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Synthesis of Chiral ^{13}C,^{77}Se-Labeled Selones

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Abstract: Stable isotope-labeled *N*-acyl selones have been constructed in fewer than four steps from readily available starting materials. Site-specific labeling was achieved using the following synthons: bromo[2-^{13}C]acetic acid, [^{13}C]formic acid, and elemental ^{77}Se. These labeled selones have been found to provide unique insights into enolate structure and may be useful in the detection and quantitation of remotely disposed chiral centers in compounds in short supply.

During the past several decades, we have been interested not only in developing the unique chemistry associated with the selenocarbonyl but also in applying the extreme chemical shift sensitivity of the selenium nucleus in these systems to a wide variety of inorganic, organic, and biological systems.[1] This chemical shift sensitivity (CSS) has been harnessed for the detection and quantitation of remotely disposed chiral centers.[2] In that initial report, the method proved to be useful in detecting chiral centers seven bonds removed from the observing selenium nucleus. In addition, in a series of studies it was demonstrated that a particularly useful structural motif to have optimal sensitivity for the selenium nucleus is the selenocarbonyl (Figure 1).[3] More recently, the application of the CSS was demonstrated for a variety of carboxylic esters that were subjected to enzymatic (hydrolysis) resolution.[4] This study also served to reveal the limits of detection of the chiral center by the observed selenium nucleus. If a chiral center was more than eight bonds removed from the selenium atom the method failed to detect the diastereomers, and only a singlet was observed in the 1D ^{77}Se NMR spectrum. More recently, these chiral selone systems were found to provide a unique platform for aldol reactions.[5] In-depth studies using stable isotope labeling with ^{77}Se and ^{13}C NMR spectroscopy and molecular modeling have provided unique mechanistic insights into aldol reactions that involve discrete monomeric titanium complexes.[6] In this paper, we describe the synthesis of stable isotope-labeled selones and *N*-acyl selones. These may provide important details on aldol reactions using NMR spectroscopy and could prove useful in the detection and quantitation of chiral centers of natural products in limited supply.

SCHEME 1

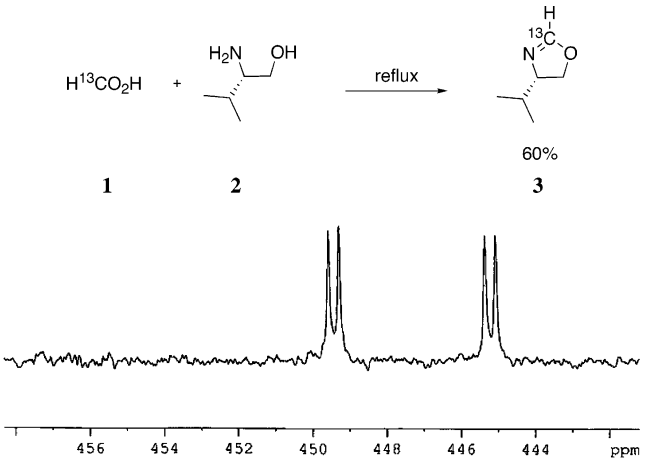

FIGURE 1. ^{77}Se NMR 1D proton-decoupled spectrum of oxazolidine selone **7**.

Key to gaining insights into the structure of titanium-based enolates by NMR spectroscopy is the ability to incorporate strategic stable isotope labeling. Because these chiral selones provide a platform for aldol reactions and, in addition, a rare example of a chiral auxiliary promoted anti-aldol process, one of the more important atoms to label is selenium. In addition, changes in the selenocarbonyl bond length could be monitored by measuring the coupling constant of the directly bonded carbon and selenium atoms.[7] Due to the instability of the Ti complexes and enolates for long periods, dual labeling was required to allow measurement of the $J_{^{13}C-^{77}Se}$ in a reasonable amount of time. In an effort to monitor the side-chain dynamics and local environment the α-carbon also required labeling. A reporter at this position may also allow better understanding of the unique couplings which occur in these systems.

Starting with commercial L-valinol **2** and formic acid **1**, chiral oxazolines are formed in enantiomerically pure form using the modified method of Meyers et al.[8] (Scheme 1). In the case of the oxazoline **3**, the ^{13}C formic acid **1** was synthesized from the reaction of sodium [^{13}C]formate and 85% phosphoric acid followed by distillation. If sulfuric acid is used instead, the formic acid decomposes giving rise to carbon monoxide.[9] Interestingly, the solu-

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(1) Wu, R.; Hernandez, G.; Dunlap, R. B.; Odom, J. D.; Martinez, R. A.; Silks, L. A. *Trends Org. Chem.* **1998**, *7*, 105.
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(6) Kimball, D. B.; Michalczyk, R.; Moody, E.; Ollivault-Shiflett, M.; De Jesus, K.; Silks, L. A. P. *J. Am. Chem. Soc.* **2003**, *125*, 14666.
(7) Typical J_{Se-C} for selenocarbonyls range from 220 to 242 Hz. The decrease in the value of the coupling constant indicates less s character in the bonding system, which results in a longer bond.
(8) For the construction of the valinol-derived oxazoline: Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676. Also see: Leonard, W. R.; Romine, J. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 1961.
(9) (a) Meyer, J. *Z. Elektrochem. Angew. Phys. Chem.* **1909**, *15*, 506. (b) Schierz, E. R. *J. Am. Chem. Soc.* **1923**, *45*, 447.

