Dess–Martin Periodinane Mediated Intramolecular Cyclization of Phenolic Azomethines: A Solution-Phase Strategy toward Benzoxazoles and Benzothiazoles

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Abstract: Dess–Martin periodinane (DMP), a highly versatile hypervalent iodine(V) reagent, was found to efficiently mediate the intramolecular cyclization of phenolic azomethines/Schiff bases at ambient temperature leading to the rapid and expeditious synthesis of substituted benzoxazoles and benzothiazoles. Furthermore, a solution-phase strategy has been developed by treating the reaction mixtures sequentially with Amberlyst A-26 thiosulfate resin and diisopropylaminomethyl resin (PS-DIEA), which remove excess reagent and byproducts, to give pure products.

Key words: Dess–Martin periodinane, intramolecular cyclization, azomethines, benzoxazoles, benzothiazoles, solution-phase strategy

In recent years, organic derivatives of hypervalent iodine reagents have become widely accepted as a promising synthetic tool for the development of environmentally benign oxidations and for the construction of carbon–heteroatom and carbon–carbon bonds[1] due to their low toxicity, readily availability, mild reactivities, and ease of handling. The innovative work reported in 1983 by Dess and Martin on the discovery of what became known as the Dess–Martin periodinane (DMP),[2] has opened the door to a wide range of highly useful organic reactions, most significantly the mild oxidation procedures that allow alcohols to be converted into the corresponding carbonyl compounds.[3] Investigations in our laboratory on the efficient use of hypervalent iodine(V) reagents in medicinally significant reactions have revealed a myriad of useful reactions.[4] In continuation of this work, we herein report an efficient intramolecular cyclization of phenolic azomethines mediated by Dess–Martin periodinane that enables the synthesis of substituted benzoxazoles and benzothiazoles in high yields at ambient temperatures within 10–15 minutes.

Benzoxazoles and benzothiazoles are an important class of privileged heterocyclic structures that are found in biologically active and medicinally significant compounds. In particular, the benzoxazole ring system is found in variety of biologically active natural products such as cytotoxic UK-1,[5] microsomal triglyceride transfer protein (MTP) inhibitors,[5b] Gram-positive antibacterial calcimycin,[6] antimycobacterial pseudopteroxazole,[7] and antimicrobial salvianen[8] (Figure 1). Recent medicinal chemistry applications of benzoxazoles include the reverse transcriptase inhibitor L-697661,[9] a potent and highly selective estrogen receptor β agonist ERB-041[10] (under clinical development for rheumatoid arthritis and endometriosis), and a selective antagonist for peroxisome proliferator-activated γ antagonist JTP-426467,[11] which is useful in diabetic and osteoporosis mechanistic studies. Similarly, the benzothiazole structural motif has recently attracted considerable attention for the development of novel and selective anticancer drug candidates (e.g., Phortess),[12] and has been widely applied in the development of calcium channel antagonists and orexin receptor antagonists, as well as for antituberculotics, antiparasitics and chemiluminescent agents, and photosensitizers.[13] More recently, benzothiazoles and benzoxazoles have been shown to be promising tools for the development of in vivo biomarkers of β-amyloid deposits in the brain and would be useful for the identification of individuals at risk of Alzheimer's disease.[14]

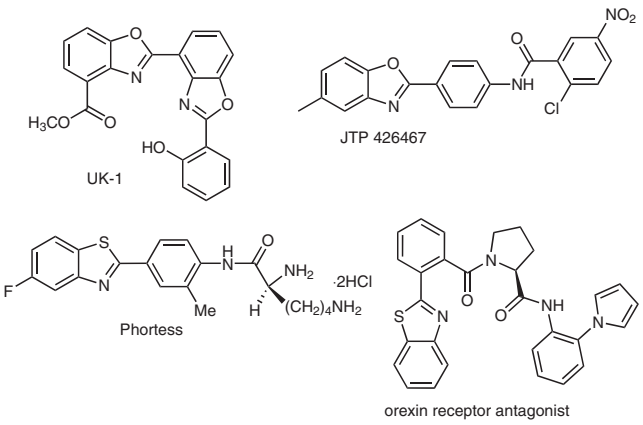

Figure 1 Structures of pharmaceutically important benzoxazoles and benzothiazoles

