A highly efficient strategy for the synthesis of 3-substituted salicylic acids by either directed *ortho*-lithiation or halogen–metal exchange of substituted MOM protected phenols followed by carboxylation.

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Abstract: A highly efficient synthesis of various 3-substituted salicylic acids is described starting from inexpensive starting materials and requiring no special apparatus.

Key words: salicylic acids, *ortho*-metalation, halogen–metal exchange, methoxymethyl group.

Résumé : On décrit une synthèse très efficace d'acides salicyliques substitués en position 3, à partir de produits peu dispendieux et ne requérant pas d'appareils spéciaux.

Mots clés : acides salicyliques, *ortho*-métallation, échange halogène–métal, groupe méthoxyméthyle.

[Traduit par la Rédaction]

Introduction

During the course of our study on the effect of remote substituents on the enantioselectivity of a palladium-catalyzed polyene cyclization (**3** → **4**) (1), which has been used in the synthesis of (+)-xestoquinone (2), we required various 3-substituted salicylic acid derivatives **1** (Scheme 1). As only 3-chlorosalicylic acid was commercially available, other methods for the preparation of 3-substituted salicylic acids were found in the literature. Currently, there exist relatively few direct methods for the synthesis of 3-substituted salicylic acids (3, and for recent reports involving the use of 3-halogen substituted salicylic acids, see ref. 4). Some salicylic acid derivatives can be synthesized directly from their corresponding phenols via a Kolbe–Schmidt carboxylation (5), however, we did not possess the proper apparatus to work with carbon dioxide at high pressures and temperatures. Another common route is through Reimer–Tiemann (6) or Duff formylations (7) of the 2-substituted phenols to give the 3-substituted salicylaldehydes followed by oxidation to the acid (8). The main drawback of this reaction is that the formylation is rarely selective and the aldehyde can be introduced *ortho* and (or) *para* to the phenol (9). In our hands, formylation of 2-substituted phenols provided a mixture in which the *para* isomer was the major product. Other strategies, such as the direct bromination of salicylic acid, which is reported to give only the 3-brominated isomer (10), gave us mixtures of the 5-bromo- and 3,5-dibromo- products and never the desired isomer. An alternative synthesis of 3-bromosalicyclic acid was reported in 1923 (11) in which the 5-position of salicyclic acid could be blocked as a sulfonic acid, brominated in the 3-position, and then the sulfonic acid removed. However, bromination of 5-protected salicyclic acid gave only 2,4,6-tribromophenol. As we had no luck with existing procedures we designed a new synthetic strategy for preparing various 3-substituted salicyclic acids and report herein simple and inexpensive procedures for their preparation.

Our initial attempts at synthesizing 3-chlorosalicylic acid from 2-chlorophenol, using either 2 equiv. of *n*-BuLi or 1 equiv. of NaH and 1 equiv. of *n*-BuLi followed by treatment with CO_2 gas at ambient pressure, met with little success due to the weakness of the phenolic OLi group as an *ortho*-lithiation director (12). The methoxymethyl (MOM) ether of phenols is known to be a more efficient *ortho*-lithiation director than phenolic hydroxyl groups (13). Thus, treatment of either the *ortho*-fluoro- (**5**) or *ortho*-chlorophenol MOM ether (**6**) (14) with 1 equiv. of *n*-BuLi generated the *ortho*-anion, which was trapped with gaseous CO_2 at low temperature (15). An acidic workup with 6 M HCl protonated the carboxylic acid and cleaved the MOM ether in situ to afford the 3-fluoro- (**7**) or 3-chlorosalicylic acid (**8**) in 86 and 91% yields, respectively (Scheme 2). As expected, there was no evidence of halogen–lithium exchange with either sample. This method for the preparation of 3-fluorosalicyclic acid (**7**) is more efficient than a recently reported synthesis (3).

