A Mechanistic Dehydration Study with [2-^{13}C]-DIMBOA

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Dehydration of a 2-^{13}C-labeled synthetic sample of the natural aglucone 2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one ([2-^{13}C]-DIMBOA, **10**) using *N*-ethoxycarbonyltrichloroacetaldimine led to 3-formyl-6-methoxybenzoxazolin-2(3*H*)-one (^{13}C-labeled FMBOA, **11**) with complete transfer of the ^{13}C label into the −CHO group. On the basis of this finding, a mechanism for the dehydration is proposed.

A natural preinfectional resistance system[1,2] toward pathogens structurally based upon acetal 2-β-D-glucosides of the (*2R*)-2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one skeleton occurs in crop plants such as maize,[3] rye,[4] and wheat.[5] Aglucones released by β-glucosidase after a pest attack are the carriers of bioactivity within the plant and in phytotoxic root exudates.[6] 2,4-Dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (DIMBOA) of maize[7] is by far the best investigated aglucone. Its biosynthesis has been elucidated,[8,9] and synthetic approaches have been reviewed.[10] Recently, we reported on the formation of 3-formyl-6-methoxybenzoxazolin-2(3*H*)-one (FMBOA)[11] by dehydration of DIMBOA without any proof for the mechanism. However, FMBOA was shown to be a very reactive formyl donor toward *N*-, *O*-, and *S*-nucleophiles, which may be important in case it is formed under biological conditions. We now report on the synthesis of 2-^{13}C-DIMBOA (**10**) and a study of the mechanism of its dehydration by *N*-ethoxycarbonyltrichloroacetaldimine leading to a pure isotopomer of ^{13}C-labeled FMBOA (**11**). On the basis of the finding that the ^{13}C label is completely transferred into the −CHO group of **11**, a mechanism for the dehydration is proposed.

Our aim was to synthesize [2-^{13}C]-DIMBOA, to dehydrate it, to assign the position of the label in ^{13}C-FMBOA, and thus to draw a conclusion for the mechanism of dehydration. A comparison of all known syntheses for DIMBOA with available ^{13}C-labeled precursors that finally lead to a labeled position 2 in DIMBOA led to a DIMBOA synthesis recently reported[12] using [2-^{13}C]-bromoacetic acid as starting material. Doing this in a labeled manner compelled us to elaborate the middle part of this procedure in more detail than hitherto published.[12]

Results and Discussion

The preparative route is outlined in Scheme 1. The synthetic sequence for the isotopomers of ^{13}C-labeled FMBOA (**11**) was optimized using unlabeled compounds beforehand. The label was introduced using [2-^{13}C]-glycolic acid (**2**). This labeled precursor was synthesized starting from commercially available [2-^{13}C]-bromoacetic acid **1** according to a literature procedure in 69% yield.[13] A lower ^{13}C-enrichment was obtained by diluting it with unlabeled glycolic acid in a ratio of 1:19. Esterification of **2** with anhydrous MeOH catalyzed by Amberlite IR-120 resin gave the corresponding [2-^{13}C]-glycolic acid methyl ester (**3**) in 65% yield. MOM protection of the hydroxyl group in **3** was accomplished by refluxing it with 5 equiv of dimethoxymethane in the presence of Amberlite IR-120 resin in CH_2Cl_2. Methoxymethoxyacetic acid methyl ester (**4**) was obtained in 63% isolated yield after distillation in vacuo. Bromination of ester **4** with NBS initiated with dibenzoyl peroxide in CCl_4 afforded a product mixture containing [2-^{13}C]-2-bromomethoxymethoxyacetic acid methyl ester (**5**) and the main byproduct, bromomethoxymethane (**6**).

