaction of Arylboronic Acids and Aryl Mesylates

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Received 7 August 1998; accepted 26 August 1998

Abstract: The cross-coupling reaction of arylboronic acids (1.3 equivs) with aryl methanesulfonates was carried out in the presence of a nickel(0) catalyst $(3 \mod K_3 PO_4 \oplus H_2 O (3 equivs))$. The use of toluene as the solvent and the nickel(0)-dppf catalyst prepared from NiCl₂(dppf) plus dppf with BuLi were recognized to be the most efficient to achieve both high yields and high selectivity. The reaction can be applied to various electron-deficient and -rich aryl methanesulfonates to give high yields. © 1998 Elsevier Science Ltd. All rights reserved.

Palladium complexes are an excellent catalyst for the cross-coupling reaction of arylboronic acids with aryl iodides, bromides or triflates for the synthesis of biaryls.¹ However, an economical reaction by the use of inexpensive substrates and catalysts is desirable for large-scale preparation in industry. Arene chlorides and sulfonates are less expensive, but they have not received much attention because of their low reactivity on the oxidative addition to palladium(0) complexes. In 1995, Percec and co-workers first demonstrated the nickel(0)-catalyzed cross-coupling reaction of arylboronic acids with aryl mesylates.² Ni(0)-dppf (1,1'-bis(diphenylphosphino)ferrocene), *in situ* generated by the reduction of NiCl₂(dppf) with zinc, was recognized to be the most efficient catalyst and the reaction was highly selective and tolerated various functional groups. Kobayashi demonstrated the efficiency of the boron ate-complexes which *in situ* reduce the NiCl₂-phosphine complexes and couple to aryl mesylates at room temperature.³ The reduction of NiCl₂(dppf) with BuLi or DIBAL produced an catalyst which effectively catalyzes the cross-coupling reaction with chloroarenes.⁴ The nickel catalyst has an advantage over the palladium because the coupling to the phosphine-bound aryls,⁵ which is often unavoidable in the palladium-catalyzed coupling, was not observed.



Here, we reinvestigated the nickel-catalyzed cross-coupling reaction of arylboronic acids with aryl mesylates which has been limitedly used for the activated aryl mesylates having an electron-withdrawing

group.^{2.3} The reduction of NiCl₂(dppf) to the corresponding nickel(0), and the use of $K_3PO_4 \circ nH_2O$ in toluene were found to be essential to achieve high catalyst efficiency, giving high yields for various aryl mesylates having an electron-withdrawing or -donating group (Eq. 1).

Reaction Conditions

The results of the cross-coupling reaction of o-tolylboronic acid with aryl mesylates under similar conditions used for chloroarenes⁴ and mesylates² (NiCl₂ dppf/dioxane/80 °C) are shown in Table 1. The electron-deficient mesylates readily participated in the coupling reaction (entries 1 and 2), but the presence of an electron-donating group greatly reduced the yields of biaryls because of their slow oxidative addition to the nickel(0) complex (entries 3-5). The order of yields was parallel to the Hammett σ - rather than the σ constant, as was previously demonstrated by Milstein in the reaction of chloroarenes with a palladium(0) complex.⁶

Table 1. The Effect of Substituents on the Cross-Coupling Reaction of o-Tolylboronic Acid with Aryl Mesylates in Dioxane^a

entry	XC ₆ H ₄ OMs (X=)	σ⁻	(σ) ^b	yield/%
1	4-C≡N	0.66	(1.00)	93
2	4-COCH ₃	-	(0.87)	92
3	4-CH ₃	-0.31	(-0.17)	69
4	4-SCH ₃	-0.60	(-0.05)	35
5	4-0CH3	-0.78	(-0.27)	36

^aA solution of NiCl₂(dppf) (0.03 mmol) and dppf (0.03 mmol) in dioxane (6 ml) was treated with BuLi (0.12 mmol in hexane). A mesylate (1 mmol), *o*-tolylboronic acid (1.3 mmol) and

K₃PO₄•nH₂O (2 mmol) were added and the mixture was then stirred at 70 °C for 16.

^bHammett constant.