The 3-bromo derivative could not be synthesized in the same manner from *ortho*-bromophenol because, in this case,

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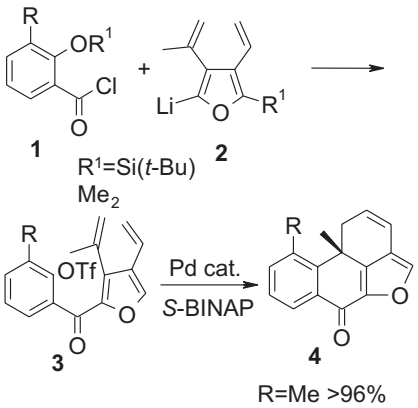
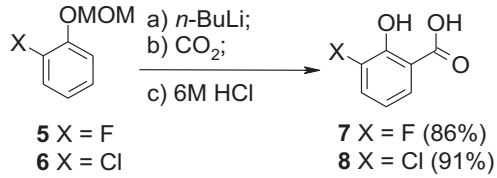
Scheme 1.



Scheme 2.

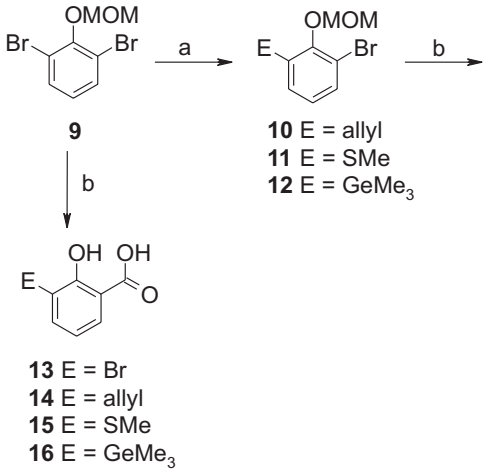


halogen–lithium exchange would occur more rapidly than deprotonation. We, thus, developed an alternative strategy starting from 2,6-dibromophenol that was easily prepared by treatment of a mixture of phenol and *tert*-butylamine with 2 equiv. of bromine at low temperature (16). The MOM protected 2,6-dibromophenol **9** (Scheme 3) was subjected to a monohalogen–lithium exchange with 2.1 equiv. of *t*-BuLi followed by quenching the anion with carbon dioxide. An acidic workup afforded the desired 3-bromosalicylic acid **13** in 97% yield.

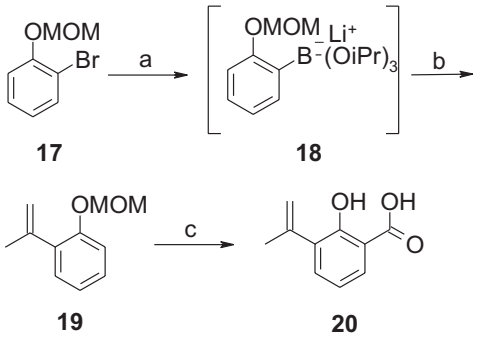
We decided to extend the above strategy towards other 3-substituted salicylic acids by using **9** as the starting material. By trapping the initial anion formed by a monohalogen–metal exchange with suitable electrophiles, the remaining bromide could subsequently be exchanged and trapped with carbon dioxide to give 3-substituted salicylic acids. Allyl bromide, dimethyl disulfide, and trimethygermanium bromide were used as electrophiles to quench the initial anion to give the corresponding products (Scheme 3). 3-Substituted salicylic acids were prepared in high yield by subsequent treatment of **10**–**12** with *t*-BuLi followed by the addition of carbon dioxide and acidic workup. We realized that **14**–**16** could have been obtained from the MOM-ether of phenol via successive deprotonations *ortho* to the MOM group followed by quenching with suitable electrophiles; however, problems could arise in the second lithiation if the first electrophile introduced is itself an *ortho*-lithiation director. For example, it is well-documented that an SMe group will direct an *ortho*-lithiation (17). Thus, the second lithiation of 2-methylthio-*O*-methoxymethylphenol might have led to some lithiation *ortho* to the thiomethyl group. Having the bromide in compound **11** ensured that the subsequent anion would be formed *ortho* to the MOM group.

Finally, we decided to extend this strategy towards our in situ Suzuki coupling methodology (1*c*, 18) to synthesize various 3-substituted salicylic acids in which the substituent could

Scheme 3. Reagents: (*a*) 2.1 equiv. *t*-BuLi, Et_2O, then allyl bromide, MeSSMe or Me_3GeBr; (*b*) 2.1 equiv. *t*-BuLi, THF, then CO_2, then 6 M HCl.