This reaction proved to be difficult to repeat with the same product distribution. In our best trial the ratio of **5**:**6** was 8:1, as evidenced from the ^{1}H NMR spectrum. Attempts to purify the bromide **5** by distillation in vacuo failed, as **5** was too labile to be purified. Hence, the crude product was used directly without further purification. Coupling reaction of the crude bromide **5** with 5-methoxy-2-nitrophenol in the presence of K_2CO_3 in anhydrous acetone[14] afforded a mixture of hitherto undescribed [2-^{13}C]-methoxymethoxy(5-methoxy-2-nitrophenoxy)acetic acid methyl ester (**7**) and 4-methoxy-2-(methoxymethoxy)nitrobenzene[15] (**8**), which were separated by column chromatography to give **7** in 61% yield. Reductive cyclization of **7** was performed using $NaBH_4$ and 10% Pd/C in a 1:1 H_2O/THF solvent system giving rise to [2-^{13}C]-4-hydroxy-7-methoxy-2-methoxymethoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**9**) in excellent yield. The ^{1}H NMR spectrum of **9** revealed the characteristic singlet of H-2 at δ 5.79. Incorporation of the ^{13}C label at C-2 was evident from the ^{13}C NMR spectrum by comparison with the spectrum of the natural abundance 2-MOM-DIMBOA. The integration intensity for the C-2 signal (δ 93.6) showed 5-fold enhancement, indicating that no loss of label occurred during the synthetic procedures. The structure of **9** was firmly established by a single-crystal X-ray structure determination (Figure 1).[16] Whereas an X-ray structure of DIMBOA is hitherto unknown, the analysis of **9** represents the first X-ray structure of this natural product in the form of a derivative. In the crystal, two molecules of **9** undergo dimerization by formation of O−H···O hydrogen bonds between the their hydroxamic acid units (Figure 2).

The regioselective ether cleavage of compound **9** was accomplished with 3.5 equiv of 1.0 M BCl_3 solution at −40 °C. Thus, [2-^{13}C]-2,4-dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (**10**) was obtained in 81% yield. The spectroscopic data of **10** are in complete accordance with those from natural DIMBOA. All of the ^{13}C incorporation remained on C-2.

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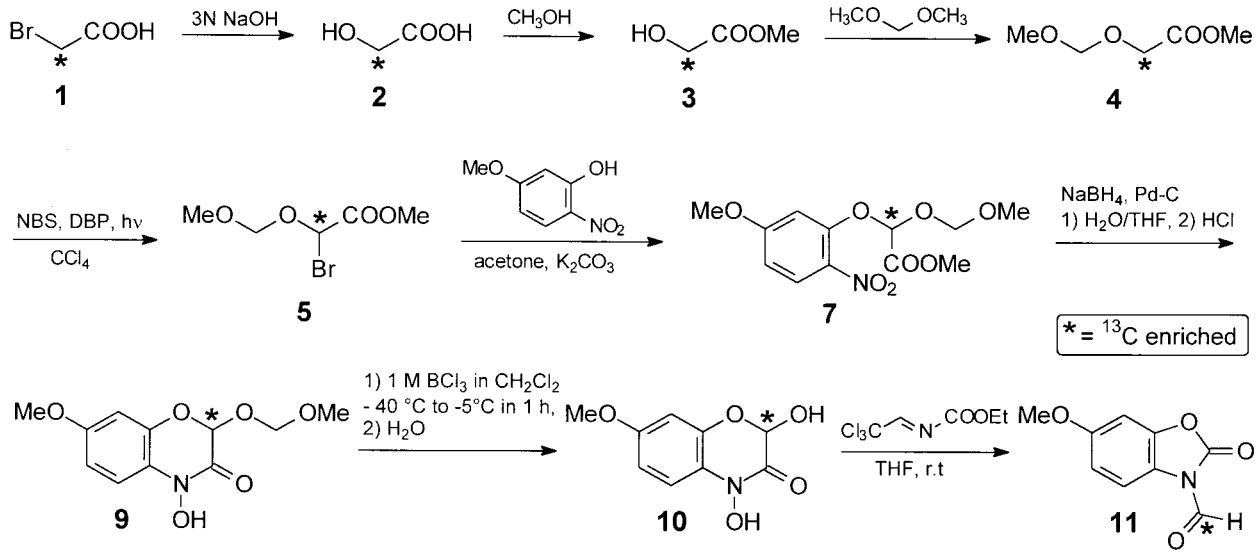
Scheme 1. Synthesis and Dehydration of [2-^{13}C]-DIMBOA (**10**)



Finally, the [2-^{13}C]-labeled DIMBOA gave rise to ^{13}C-FMBOA (**11**) when subjected to *N*-ethoxycarbonyltrichloroacetaldimine.[17] The yield for this conversion was believed higher than the isolated yield, as judged from the ^{1}H NMR spectrum of the crude product mixture, but the feature of FMBOA being an active formyl donor toward nucleophiles made the workup procedure laborious.