Owing to the importance of benzoxazoles and benzothiazoles, several synthetic protocols have been developed for their acquisition. In this direction, 2-arylbenzoxazoles are generally synthesized either by coupling of carboxylic acids with 2-aminophenol using strong acids, such as boric acid or polyphosphoric acid,[15] or through the reaction of 2-aminophenols with aldehydes and subsequent oxidative cyclization of the imine intermediate using various oxidants.[16,17] On the other hand, 2-arylbenzothiazoles are

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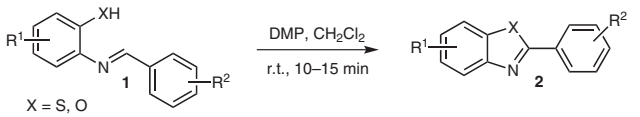
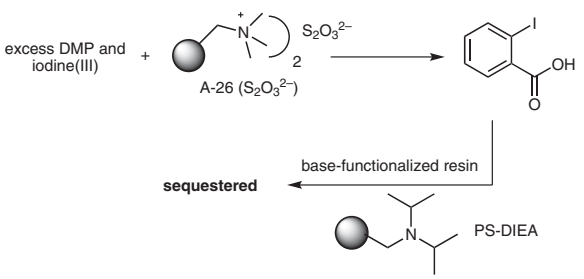
commonly synthesized via Jacobson's cyclization of thiobenzanilides,[18] reaction of benzyl disulfides with *o*-aminothiophenol, reaction of *S*-aryl thiobenzoate with arylhaloamines, radical cyclization of benzyne intermediates, or Grignard reactions of arylisothiocyanates.[19] We noticed that the efficient DMP-promoted intramolecular cyclization of phenolic Schiff bases could be used to generate both of these privileged heterocycles through a common route under mild and environmentally benign conditions, and envisioned that such an approach could be applied in a solution-phase strategy to rapidly generate lead candidates for a drug-discovery program.

This oxidative cyclization methodology uses azomethines as starting materials, which can be obtained by the condensation of a variety of 2-aminophenols or 2-aminothiophenols with substituted aromatic aldehydes in methanol in the presence of catalytic K-10 montmorillonite clay. The resulting azomethines undergo oxidative cyclization in the presence of DMP at room temperature in dichloromethane to generate 2-arylbenzoxazoles and 2-arylbenzothiazoles in high yields within 10–15 minutes, leaving no trace of the starting material (Scheme 1, Table 1).



Scheme 1 DMP-mediated intramolecular cyclization of azomethines

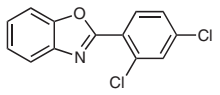
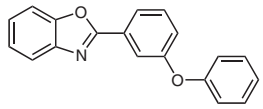
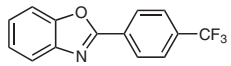
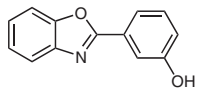
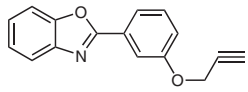
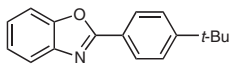
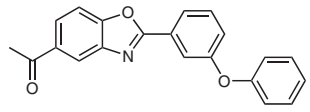
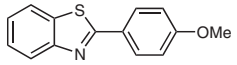
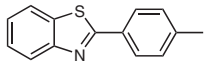
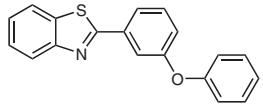
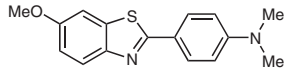
Except for the excess reagent (DMP) and the reduced form of the iodine(III) reagent formed during the reaction, the intramolecular nature of the reaction meant that no additional byproducts were formed. Encouraged by these results, we were interested in developing a solution-phase strategy for the rapid generation of a library of benzothiazole compounds. For this to be possible, the prerequisite was to remove the excess DMP and the byproduct iodine(III) in a high-throughput format. Among the various purification methods available for solution-phase combinatorial synthesis, the treatment of reaction solutions with ion-exchange resins has proven to be effective in the removal of some acidic or basic byproducts and there is a recent report demonstrating the applicability to a 96-well format.[20]