Scheme 4. Reagents: (*a*) 2.1 equiv. *t*-BuLi, THF, $B(O\text{-}i\text{-}Pr)_3$; (*b*) 2 M Na_2CO_3, $Pd(PPh_3)_4$, 2-bromopropene; (*c*) 1.1 equiv. *n*-BuLi, THF, CO_2 then 6 M HCl.



not be obtained via conventional nucleophilic displacement of a halide. This method, however, precluded the use of **9** as a starting material to prevent homo-coupling of **9** and possible polymerization. Thus the MOM ether of *ortho*-bromophenol **17** underwent a halogen–lithium exchange with *t*-BuLi and the resulting anion was treated with triisopropylborate to form **18** in situ (Scheme 4). After stirring the mixture for 4 h, 2-bromopropene, $Pd(PPh_3)_4$, and Na_2CO_3 (2 M) were added and the mixture was heated at reflux to afford **19**. Subsequent *ortho*-lithiation of **19** followed by trapping the anion with carbon dioxide afforded 3-isopropenylsalicylic acid (**20**) in 87% yield after an acidic workup.

In conclusion, we have developed an efficient, high yielding strategy for the synthesis of 3-substituted salicylic acids beginning with inexpensive starting materials that requires no special equipment. Although salicylic acid derivatives were our target, this strategy certainly permits further elaboration, allowing one to synthesize various 2,6-disubstituted phenols with ease.

Experimental

General

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ACE-200 (^{1}H 200 MHz, ^{13}C 50 MHz)

spectrometer. All spectra were obtained in $CDCl_3$ and the chemical shifts (ppm) are relative to the $CHCl_3$ peak as an internal reference (^{1}H 7.27 ppm, ^{13}C 77.00 ppm). Infrared (IR) spectra were recorded using a Mattson Galaxy Series 4030 FT-IR or a Nicolet Nexus 470 FT-IR ESP spectrophotometer. Mass spectra (MS) were run on either a Hewlett-Packard 5890 Series II gas chromatograph interfaced to a Hewlett-Packard 5971A mass selective detector or acquired by Mrs. Q. Wu, Department of Chemistry, University of Calgary, using a VG 7070 instrument. High resolution mass spectra (HRMS) were obtained by Mrs. D. Fox, Department of Chemistry, University of Calgary, on a Kratos MS-80 spectrometer. Elemental analyses were also performed by Mrs. D. Fox using a Control Equipment Corporation 440 Elemental Analyzer. All melting and boiling points are uncorrected. Anhydrous THF was distilled from sodium benzophenone ketyl. Anhydrous diethyl ether was distilled from CaH_2.

General procedure for the MOM protection of phenols (19)

Dry sodium hydride (432 mg, 18 mmol) was suspended in THF (10 mL) and was cooled to 0°C under N_2. A suitable phenol (12 mmol) was dissolved in THF (10 mL) and was added slowly dropwise to the NaH suspension over 10 min. The reaction mixture was allowed to stir at room temperature for 2 h. MOMCl (20) (6 mL, 6 M in methyl acetate, 36 mmol) was then added to the reaction mixture over 10 min and the reaction was stirred 2 h. The reaction mixture was concentrated in vacuo and the residue partitioned between diethyl ether and NaOH (0.1 M). The aqueous layer was extracted with diethyl ether and the organic layers were combined, washed once with NaOH (0.1 M), then with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified via air bath distillation at reduced pressure to give a colorless oil.

*1-Fluoro-2-methoxymethoxybenzene (**5**)*

Yield 1.70 g (94%, 10.9 mmol); bp 90°C at 13 torr (lit. (21) 100°C at 20 torr) (1 torr = 133.322 Pa). ^{1}H NMR δ: 3.52 (s, 3H), 5.22 (s, 2H), 6.9–7.3 (m, 4H).

*1-Chloro-2-methoxymethoxybenzene (**6**)*

Yield 1.92 g (96%, 11.1 mmol); bp 100–110°C at 13 torr (lit. (21) 100–102°C at 11 torr). ^{1}H NMR δ: 3.53 (s, 3H), 5.27 (s, 2H), 6.9–7.01 (m, 1H), 7.18–7.23 (m, 2H), 7.34–7.41 (m, 1H).