Tracking the course of the ^{13}C label in the conversion of **10** to **11** provided clear information regarding the mechanism of the dehydration reaction. The ^{13}C NMR spectra of **10** and **11** clearly show that the ^{13}C label is transferred completely into the formyl group in the ^{13}C-labeled FMBOA **11**. Hence, the synthesis of [2-^{13}C]-labeled DIMBOA (**10**) and its dehydration and rearrangement to [^{13}C-formyl]-labeled FMBOA **11** provide data that suggest a mechanism of dehydration as proposed in Scheme 2.

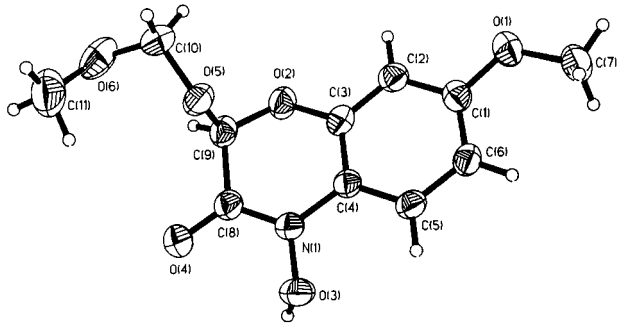


Figure 1. Molecular structure and atom numbering of **9**.

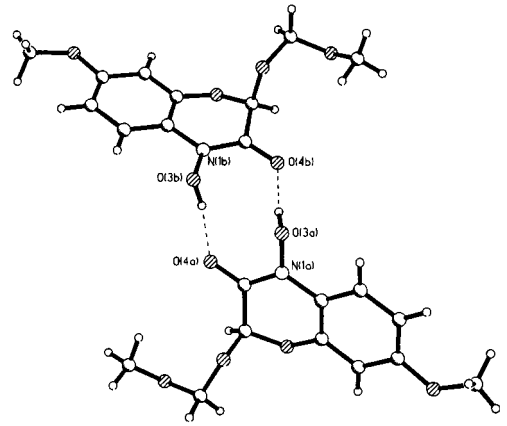
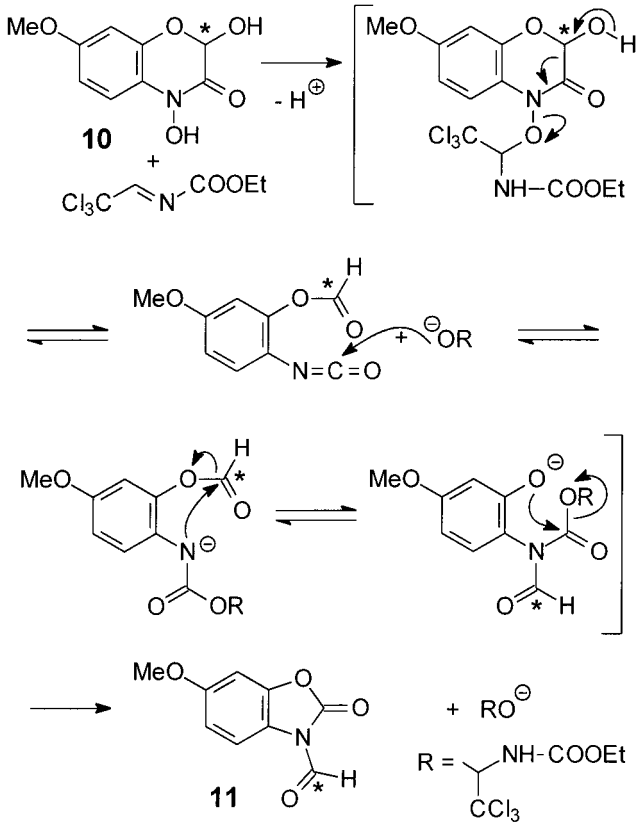


Figure 2. Dimerization by O−H···O hydrogen bonds of **9**. Symmetry: a: *x*, *y*, *z*; b: −*x*+1, *y*, −*z*+1/2.