The coupling of tolylboronic acid with *p*-methoxyphenyl mesylate was carried out by using various solvents and catalysts to optimize the reaction conditions (Table 2). The reaction in the presence of a reduced nickel(0) catalyst and $K_3PO_4 \cdot nH_2O$ in dioxane again did not give good results, though the yield slightly increased when an additional dppf ligand was used (entries 1 and 2). An addition of metal halides exhibits a remarkable accelerating effect in various coupling reactions of aryl triflates,⁷ but the presence of LiBr or LiCl was not effective for the mesylates (entry 3). The formation of in small amount *p*-methoxyphenol derived from the saponification of the mesylates was observed on prolongation of the reaction time in dioxane. Thus, the conditions were next optimized in a toluene solution because a solvent which is not miscible with the inorganic base will avoid such saponification (entries 4-14). The effect of a ligand revealed the following order of yields, thus suggesting the effectiveness of bidentate ligands having a large bite angle;⁸ dppf > dppp ~ PCy₃ > PPh₃ > dppe (entries 4-9). Higher yields were obtained when the

ratio of P/Ni is 4 (for an example, entries 8 and 9), except the strongly coordinating ligands such as tricyclohexylphosphine (entry 5). The use of excess phosphine, in general, retards the oxidative addition, but an additional ligand can be necessary to stabilize the catalyst because the nickel(0) complexes are a highly reactive, but highly labile species. The reaction was further accelerated at 100 °C and the best yield was finally achieved when 3 equivalents of K_1PO_4 enH₂O was used (entry 11).

The reduction of the nickel chloride complex with BuLi or DIBAH is recommended both to reduce the formation of homo-coupling products of arylboronic acids and to achieve reproducible results. However, slightly lower, but almost comparable yields can be also obtained without the reduction of the nickel(II) catalyst (entry 12). The finely powdered and hydrated phosphate which contains 2~3 moles of water worked efficiently as the base, but the anhydrous phosphate was not effective (entry 13).⁹

entry	catalyst	additive (equivs)	solvent	temp/°C	yicld/%
1	NiCl ₂ (dppf)	$K_3PO_4 \cdot nH_2O(2)$	dioxane	80	39
2	NiCl ₂ (dppf)/dppf	$K_3PO_4 \cdot nH_2O(2)$	dioxane	80	50
3	NiCl2(dppf)/dppf	$K_{3}PO_{4}$ •n $H_{2}O(2)/LiBr(1.1)$	dioxane	80	2
4	NiCl ₂ (PPh ₃) ₂ /2PPh ₃	$K_3PO_4 \cdot nH_2O(2)$	toluene	80	30
5	NiCl ₂ (PCy ₃) ₂	$K_3PO_4 \circ nH_2O(2)$	toluene	80	44
6	NiCl ₂ (dppe)/dppe	$K_3PO_4 \cdot nH_2O(2)$	toluene	80	19
7	NiCl2(dppp)/dppp	$K_3PO_4 \cdot nH_2O(2)$	toluene	80	43
8	NiCl ₂ (dppf)	$K_3PO_4 \cdot nH_2O(2)$	toluene	80	50
9	NiCl2(dppf)/dppf	$K_3PO_4 \cdot nH_2O(2)$	toluene	80	57
10	NiCl2(dppf)/dppf	$K_3PO_4 \cdot nH_2O(2)$	toluene	100	59
11	NiCl ₂ (dppf)/dppf	$K_3PO_4 \cdot nH_2O(3)$	toluene	100	85
12	NiCl ₂ (dppf)/dppf ^b	$K_3PO_4 \cdot nH_2O(3)$	toluene	100	74
13	NiCl ₂ (dppf)/dppf	K ₃ PO ₄ (3)	toluene	100	25

Table 2. Reaction Conditions^a

^aA solution of NiCl₂•L₂ (3 mol%) and additional ligand (L, 3 mol%) was treated with BuLi (4 equivs) at room temperature to give a nickel(0) catalyst. p-MeC₆H₄B(OH)₂ (1.3 equivs), p-MeOC₆H₄OMs (1.0 equivs) and K₃PO₄•nH₂O (2~3 equivs) were added to the catalyst solution, and the mixture was then stirred for 16 h at the temperature shown in Table. ^bThe nickel chloride complex was directly used without the reduction.

Scope and Limitation

The synthesis of biaryls via the cross-coupling reaction of the representative aryl mesylates is summarized in Table 3.