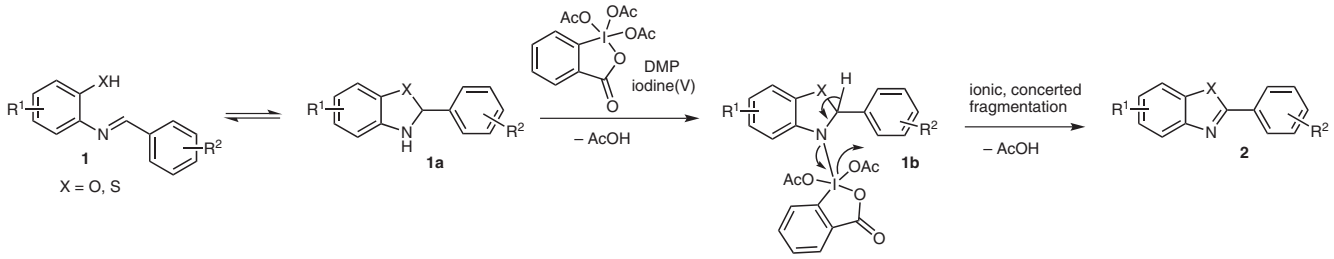
Scheme 2 Schematic representation of the solution-phase strategy

In this direction, we found that Parlow et al. applied Amberlyst A-26 thiosulfate resin for the removal of DMP and its byproducts in the solution-phase combinatorial oxidation of alcohols.[21] Here, we sequentially used Amberlyst A-26 thiosulfate resin (obtained by the treatment of Amberlyst A-26 bromide with aqueous sodium thiosulfate so-

Table 1 DMP-Promoted Oxidative Cyclization of Azomethines

Entry	Product	Isolation method A (%)[a]	Isolation method B (%)[b]	Purity (%)[c]
1	 **2a**	95	92	99
2	 **2b**	92	89	98
3	 **2c**	95[22]	90	95
4	 **2d**	85[23]	84	95
5	 **2e**	90	86	92
6	 **2f**	91	88	98
7	 **2g**	90	85	94
8	 **2h**	94[24]	90	96
9	 **2i**	92[25]	89	99
10	 **2j**	95[4a]	91	98
11	 **2k**	88[18b]	82	96

[a] Product isolated by column chromatography.
[b] Crude yields after resin treatment.
[c] HPLC purity of compounds isolated by method B, determined by integration of peak areas at 255 nm without calibration.



Scheme 3 A plausible mechanism for the oxidative cyclization of azomethines mediated by Dess–Martin periodinane

lution) and a base-functionalized resin to sequester the byproducts from the reaction; the results were very impressive. It was envisioned that the thiosulfate resin would reduce the Dess–Martin periodinane reagent and the byproduct iodine(III) reagent to 2-iodobenzoic acid, thereby allowing its sequestration with a base-functionalized resin e.g., diisopropylaminomethyl resin (PS-DIEA). As a general procedure for the solution-phase strategy, after completion of the DMP-mediated azomethine cyclization reaction (which was monitored by TLC), the reaction mixture was treated with the Amberlyst A-26 thiosulfate resin. This leads to reduction of both the excess DMP and its byproduct formed in the cyclization reaction to give 2-iodobenzoic acid [i.e. iodine(I)]. This acidic impurity was then removed from the reaction mixture by treatment with diisopropylaminomethyl resin (PS-DIEA, a base functionalized resin) to obtain pure products (Scheme 2).