Experimental Section

General Experimental Procedures. Commercial reagents were used without further purification. CCl_4 and acetone were dried and distilled before use. Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately before use. All air-moisture sensitive reactions were performed under a positive pressure of N_2. Air-sensitive solution was introduced into the reaction vessels through rubber septa via syringe. Melting points were measured on a Boetius micro hot-stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were

Scheme 2. Mechanistic Proposal for the Dehydration of **10** to [^{13}C-formyl]-Labeled FMBOA (**11**)



measured with Varian Gemini 200 (^{1}H, 199.975 MHz; ^{13}C, 50.289 MHz) and 300 (^{1}H, 300.063 MHz; ^{13}C, 75.451 MHz) spectrometers with hexamethyldisiloxane as the internal standard. Chemical shifts are given on the δ scale, and carbon signals increased by labeling are indicated by an asterisk*. IR spectra were obtained with a FT-IR spectrometer GENESIS SERIES from ATI/MATTSON. The MS was recorded on a VG Masslab Manchester VG 12-250 spectrometer (70 eV EI ionization). Elemental analyses were performed on a Heraeus CHN-O-Rapid analyzer. Data collection and structural refinement of **9**: Crystallographic data are given in Tables 1 and 2 as Supporting Information. Data ((Mo Kα) = 0.71073 Å) were collected with a Siemens CCD (SMART) diffractometer. All observed reflections were used for determination of the unit cell parameters. Empirical absorption correction utilized SADABS.[18] The structures were solved by direct methods (SHELXTL PLUS[19]). Restrictions for **9**: O, N, and C atoms anisotropic. H atoms were located by difference maps and refined isotropically. *N*-Ethoxycarbonyltrichloroacetaldimine[17] and 5-methoxy-2-nitrophenol[20] were prepared following the literature methods.

[2-^{13}C]-Glycolic Acid (2). [2-^{13}C]-Bromoacetic acid (5.0 g, 35.5 mmol) was added to 50 mL of a 3 N NaOH solution. The mixture was stirred at 50 °C for 5 h. After acidification to pH 1 with 1 N HCl, the reaction mixture was transferred to a vacuum line and evaporated to dryness. The residue was extracted with three 40 mL portions of ether. The organic layer was concentrated in vacuo to give an oily yellow solid (1.9 g, 69%). This 99% ^{13}C-enriched material was then used at a lower ^{13}C-enrichment by diluting it with 36.0 g of unlabeled glycolic acid to maintain a 5% ^{13}C enrichment in the starting synthon **2**: ^{1}H NMR (200 MHz, D_2O) δ 4.11 (s, 2H, CH_2); ^{13}C NMR (50 MHz, D_2O) δ 180.7 (C-1), 63.9 (*C-2).

[2-^{13}C]-Glycolic Acid Methyl Ester (3). [2-^{13}C]-Glycolic acid (37.9 g, 72 mmol) was dissolved in 300 mL of MeOH containing 5.0 g of Amberlite IR-120 resin. The solution was set to reflux overnight in a Soxhlet extractor containing 4 Å molecular sieves. After cooling, the reaction mixture was filtered and the solvent evaporated in vacuo to give a clear light yellow liquid. Distillation of this liquid (60 °C, 24 mmHg) gave **3** (28.3 g, 65%) as a colorless liquid: n_D (22 °C) 1.4138; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.15 (s, 2H, CH_2), 3.76 (s, 3H, $-OCH_3$), 3.0 (br s, $-$OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.9 (C-1), 60.5 (*C-2), 52.3 ($-OCH_3$).

[2-^{13}C]-Methoxymethoxyacetic Acid Methyl Ester (4). Methyl [2-^{13}C]-glycolate **3** (28.0 g, 0.31 mol) was dissolved in 300 mL of CH_2Cl_2 containing 2.5 g of Amberlite IR-120 resin, and 5 equiv of dimethoxy methane (118 g, 1.55 mol) was added. The solution was refluxed overnight in a Soxhlet extractor containing anhydrous $CaCl_2$. After cooling, the reaction mixture was filtered to remove Amberlite IR-120 resin, and the filtrate evaporated to give a light yellow liquid. Distillation of this material (72 °C, 20 mmHg) gave **4** as a clear colorless liquid (26.0 g, 63%): n_D (22 °C) 1.4070; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.65 (s, 2H, $-O-CH_2-O$), 4.11 (s, 2H, CH_2-CO-), 3.73 (s, 3H, $-COOCH_3$), 3.34 (s, 3H, $-OCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6 (C-1), 96.4 ($O-CH_2-O$), 64.2 (C-2), 55.9 ($-COOCH_3$), 52.0($-CH_2-OCH_3$); IR (film) 3519, 2900, 1756, 1284, 1062, 846 cm^{-1}; EIMS, *m*/*z* 133 [M $-$ 1]$^+$ (2), 103 (5), 74 (40), 58 (5), 45 (100).