Aryl mesylates having both an electron-withdrawing and -donating group at the *para* and the *meta* position gave excellent yields of biaryls often exceeding 90% (entries 1-10). The electron-withdrawing

entry	ArB(OH) ₂	ArOMs		product No.	yield/% ^b
1	Me-B(OH)2	MsO-X=	<i>p-</i> C≡N	3a	97
2	U	× ×	p-COMe	3b	86
3		A	p-CO ₂ Me	3c	90
4			m-CO ₂ Me	3d	76
5			o-CO ₂ Me	3e	47
6			<i>p</i> -Ph	3f	75
7			p-CH ₂ Ph	3g	67
8			p-CH ₂ CH ₂ COCH ₃	3h	90
9			p-OMe	3i	77 (85) ^c
10			m-OMe	3ј	95
11		MsO-COCH ₃		3k	81
12		MsO		31	85
13		MsO -		3m	trace
14	F-B(OH)2	MsO-OMe		3n	62
15	MeCO-B(OH) ₂	MsO-X	X = CN	30	55 (98) ^d
16	<u> </u>		X = OMe	3р	$27(34)^d$
	Me			-	. ,
17	Me-B(OH) ₂	MsO-X	X = CN	3q	56
18	Me	<u></u>	X = OMe	3r	53

Table 3. The Synthesis of Biaryls (Eq. 1)^{*a*}

^aA mixture of NiCl₂(dppf) (0.04 mmol) and dppf (0.04 mmol) in toluene was treated with BuLi (4 equivs) to reduce to the nickel(0) compex. The catalyst solution was added to a mixture of arylboronic acid (1.3 mmol), aryl mesylate (1.0 mmol), and K_3PO_4 •nH₂O (3 mmol) in toluene, and the mixture was stirred at 100 °C for 16 h. The reactions in entries 1-4, 15, and 17 were carried out at 80 °C. ^bIsolated yields by chromatography. ^cGC yields. ^aThe reaction was carried out in DME at 80 °C.

group accelerates the rates of oxidative addition and the transmetalation among the three steps involved in the catalytic cycle. The *ortho*-substitution decreased the yield due to its steric hindrance (entry 5), but this was not the case for further electron-deficient mesylate (entry 11). 4-Methanesulfoxyindole underwent smooth coupling without any difficulty (entry 12), but the reaction failed with 2-methanesulfoxyquinoline (entry 13). Arylboronic acids are, in general, stable to water and base, but the presence of an electronwithdrawing group enhances the rate of protodeboronation¹⁰ which often reduces the yield of a crosscoupling reaction of organoboronic acids. Indeed, the reaction of 4-acetylphenylboronic acid suffered from the formation of acetophenone and low coupling yields (entries 15 and 16). However, it was interesting that the coupling was exceptionally faster than the protodeboronation when the reaction was carried out at 80 $^{\circ}$ C in dimethoxyethane (DME) (entry 15). The coupling of mesitylboronic acid often fails because of its large steric hindrance during the transmetalation. Although the nickel-catalyzed reaction is more sensitive to steric hindrance than that catalyzed by palladium,⁴ both reactions with electron-rich and -deficient mesylates resulted in moderate yields (entries 17 and 18).

Experimental Section

Reagents. The reaction of NiCl₂· $6H_2O$ with a commercially available phosphine in benzene at 50 $^{\circ}C$ gave the nickel chloride complexes with dppf (1,1'-bis(diphenylphosphino)ferrocene), dppe (Ph₂PCH₂CH₂PPh₂), dppp (Ph₂PCH₂CH₂CH₂PPh₂), tricyclohexylphosphine (PCy₃), and triphenylphosphine.¹¹ Aryl mesylates were prepared by the reaction of methanesulfonyl chloride with phenol in ether in the presence of triethylamine. 4-Tolylboronic acid, 4-acetylphenylboronic acid, and mesitylboronic acid were commercially available from Lancaster.¹² K₃PO₄·nH₂O (n = 2~3) from Nakarai Tesque Co. was used directly. Dioxane and toluene were distilled from benzophenone ketyl.