To explore the generality and scope of this process, diverse substituted azomethines were submitted to the conditions described above to generate a range of substituted benzoxazoles and benzothiazoles; the results are illustrated in Table 1. Among the hypervalent iodine reagents studied for this transformation [*o*-iodoxybenzoic acid (IBX), and iodosobenzene diacetate (DAIB)], DMP was found to be the most effective in terms of both conversion and reaction rates. Azomethines with both electron-donating and electron-withdrawing groups showed high reactivity with DMP and give similar yields. Furthermore, azomethines containing heterocyclic systems could also be used efficiently. This reaction is very clean, efficient and involves a simple work-up procedure. Moreover, alternative solvents such as acetonitrile, tetrahydrofuran and methanol also proved to be effective. The feasibility of this methodology has been successfully applied for the synthesis of novel and highly functionalized library of benzoxazoles and benzothiazoles with potent cytotoxic activities, which will be discussed elsewhere.

A plausible mechanism for the DMP-promoted cyclization of azomethines is presented in Scheme 3. It is presumed that an equilibrium exists between the Schiff base **1** and the cyclized oxazoline or thiazoline system **1a** formed in situ by the cyclization of the imine functionality with the phenol or thiophenol moiety of the Schiff base. Dess–Martin periodinane reacts with the secondary amine of the cyclized oxazoline or thiazoline system to form the transition-state **1b**, which, upon oxidative ionic concerted fragmentation, gives the desired product **2** and the reduced byproduct of iodine(III); in a similar mechanism, the oxidation of secondary amines to form imines by the hypervalent iodine(V) reagents has been reported in the literature.[26] The excess iodine(V) and the byproduct iodine(III) are reduced by Amberlyst 26 thiosulfate resin to iodine(I), i.e. 2-iodobenzoic acid, which was finally sequestered from the reaction mixture by treatment with the base-functionalized resin (PS-DIEA) to obtain the pure product (Scheme 2).

In summary, it is one of our goals to broaden the applicability of Dess–Martin periodinane for the generation of biologically significant heterocycles and develop medicinally relevant transformations. We described here an efficient conversion of phenolic Schiff bases by the DMP reagent to generate substituted benzoxazoles and benzothiazoles at ambient temperature within 10–15 minutes, in high yields. The conversion and its solution-phase strategy could be of high value in diversity-oriented synthesis for the generation of functionalized and substituted benzothiazole and benzoxazole libraries for lead generation and SAR studies. To our knowledge, the current method is the first report of solution-phase generation of both benzothiazoles and benzoxazoles via a common route.

Column chromatography was performed using silica gel (Acme, 60–120 mesh). Solvents for chromatography (*n*-hexane, cyclohexane, EtOAc) were distilled prior to use. For analytical TLC, Merck pre-coated silica gel 60 F-254 plates were used; the plates were visualized using UV light (254 nm). Melting points were obtained using a precision digital melting point Veego VMP-DS apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 (300.132 MHz for ^{1}H, 75.473 MHz for ^{13}C), or Varian FT-200MHz (Gemini) spectrometer in $CDCl_3$. Chemicals shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS; δ = 0.00 ppm) as an internal standard. Elemental analyses were performed on an Elementar Vario EL microanalyzer. Low-resolution mass spectra (ESI-MS) and HRMS were recorded on Quattro LC, Micromass, and Q STAR XL, Applied Biosystems respectively.

Substituted 2-Arylbenzothiazoles and 2-Arylbenzoxazoles (2a–k); General Procedure

Dess–Martin periodinane (0.55 mmol) was added to a stirred solution of azomethine (0.5 mmol) in CH_2Cl_2 (2 mL) at r.t. The solution was stirred for 10–15 min, until TLC indicated the reaction was complete. Amberlyst 26 ($S_2O_3^{2-}$) resin was added and the mixture was stirred vigorously on an orbital shaker for 5–6 h. Finally, PS-DIEA resin was added to the mixture and agitated vigorously for 1–

2 h. The reaction mixture was filtered and the polymer was rinsed with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo to give pure products **2a–k** (85–95%).