[2-^{13}C]-Bromomethoxymethoxyacetic Acid Methyl Ester (5) and Bromomethoxymethane (6). [2-^{13}C]-Methoxymethoxyacetic acid methyl ester **4** (2.68 g, 20 mmol) was dissolved in 50 mL of dry CCl_4 under a nitrogen atmosphere. To the solution was added 3.56 g (20 mmol) of *N*-bromosuccinimide and 10 mg of dibenzoyl peroxide. A 250 W infrared heating lamp was placed close to the reaction vessel, and the reaction system was irradiated by the infrared lamp. The vigorous reaction was modified by switching off the lamp. An orange color developed after the first 2 min of irradiation and then gradually disappeared after an additional 3 min of refluxing. The mixture was cooled in an ice bath and filtered to remove succinimide. The CCl_4 was removed from the filtrate by evaporation in vacuo to give a pale oily mixture of **5** and **6** in a ratio of ~8:1. The crude bromides **5** and **6** were used for the coupling step without further purification.

The ratio of **5** to **6** was determined by integration values of ^{1}H NMR for the methine signal at 6.25 ppm in compound **5** vs 5.65 ppm in compound **6**. Data for **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H, H-2), 5.00 (ABd, 1H, J = 6.6 Hz, $O-CH_AH_B-O$), 4.75 (ABd, 1H, J = 6.6 Hz, $O-CH_AH_B-O$), 3.86 (s, 3H, $-COOCH_3$), 3.42 (s, 3H, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (C-1), 95.0 ($O-CH_2-O$), 75.8 (*C-2), 57.3 ($-COOCH_3$), 53.6 ($-CH_2-O-CH_3$).

[2-^{13}C]-Methoxymethoxy(5-methoxy-2-nitrophenoxy)-acetic Acid Methyl Ester (7) and 4-Methoxy-2-(methoxymethoxy)nitrobenzene (8). Freshly prepared crude bromides **5** and **6** (3.0 g) were added to a stirred solution of 5-methoxy-2-nitrophenol (1.9 g, 11.2 mmol) in anhydrous acetone in the presence of K_2CO_3 (1.4 g, 11 mmol), and the solution was refluxed under a nitrogen atmosphere for 2 h. When the couplings were complete as judged by TLC (7:3, hexane/EtOAc), the solution was cooled, filtered, and dried to give an orange residue. The residue was dissolved in CH_2Cl_2 (100 mL), extracted with 10% K_2CO_3 (3 × 50 mL), and dried over anhydrous $MgSO_4$. The crude coupling products (2.4 g), including **7** and **8**, were obtained after removal of CH_2Cl_2. Purification by column chromatography (ethyl acetate/hexane, 1:3, v/v) gave **7** (1.6 g) as a yellow oil, which crystallized on standing, and **8** (360 mg) with a mp of 46−48 °C. Data for **7**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 9.2 Hz, H-3′), 6.74 (d, 1H, J = 2.5 Hz, H-6′), 6.63 (br d, 1H, J = 9.2 Hz, H-4′), 5.76 (s, 1H, H-2), 5.01 (ABd, 1H, J = 6.6 Hz, $-OCH_AH_B-O$), 4.86 (ABd, 1H, J = 6.6 Hz, $-OCH_AH_B-O$), 3.85 (s, 3H, $-COOCH_3$), 3.84 (s, 3H, $-OCH_3$), 3.43 (s, 3H, $-OCH_2O-CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.5 (C-1), 164.3 (C-5′), 151.5 (C-1′), 135.0 (C-2′), 128.0 (C-3′), 108.4 (C-4′), 105.2 (C-6′), 95.5 (*C-2), 94.6 (C-1″, $O-CH_2-O$), 56.7 ($-COOCH_3$), 56.1, 53.1 (2 × OCH_3); IR (film) 3478, 2954, 1756, 1677, 1446, 1164, 1097, and 1022 cm^{-1}; EIMS, *m*/*z* 241 [M$^+$ $-$ $COOCH_3$ $-$ H, 3]$^+$, 240 (1), 213 (47), 75 (52), 61 (65), 45 (100); *anal*. C 47.70%, H 5.38%, N 4.45%; calcd for $C_{12}H_{15}NO_8$, C 47.84%, H 5.02%, N 4.65%.