Effect of Substituents (Table 1). The flask was charged with NiCl₂(dppf) (0.03 mmol) and dppf (0.03 mmol) and then flushed with argon. The catalyst was dissolved in dioxane (6 mL) and treated with n-BuLi in hexane (0.12 mmol) at room temperature for 10 min to give a solution of the nicked(0) complex. *o*-Tolylboronic acid (1.3 mmol), $K_3PO_4 \cdot nH_2O$ (3 mmol), and aryl mesylate were added to the flask and the mixture was stirred at 70 °C for 16 h. The product was extracted with ether, washed with brine, and dried over MgSO₄. Chromatography over silica gel gave the corresponding biaryl.

Reaction Conditions (Table 2). The flask charged with NiCl₂·L (L = dppf, dppe, dppp, and 2 PPh₃, 2 PCy₃) (0.03 mmol or 0.04 mmol) and additional ligand shown in Table 2 (0.03 or 0.04 mmol) was flushed with argon. The catalyst was dissolved in solvent (2 mL) and treated with n-BuLi in hexane (4 equivs) at room temperature for 30 min to give a solution of the nickel(0) complex. *p*-Tolylboronic acid (1.3 mmol), 4-methoxyphenyl mesylate (1.0 mmol), and $K_3PO_4 \cdot nH_2O$ (2 or 3 mmol) were added to the catalyst solution, and the resulting mixture was stirred for 16 h at the temperature shown in Table 2.

Representative Procedure (Table 3). The following procedure for the cross-coupling of *p*tolylboronic acid with 4-cyanophenyl mesylates is representative (entry 1). A 25 mL-flask charged with NiCl₂(dppf) (0.028 g, 0.04 mmol) and dppf (0.022 g, 0.04 mmol) was flushed with argon. The catalyst was dissolved in toluene (2 mL) and then treated with n-BuLi (1.6 M, 0.1 mL, 0.16 mmol) at room temperature for 30 min to give a solution of nickel(0) complex. Another 25 mL-flask was charged with *p*-tolylboronic acid (0.177 g, 1.3 mmol), $K_3PO_4 \cdot nH_2O$ (0.636 g, 3 mmol), 4-cyanophenyl mesylate (1 mmol), and toluene (2 mL) under argon. The nickel(0) complex solution was added to the flask by using a syringe. After being stirred for 16 h at 80 °C, the reaction mixture was diluted with benzene, washed with water, and dried over MgSO₄. Purification by chromatography over silica gel (hexane/ethyl acetate = 10/1) afforded 0.191 g (97 %) of 4-cyano-4'-methylbiphenyl (3a) as a white crystal: IR (Nujol) 2220 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) : δ 2.41 (s, 3H), 7.28 (d, *J*= 8.0 Hz, 2H), 7.49 (d, *J*= 8.0 Hz, 2H), 7.66 (d, *J*= 8.3 Hz, 2H), 7.70 (d, *J*= 8.3 Hz, 2H); MS *m/z* 75 (3), 82 (6), 91 (8), 140 (4), 152 (4), 165 (16), 177 (7), 193 (M^{*}, 100); exact mass calcd for C₁₄H₁₁N 193.0891, found 193.0888.

The following biaryls were prepared by the above general procedure, unless otherwise noted.

3b: IR (Nujol) 1690 cm⁻¹; ¹H NMR δ 2,41 (s, 3H), 2,64 (s, 3H), 7.28 (d, *J*= 7.9 Hz, 2H), 7.53 (d, *J*= 7.9 Hz, 2H), 7.67 (d, *J*= 8.7 Hz, 2H), 8.02 (d, *J*= 8.7 Hz, 2H); MS *m/z* 76 (4), 82 (7), 98 (8), 115 (5), 128 (2), 139 (4), 152 (31), 165 (22), 195 (100), 210 (M⁺, 55); exact mass calcd for C₁₅H₄O 210.1045, found 210.1040.

3c: IR (Nujol) 1730 cm⁻¹; ¹H NMR δ 2.41 (s, 3H), 3.94 (s, 3H), 7.76 (d, J= 8.0 Hz, 2H), 7.53 (d, J= 8.0 Hz, 2H), 7.65 (d, J= 8.6 Hz, 2H), 8.09 (d, J= 8.6 Hz, 2H); MS *m/z* 76 (4), 82 (12), 98 (16), 115 (5), 128 (2), 139 (4), 152 (34), 165 (25), 195 (100), 226 (M^{*}, 90); exact mass calcd for C₁₅H₁₄O₂ 226.0994, found 226.0990.