Preparation of 1-[2-(3-Phenoxyphenyl)benzoxazol-5-yl]ethanone (2g); Typical Procedure

Dess–Martin periodinane (46.6 mg, 0.11 mmol) was added to a stirred solution of the corresponding Schiff base (33.1 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) at r.t. The solution was stirred for 10 min until TLC indicated the cyclization was complete. Isolation by method A involved standard column chromatography (EtOAc–hexane, 1:3) to afford **2g** as a colorless solid (29.6 mg, 90%).

Isolation by method B: After completion of the reaction, A-26 ($S_2O_3^{2-}$) resin (1.72 mmol/g; 0.54 g, 0.93 mmol) was added and the mixture was stirred vigorously on an orbital shaker for 5–6 h. Finally, PS-DIEA resin was added to the mixture and agitated vigorously for 1–2 h. The reaction mixture was filtered and the polymer was rinsed with CH_2Cl_2. The combined filtrate and washings were evaporated to give compound **2g**.

Yield: 27.9 mg (85%); colorless solid; mp 89–91 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 3 H), 6.98–7.21 (m, 4 H), 7.29–7.61 (m, 4 H), 7.82–8.05 (m, 3 H), 8.28–8.31 (d, *J* = 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 110.6, 117.6, 119.2, 120.9, 122.3, 122.4, 123.9, 125.9, 128.1, 130.0, 130.4, 134.3, 142.1, 153.6, 156.5, 158.0, 163.7, 197.0.

MS (EI): *m*/*z* (%) = 329 (43) [M$^+$], 315 (100), 287 (21), 142 (28), 92 (39), 63 (21).

2-(2,4-Dichlorophenyl)benzoxazole (2a)

Mp 127–130 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.43 (m, 3 H), 7.55–7.62 (m, 2 H), 7.78–7.83 (m, 1 H), 8.12–8.17 (d, *J* = 9.06 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.7, 120.5, 124.7, 124.8, 125.7, 127.4, 131.3, 132.5, 134.2, 137.5, 141.5, 150.5, 160.0.

MS (EI): *m*/*z* (%) = 268 (8) [M + 4], 266 (64) [M + 2], 264 (100) [M$^+$], 236 (10), 92 (10), 64 (44), 63 (50), 43 (15).

2-(3-Phenoxyphenyl)benzoxazole (2b)

Mp 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–7.09 (m, 4 H), 7.21–7.31 (m, 4 H), 7.36–7.48 (m, 2 H), 7.62–7.68 (m, 1 H), 7.79 (s, 1 H), 7.88–7.92 (m, 1 H).

MS (EI): *m*/*z* (%) = 287 (100) [M$^+$], 286 (88) [M – 1], 141 (13), 77 (30), 43 (25).

2-[4-(Trifluoromethyl)phenyl]benzoxazole (2c)

Mp 146–147 °C (Lit.[22] 143–145 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.42 (m, 2 H), 7.53–7.61 (m, 1 H), 7.75–7.84 (m, 4 H), 8.33–8.42 (d, *J* = 8.47 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.7, 120.3, 121.9, 124.9, 125.8, 125.8, 125.9 (q, *J* = 4.4 Hz), 127.8, 129.8, 130.3, 131.2, 141.8, 150.8, 161.4.

MS (EI): *m*/*z* (%) = 263 (100) [M$^+$], 262 (13) [M – 1], 235 (10), 63 (48).

2-(3-Hydroxyphenyl)benzoxazole (2d)

Mp 149–150 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.96–7.12 (m, 1 H), 7.27–7.39 (m, 3 H), 7.52–7.75 (m, 4 H), 9.31 (br s, 1 H, OH).

MS (EI): *m*/*z* (%) = 211 (100) [M$^+$], 183 (24), 155 (6), 141 (25), 93 (50), 65 (56), 63(56), 40 (37).