*1-Bromo-2-methoxymethoxybenzene (**17**)*

Yield 2.18 g (91%, 10.1 mmol); bp 105–110°C at 13 torr (lit. (22) 98–99°C at 6 torr). ^{1}H NMR δ: 3.54 (s, 3H), 5.27 (s, 2H), 6.90 (ddd, J = 1.71, 7.13, 7.86 Hz, 1H), 7.16 (dd, J = 1.71, 8.29 Hz, 1H), 7.20–7.32 (m, 1H), 7.56 (dd, J = 1.54, 7.86 Hz, 1H).

*1,3-Dibromo-2-methoxymethoxybenzene (**9**)*

Yield 3.38 g (99%, 11.5 mmol); bp 60°C at 0.08 torr (lit. (23) 118–121°C at 5 torr). ^{1}H NMR δ: 3.73 (s, 3H), 5.20 (s, 2H), 6.90 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H).

*1-Isopropenyl-2-methoxymethoxybenzene (**19**)*

1-Bromo-2-methoxymethoxybenzene (11 mmol) was dissolved in THF (10 mL) and cooled to –78°C under N_2. *t*-BuLi (13.6 mL, 1.7 M in pentane, 23.1 mmol) was added dropwise over 10 min and then allowed to stir at –78°C for 1 h. Triisopropylborate (13.2 mmol) was added dropwise over 5 min and reaction mixture was stirred at room temperature for 4 h. Na_2CO_3 (6.6 mL, 2 M in H_2O, 13.2 mmol) was added and the mixture was allowed to stir for 10 min. $Pd(PPh_3)_4$ (0.55 mmol, 5 mol%) and 2-bromopropene (24.2 mmol) were added and the reaction mixture was heated to 50°C with vigorous stirring overnight. The reaction was diluted with diethyl ether and quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with diethyl ether and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified via air bath distillation at reduced pressure to give a colourless oil. Yield 1.63 g (83%, 9.1 mmol); bp 100°C at 13 torr. MS *m*/*z* (%): 178 (25, M^+), 163 (13, $[M - 15]^+$). HRMS calcd. for $C_{11}H_{14}O_2$: 178.0994; found: 178.1005. IR (thin film) (cm^{-1}): 1598 (C=C), 1229 (C–O). ^{1}H NMR δ: 2.10–2.20 (m, 3H), 3.50 (s, 3H), 5.00–5.10 (m, 1H), 5.10–5.20 (m, 1H), 5.22 (s, 2H), 6.90–7.05 (m, 1H), 7.05–7.18 (m, 1H), 7.18–7.25 (m, 2H). ^{13}C NMR δ: 23.3, 56.1, 94.6, 114.9, 115.1, 121.8, 128.2, 129.5, 133.7, 144.1, 154.1.

General procedure for the formation of 2-bromo-6-substituted MOM protected phenols

1,3-Dibromo-2-methoxymethoxybenzene (12 mmol) was dissolved in diethyl ether (10 mL) and was cooled to –78°C under N_2. *t*-BuLi (15.5 mL, 1.7 M in pentane, 26.4 mmol) was added dropwise over 10 min and was allowed to stir at –78°C for 1 h. A suitable electrophile (14.4 mmol) was added dropwise over 5 min and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with diethyl ether and quenched with saturated sodium bicarbonate solution (10 mL). The aqueous layer was extracted with diethyl ether and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified via air bath distillation at reduced pressure to give a colorless oil.

*1-Allyl-3-bromo-2-methoxymethoxybenzene (**10**)*

Yield 2.70 g (88%, 10.6 mmol); bp 70°C at 0.08 torr. MS *m*/*z* (%): 256 (3, M^+), 258 (3, $[M + 2]^+$). HRMS calcd. for $C_{11}H_{13}O_2{}^{79}Br$: 256.0099; found: 256.0092. IR: (thin film) (cm^{-1}): 1159 (C–O). ^{1}H NMR δ: 3.48–3.55 (m, 2H), 3.67 (s, 3H), 5.0–5.15 (m, 2H), 5.10 (s, 2H), 5.88–6.10 (m, 1H), 6.97 (t, J = 7.78 Hz, 1H), 7.15 (dd, J = 1.71, 7.78 Hz, 1H), 7.42 (dd, J = 1.71, 7.78 Hz, 1H). ^{13}C NMR δ: 34.7, 57.7, 99.8, 116.2, 117.5, 125.6, 129.5, 131.5, 135.8, 136.5, 152.7. Anal. calcd. for $C_{11}H_{13}BrO_2$: C 51.38, H 5.10; found: C 50.07, H 5.10.