3d: IR (Nujol) 1730 cm⁻¹; ¹H NMR δ 2.41 (s, 3H), 3.94 (s, 3H), 7.27 (d, J= 8.9 Hz, 2H), 7.49 (dd, J= 7.6 and 7.8 Hz, 1H), 7.52 (d, J= 8.9 Hz, 2H), 7.77 (d, J= 7.8 Hz, 1H), 7.99 (d, J= 7.6 Hz, 1H), 8.27 (s, 1H); MS *m*/z 76 (4), 91 (3), 98 (7), 115 (9), 128 (3), 139 (9), 152 (50), 167 (42), 195 (72), 226 (M⁺, 100); exact mass calcd for C₁₅H₁₄O₂ 226.0994, found 226.0993.

3e: IR (Nujol) 1720 cm⁻¹; ¹H NMR δ 2.39 (s, 3H), 3.66 (s, 3H), 7.18-7.24 (m, 4H), 7.36 (dd, J = 1.4 and 7.6 Hz, 1H), 7.38 (ddd, J = 1.4, 7.6 and 7.6 Hz, 1H), 7.51 (ddd, J = 1.4, 7.6 and 7.6 Hz, 1H), 7.80 (dd, J = 1.4 and 7.8 Hz, 1H); MS m/z 76 (5), 98 (3), 115 (9), 128 (4), 139 (10), 152 (47), 167 (26), 195 (100), 226 (M^{*}, 73); exact mass calcd for C₁₅H₁₄O₂ 226.0994, found 226.1003.

3f: ¹H NMR δ 2.41 (s, 3H), 7.27 (d, J= 8.1 Hz, 2H), 7.35 (dd, J= 7.3 and 7.3 Hz, 1H), 7.46 (dd, J= 7.3 and 8.1 Hz, 2H), 7.54 (d, J= 8.1 Hz, 2H), 7.63-7.66 (m, 6H); MS *m/z* 77 (4), 91 (10), 115 (7), 122 (10), 152 (6), 165 (15), 202 (6), 215 (5), 228 (9), 244 (M^{*}, 100); exact mass calcd for C₁₉H₁₆ 244.1252, found 244.1249.

3 g: ¹H NMR δ 2.38 (s, 3H), 4.01 (s, 2H), 7.22-7.32 (m, 9H), 7.46 (d, J= 8.3 Hz, 2H), 7.49 (d, J= 8.3 Hz, 2H); MS *m/z* 77 (4), 91 (15), 115 (9), 128 (9), 139 (4), 152 (8), 165 (44), 181 (13), 243 (15), 258 (M⁺, 100); exact mass calcd for C₂₀H₁₈ 258.1409, found 258.1408.

3h: IR (Nujol) 1710 cm⁻¹; ¹H NMR δ 2.16 (s, 3H), 2.39 (s, 3H), 2.80 (t, *J*= 7.3 Hz, 2H), 2.93 (t, *J*= 7.3 Hz, 2H), 7.23 (d, *J*= 8.1 Hz, 2H), 7.24 (d, *J*= 8.1 Hz, 2H), 7.47 (d, *J*=8.1 Hz, 2H), 7.49 (d, *J*= 8.1 Hz, 2H); MS *m*/z 77 (6), 91 (5), 115 (9), 128 (4), 139 (4), 152 (13), 165 (37), 181 (100), 195 (14), 238 (M^{*}, 55); exact mass calcd for C₁₅H₁₄O₂ 238.1358, found 238.1358.

3i: ¹H NMR δ 2.38 (s, 3H), 3.85 (s, 3H), 6.96 (d, J= 8.8 Hz, 2H), 7.22 (d, J= 8.1 Hz, 2H), 7.45 (d, J= 8.1 Hz, 2H), 7.51 (d, J= 8.8 Hz, 2H); MS *m*/z 76 (4), 82 (2), 99 (9), 115 (5), 128 (6), 139 (4), 155 (24), 165 (3), 183 (51), 198 (M⁺, 100); exact mass calcd for C₁₄H₁₄O 198.1045, found 198.1034.