2-[3-(2-Propynyloxy)phenyl]benzoxazole (2e)

Mp 61–63 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.49–2.51 (t, *J* = 2.26 Hz, 1 H), 4.78–4.80 (d, *J* = 2.26 Hz, 2 H), 7.10–7.14 (dd, J_1 = 8.31 Hz, J_2 = 3.77 Hz, 1 H), 7.29–7.35 (m, 2 H), 7.39–7.45 (t, *J* = 7.55 Hz, 2 H), 7.52–7.59 (m, 1 H), 7.71–7.77 (m, 1 H), 7.81–7.89 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.0, 75.9, 78.1, 110.5, 113.2, 118.8, 120.0, 120.9, 124.5, 125.1, 128.3, 130.0, 142.0, 150.7, 157.8, 162.6.

MS (EI): *m*/*z* (%) = 249 (40) [M$^+$], 248 (36) [M – 1], 182 (25), 160 (100), 131 (100), 103 (58), 77 (42), 64 (25), 40 (31.2).

2-(4-*tert*-Butylphenyl)benzoxazole (2f)

Mp 102–104 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 9 H), 7.28–7.34 (m, 2 H), 7.48–7.57 (m, 3 H), 7.71–7.80 (m, 1 H), 8.12–8.18 (d, *J* = 9.06 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.4, 119.8, 124.3, 124.4, 124.8, 125.8, 127.4, 142.1, 150.63, 155.0, 163.1.

MS (EI): *m*/*z* (%) = 251 (63) [M$^+$], 236 (100), 147 (12), 63 (5).

2-(4-Methoxyphenyl)benzothiazole (2h)

Mp 119–120 °C (Lit.[24] 121–122 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 6.93–6.99 (m, 2 H), 7.28–7.34 (m, 1 H), 7.40–7.46 (m, 1 H), 7.81–7.85 (m, 1 H), 7.96–8.03 (m, 3 H).

MS (ESI): *m*/*z* (%) = 242 (100) [M + H]$^+$.

MS (EI): *m*/*z* (%) = 241 (100) [M$^+$], 225 (40), 198 (42), 69 (20), 63 (15).

2-(4-Methylphenyl)benzothiazole (2i)

Mp 82–84 °C (Lit.[25] 87–88 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 7.22–7.35 (m, 3 H), 7.40–7.46 (m, 1 H), 7.81–7.87 (d, *J* = 7.55 Hz, 1 H), 7.93–8.03 (m, 3 H).

MS (ESI): *m*/*z* (%) = 226 (100) [M + H].

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.32; H, 4.78; N, 6.05; S, 14.15.

2-(3-Phenoxyphenyl)benzothiazole (2j)

Mp 87–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04–7.18 (m, 4 H), 7.35–7.53 (m, 5 H), 7.74–7.82 (m, 2 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 8.06 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.7, 119.1, 121.2, 121.6, 122.4, 123.4, 123.7, 125.3, 126.4, 129.9, 130.4, 135.1, 154.1, 156.9, 158.0.

MS (ESI): *m*/*z* (%) = 303 (100) [M$^+$], 239 (25), 141 (10).

6-Methoxy-2-(4-dimethylami nophenyl)benzothiazole (2k)

Mp 178–180 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.05 (s, 6 H), 3.86 (s, 3 H), 6.70 (d, *J* = 9.06 Hz, 2 H), 6.98 (dd, *J* = 9.06, 3.02 Hz, 1 H), 7.24–7.27 (m, 1 H), 7.80–7.88 (m, 3 H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 40.1, 55.8, 104.4, 111.7, 114.8, 121.6, 122.7, 128.5, 135.8, 148.9, 151.9, 157.0, 166.4.

MS (EI): *m*/*z* (%) = 284 (100) [M$^+$], 269 (80), 253 (55), 241 (75), 149 (75), 95 (50), 85 (50), 43 (75).

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