*1-Bromo-2-methoxymethoxy-3-methylsulfanylbenzene (**11**)*

Yield 2.45 g (78%, 9.4 mmol); bp 80–85°C at 0.08 torr. MS *m*/*z* (%): 262 (56, M^+), 264 (56, $[M + 2]^+$), 232 (42, $[M - 30]^+$), 234 (42, $[(M + 2) - 30]^+$. HRMS calcd. for $C_9H_{11}O_2S^{79}Br$: 261.9663; found: 261.9646. IR (thin film) (cm^{-1}): 1562 (C=C), 1158 (C–O). ^{1}H NMR δ: 2.43 (s, 3H), 3.73 (s, 3H), 5.15 (s, 2H), 6.95 (t, J = 7.8 Hz, 1H), 7.10

(dd, *J* = 1.7, 7.8 Hz, 1H), 7.35 (dd, *J* = 1.7, 7.8 Hz, 1H) (23). ^{13}C NMR δ: 15.1, 58.3, 99.0, 117.5, 125.3, 125.8, 128.1, 129.8, 135.4, 150.7. Anal. calcd. for $C_9H_{11}BrO_2S$: C 41.08, H 4.21; found: C 42.18, H 4.23.

*3-Bromo-2-methoxymethoxy-1-(trimethylgermanyl)benzene (**12**)*

Yield 3.33 g (83%, 10.0 mmol); bp 90–95°C at 0.08 torr. MS *m*/*z* (%): 334 (1, M^+), 319 (100, $[M - 15]^+$), 289 (62, $[M - 45]^+$). HRMS calcd. for $C_{10}H_{14}O_2{}^{79}Br^{74}Ge$: 318.9389 ($[M + CH_3]$); found 318.9390. IR: (thin film) (cm^{-1}): 1164 (C–O). ^{1}H NMR δ: 0.47 (s, 9H), 3.64 (s, 3H), 5.12 (s, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 7.35 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.55 (dd, *J* = 1.6, 7.5 Hz, 1H). ^{13}C NMR δ: –0.4, 58.0, 99.6, 116.9, 125.5, 128.3, 133.9, 134.3, 135.8, 138.1, 157.5. Anal. calcd. for $C_{11}H_{17}BrO_2Ge$: C 39.58, H 5.19; found: C 39.40, H 5.13.

General procedure for (*i*) *ortho*-lithation; (*ii*) direct carboxylation; (*iii*) deprotection

The 1-substituted-2-methoxymethoxybenzene (11 mmol) was dissolved in THF (10 mL) and cooled to 0°C under N_2. *n*-BuLi (8.6 mL, 1.4 M in hexanes, 12.1 mmol) was added dropwise over 5 min and the reaction mixture was stirred at 0°C for 1.5 h. The mixture was then cooled to –78°C and CO_2(g) was passed through a column of Drierite and bubbled into the reaction for 1.5 h. The mixture was allowed to warm to room temperature, HCl (6 M, 10 mL) was added, and the reaction mixture was stirred vigorously overnight. The reaction mixture was extracted with diethyl ether and the combined organic layers was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a solid, which was purified by flash chromatography.

*3-Fluorosalicylic acid (**7**)*

Yield 1.48 g (86%, 9.5 mmol); mp 144–147°C (lit. (3) 146–148°C). ^{1}H NMR δ: 6.84 (dt, *J* = 1.54, 8.04 Hz, 1H), 7.22–7.36 (m, 1H), 7.68 (dt, *J* = 4.62, 8.04 Hz, 1H).

*3-Chlorosalicylic acid (**8**)*

Yield 1.72 g (91%, 10.0 mmol); mp 183–185°C (lit. (24) 184–185°C). ^{1}H NMR δ: 6.90 (t, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 1.7, 8.0 Hz, 1H), 7.87 (dd, *J* = 1.7, 8.0 Hz, 1H).