[2-^{13}C]-4-Hydroxy-7-methoxy-2-methoxymethoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (9). The nitroester **7** (1.2 g, 3.99 mmol in 15 mL of THF) was added dropwise to a stirring mixture of 500 mg of $NaBH_4$ and 50 mg of 10% Pd/C in a 1:1 H_2O/THF (40 mL) solvent system, and the reaction was complete after 1 h. The mixture was stirred for another 30 min, the catalyst was filtered off, and the solution was acidified with HCl to pH 3, extracted with ethyl acetate (3 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated to afford **9** (1.0 g) in 95% yield: mp 142−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (br s, $-$OH), 7.42 (d, 1H, J = 8.7 Hz, H-5), 6.72 (dd, 1H, J = 8.7, 2.4 Hz, H-6), 6.66 (d, 1H, J = 2.4 Hz, H-8), 5.79 (s, 1H, H-2), 5.03 (ABd, 1H, J = 6.6 Hz, $O-CH_AH_B-O$), 4.65 (ABd, 1H, J = 6.6 Hz, $O-CH_AH_B-O$), 3.83 (s, 3H, $-OCH_3$), 3.40 (s, 3H, OCH_2-OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8 (C-7), 155.7 (C-3), 142.0 (C-8a), 120.5 (C-4a), 114.9 (C-5), 108.6 (C-6), 103.8 (C-8), 94.0 (*C-2), 93.6 (C-1′, $-OCH_2O-$), 56.3, 55.8 (2 × OCH_3); IR (KBr) 3020, 2971, 1691, 1600, 1511, 1448, 1344, 1319, 1277, 1190,1155, 1139, 1103, 1028, 1004, 958, 914, 800 cm^{-1}; EIMS, *m*/*z* 255 [M]$^+$ (24), 194 (14), 166 (13), 150 (13), 136 (9), 109 (9), 45 (100); *anal*. C 51.80%, H 5.45%, N 5.65%; calcd for $C_{11}H_{13}NO_6$, C 51.77%, H 5.13%, N 5.15%.

[2-^{13}C]-2,4-Dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (10). The C-2-labeled MOM-protected DIMBOA, **9** (900 mg, 3.5 mmol), was dissolved in 50 mL of dry CH_2Cl_2 and cooled to −40 °C using a liquid nitrogen/2-propanol bath under a nitrogen atmosphere. To the stirring mixture was added 3.5 equiv (12 mL) of 1.0 M BCl_3 solution in CH_2Cl_2. The mixture was allowed to warm to −5 °C over 1 h, and then 50 mL of water was added. After transfer to a separatory funnel the aqueous solution was extracted with EtOAc (3 × 30 mL), and the organic phases were combined, dried, and evaporated to yield **10** (600 mg, 81%): off-pink solid; mp 163−165 °C (lit.[7] 168−169 °C); ^{1}H NMR (200 MHz, CD_3OD) δ 7.26 (d, 1H, J = 9.0 Hz, H-5), 6.65 (dd, 1H, J = 9.0, 2.5 Hz, H-6), 6.63 (d, 1H, J = 2.5 Hz, H-8), 5.67 (s, 1H, H-2), 3.77 (s, 3H, $-OCH_3$); ^{13}C

NMR (75 MHz, CD_3OD) δ 159.4 (C-7), 158.6 (C-3), 143.5 (C-8a), 123.5 (C-4a), 115.1 (C-5), 108.9 (C-6), 104.7 (C-8), 94.0 (*C-2), 56.1 (OCH_3).

3-^{13}C-Formyl-6-methoxybenzoxazolin-2(3*H*)-one (11). To a stirred solution of [2-^{13}C]-DIMBOA, **9** (211 mg, 1 mmol), in dry THF (30 mL) was added a solution of *N*-ethoxycarbonyltrichloroacetaldimine (219 mg, 1 mmol) in dry THF (10 mL) in one portion at room temperature. After 1 h the solvent was removed in vacuo and the oily residue dried further under vacuum, followed by triturating with EtOH (2 mL) to cause crystallization. The crude pale brown crystals were recrystallized from $CHCl_3$ to yield [formyl-^{13}C]-3-formyl-6-methoxybenzoxazolin-2(3*H*)-one (**11**, 66 mg, 39% isolated yield) as off-white crystals, mp 140−142 °C; its ^{1}H and ^{13}C NMR spectra were in accordance with those of an authentic sample.[11] In the ^{13}C NMR spectrum the *C*HO peak at δ 158.4 was increased due to the complete transfer of the ^{13}C label to this position.

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Supporting Information Available: Crystal data and atomic coordinates (Tables 1 and 2) of **9**. This material is available free of charge via the Internet at http://pubs.acs.org

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(16) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk) quoting the deposit number CCDC 163394.
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