3 j: ¹H NMR δ 2.39 (s, 3H), 3.86 (s, 3H), 6.87 (dd, J= 2.4 and 8.0 Hz, 1H), 7.10 (dd, J= 1.7 and 2.4 Hz, 1H), 7.16 (d, J= 7.8 Hz, 1H), 7.24 (d, J= 7.9 Hz, 2H), 7.34 (dd, J= 7.8 and 8.0 Hz, 1H), 7.49 (d, J= 7.9 Hz, 2H); MS m/z 155 (21), 167 (19), 187 (12), 198 (M⁺, 100), 199 (18); exact mass calcd for C₁₄H₁₄O 198.1045, found 198.1049

3k: IR (Nujol) 1674 cm⁻¹; ¹H NMR δ 2.34 (s, 3H), 2.42 (s, 3H), 2.62 (s, 3H), 7.20-7.24 (m, 4H), 7.31 (d, J= 8.0 Hz, 1H), 7.81 (dd, J= 1.7 and 8.0 Hz, 1H), 7.86 (d, J= 1.7 Hz, 1H); MS *m/z* 166 (29), 181 (14), 209 (100), 224 (M⁺, 59); exact mass calcd for C₁₆H₁₆O 224.1201, found 224.1206.

31: ¹H NMR δ 2.43 (s, 3H), 6.73 (m, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.23 (dd, J= 6.1 and 6.8 Hz, 1H), 7.29 (d, J=7.9 Hz, 2H), 7.35-7.37 (m, 2H), 7.61 (d, J= 7.9 Hz, 2H); MS *m/z* 179 (15), 191 (5), 206 (29), 207 (M⁺, 100), 208 (19); exact mass calcd for C₁₅H₁₃N 207.1048, found 207.1054.

3n: ¹H NMR δ 3.85 (s, 3H), 6.97 (d, J= 8.8 Hz, 2H), 7.10 (dd, J= 8.6 and 8.8 Hz, 2H), 7.47 (d, J= 8.8 Hz, 2H), 7.49 (dd, J= 5.2 and 8.8 Hz, 2H); MS *m/z* 133 (46), 159 (69), 187 (53), 202 (M^{*}, 100); exact mass calcd for C₁₃H₁₁OF 202.0794, found 202.0792.

30: The reaction was carried out in DME at 80 °C for 16 h. IR (Nujol) 2227, 1685 cm⁻¹; ¹H NMR δ 2.66 (s, 3H), 7.68 - 7.78 (m, 6H), 8.07 (d, J = 8.3 Hz, 2H); MS m/z 151 (28), 178 (33), 206 (100), 221 (M⁺, 40); exact mass calcd for C₁₅H₁₁NO 221.0840, found 221.0835.

3p: The reaction was carried out in DME at 80 °C for 16 h. IR (Nujol) 1680 cm⁻¹; ¹H NMR δ 2.63 (s, 3H), 3.87 (s, 3H), 7.00 (d, J= 8.5 Hz, 2H), 7.58 (d, J= 8.5 Hz, 2H), 7.65 (d, J= 8.3 Hz, 2H), 8.01 (d, J= 8.3 Hz, 2H); MS m/z 76 (9), 106 (12), 139 (39), 152 (18), 128 (8), 168 (26), 183 (17), 211 (100), 226 (M⁺, 68); exact mass calcd for C_{1.5}H_{1.4}O, 226.0994, found 226.0985.

3g: IR (Nujol) 2361 cm⁻¹; ¹H NMR δ 0.197 (s, 6H), 2.33 (s, 3H), 6.95 (s, 2H), 7.27 (d, J= 7.9 Hz, 2H), 7.72 (d, J= 7.9 Hz, 2H); MS *m/z* 179 (12), 190 (25), 206 (73), 221 (M⁺, 100); exact mass calcd for C₁₆H₁₅N 221.1205, found 221.1209

3r: ¹H NMR δ 2.01 (s, 6H), 2.32 (s, 3H), 3.85 (s, 3H), 6.93 (s, 2H), 6.95 (d, *J*= 8.2 Hz, 2H), 7.05 (d, *J*= 8.2 Hz, 2H); MS *m*/z 77 (6), 112 (4), 128 (6), 141 (6), 153 (12), 165 (15), 183 (12), 195 (16), 211 (31), 226 (M⁺, 100); exact mass calcd for C₁₆H₁₈O 226.1358, found 226.1355.

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