*3-Isopropenylsalicylic acid (**20**)*

Yield 1.71 g (87%, 9.6 mmol); mp 98–100°C (lit. (25) 110–110.5°C). MS *m*/*z* (%): 178 (1, M^+), 160 (54, $[M - 18]^+$). HRMS calcd. for $C_{10}H_{10}O_3$: 178.0630; found 178.0613. IR ($CHCl_3$) (cm^{-1}): 3063 (br, OH), 1655 (C=O). ^{1}H NMR δ: 6.90 (dd, *J* = 7.52, 8.04 Hz, 1H), 7.46 (dd, *J* = 1.71, 7.52 Hz, 1H), 7.88 (dd, *J* = 1.71, 8.04 Hz, 1H), 10.75 (br s, 1H). ^{13}C NMR δ: 22.8, 111.1, 116.1, 119.1, 129.9, 132.7, 136.4, 142.6, 159.6, 174.7. Anal. calcd. for $C_{11}H_{14}O_2$: C 67.41, H 5.66; found: C 67.51, H 5.80.

General procedure for (*i*) *ortho*-lithiation via lithium–bromide exchange; (*ii*) direct carboxylation; (*iii*) deprotection

The 1-bromo-3-substituted-2-methoxymethoxybenzene (11 mmol) was dissolved in THF (10 mL) and cooled to –78°C under N_2. *t*-BuLi (13.6 mL, 1.7 M in pentane, 23.1 mmol) was added dropwise over 10 min and the reaction mixture was stirred at –78°C for 1.5 h. CO_2(g) was passed through a column of Drierite and bubbled into the reaction for 1.5 h. The mixture was allowed to warm to room temperature, HCl (6 M, 10 mL) was added, and the reaction mixture was stirred vigorously overnight. The reaction mixture was extracted with diethyl ether and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a beige solid, which was purified by flash chromatography.

*3-Bromosalicylic acid (**13**)*

Yield 2.30 g (97%, 10.7 mmol); mp 177–180°C (lit. (10) 181–181.5°C). ^{1}H NMR δ: 6.84 (t, *J* = 7.95 Hz, 1H), 7.78 (dd, *J* = 1.71, 7.95 Hz, 1H), 7.90 (dd, *J* = 1.71, 7.95 Hz, 1H).

*3-Allylsalicylic acid (**14**)*

Yield 1.78 g (91%, 10.0 mmol); mp 90–92°C (lit. (26) 90–91°C). ^{1}H NMR δ: 6.88 (dd, *J* = 7.52, 7.86 Hz, 1H), 7.41 (dd, *J* = 1.71, 7.52 Hz, 1H), 7.82 (dd, *J* = 1.71, 7.86 Hz, 1H).

*3-Methylsulfanylsalicylic acid (**15**)*

Yield 1.36 g (67%, 7.4 mmol); mp 165–169°C (lit. (27) 168–170°C). ^{1}H NMR (lit. (27)) δ: 2.49 (s, 3H), 6.95 (t, *J* = 7.95 Hz, 1H), 7.44 (dd, *J* = 1.54, 7.95 Hz, 1H), 7.78 (dd, *J* = 1.54, 7.95 Hz, 1H).

*3-Trimethylgermanylsalicylic acid (**16**)*

Yield 2.51 g (89%, 9.8 mmol); mp 138–141°C. MS *m*/*z* (%): 256 (2, M^+), 241 (72, $[M - 15]^+$), 223 (100, $[(M - 15) - 18]^+$). HRMS calcd. for $C_{10}H_{14}O_3{}^{74}Ge$: 256.0155; found 256.0131. IR ($CHCl_3$) (cm^{-1}): 3073 (br, OH), 1660 (C=O). ^{1}H NMR δ: 0.46 (s, 9H), 6.93 (dd, *J* = 7.10, 7.95 Hz, 1H), 7.60 (dd, *J* = 1.71, 7.10 Hz, 1H), 7.91 (dd, *J* = 1.71, 7.95 Hz, 1H), 10.61 (s, 1H). ^{13}C NMR δ: –1.6, 110.0, 119.3, 131.3, 141.7, 163.2, 165.8, 174.6. Anal. calcd. for $C_{10}H_{14}O_3Ge$: C 47.14, H 5.54; found: C 47.99, H 5.70.

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