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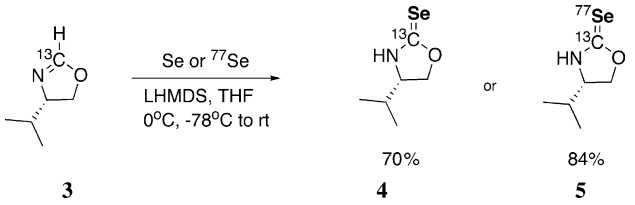
SCHEME 2



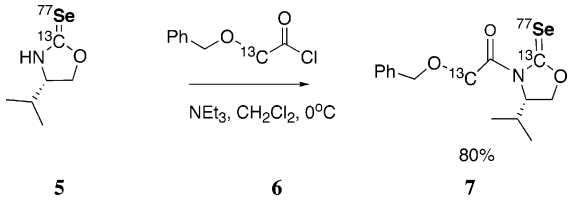
tion of the formic acid and valinol requires high temperatures before the mixture of oxazoline and water codistill. Temperatures more than 200 °C evidently cause a "cracking" event to occur. The mixture is then distilled into a diethyl ether sodium sulfate suspension. In addition, isolation of **3** is complicated by the relatively low boiling point and high volatility of the oxazoline. Despite these limitations, the process is straightforward if performed on the 10−20 g scale. In addition, for long-term storage it was found that efficient drying was required.

Metalation of oxazoline **3** was carried out with lithium bis(trimethylsilyl)amide (LHMDS) in THF (Scheme 2).[10] LHMDS was first generated at 0 °C, after which the pale yellow solution was chilled to −78 °C and the oxazoline was added dropwise as a THF solution. In a separate flask, the grey ^{77}Se was sublimed to red selenium with heat under a vacuum. The sublimation was complete when a ring of red selenium deposited just above the heating mantle and no grey selenium was observed remaining in the bottom of the flask. This sublimation was found to be essential for the following reaction to proceed. The flask was cooled, THF was added, and the contents were chilled to −78 °C. The metalated oxazoline solution was then cannula transferred into this flask. The solution was swirled to bring the red selenium into contact with the carbanion solution. After warming and stirring, the mixture was quenched with 0.1 M citric acid and an extraction/aqueous workup was performed. Unreacted selenium (39%) was recovered from the flask. The crude selone was purified by flash chromatography. Examination of the ^{77}Se NMR spectrum revealed a doublet at 112 ppm with a coupling constant of 233 Hz. Optical purity was verified via derivitization with Mosher's acid chloride.[10,11]

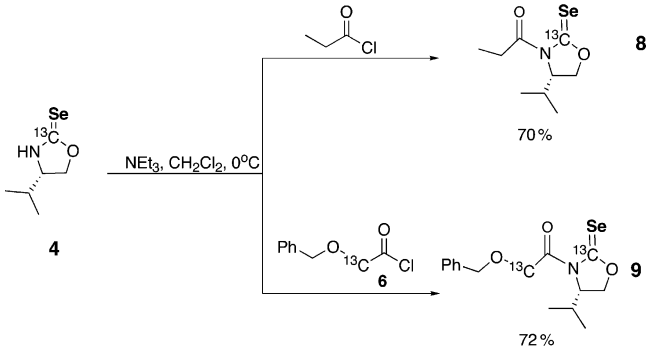
Alkylation of benzyl alcohol by ethyl bromo[2-^{13}C]-acetate with sodium hydride in THF gave the benzyloxy-[2-^{13}C]acetate. Reaction with freshly distilled oxalyl chloride at rt provided benzyloxy[2-^{13}C]acetyl chloride **6** in 60% yield for the three-step process.[12]

The triply labeled amide **7** was synthesized from [^{77}Se-^{13}C]selone **5** and the [2-^{13}C]acyl chloride **6** in CH_2Cl_2 at 0 °C with an excess of triethylamine (Scheme 3). Filtration over a pad of silica gel and flash chromatography offered the desired product.[13] The ^{77}Se NMR spectrum exhibiteda resonance at 447 ppm (dd, J = 16, 241 Hz). Interestingly, the presence of a doublet of doublets

SCHEME 3



SCHEME 4



(Figure 1) could arise from a through-bond coupling or through-space. This seemingly simple question has been investigated on both sides and has so far eluded explanation. For example, the α methylene protons are not coupled to the Se through-space, but through-bond coupling of the C═O to Se was not observed when it was ^{13}C labeled. Efforts are currently underway to help reveal the nature of this coupling system and will be reported in due course.

Selone **4** was also acetylated with propionyl chloride and benzyloxy[2-^{13}C]acetyl chloride **6** to form, respectively, amide **8** and **9** (Scheme 4).

These compounds may provide additional insight into the structural complexities of metal complexes and enolates by NMR spectroscopy. In addition to the use of ^{77}Se-labeled selones for the detection and quantitation of chirality for materials in short supply, these systems may also prove to be of some value for the synthesis of stable isotope-labeled ribonucleic acids and carbohydrates.

Experimental Section

(*S*)-(−)-4-(1-Methylethyl)-[2-^{13}C]-oxazoline-[^{77}Se]-selone (5). In a flamed three-neck flask cooled under argon, HMDS (0.222 g, 1.37 mmol) and THF (6 mL) were cooled to 0 °C and ^{n}BuLi (2.5 M in hexanes, 1.44 mmol) was added. The reaction was allowed to stir at 0 °C for 30 min. ^{77}Selenium (0.074 g, 0.96 mmol) was placed in another three-neck flask without a stir bar and was sublimed using a heating mantle under high vacuum until the selenium became red. The deprotonation reaction was cooled to −78 °C, and the oxazoline **3** (0.142 g, 1.25 mmol) in THF (1 mL) was slowly added. The reaction was stirred for 2 h at −78 °C. A stir bar and 3 mL of THF were added to the activated selenium, and the mixture was cooled to −78 °C. The LHMDS-oxazoline solution was transferred via cannula to the activated selenium mixture. After addition, the cooling bath was removed and the reaction was stirred for 2 h at rt. The reaction was quenched by addition of a 0.1 M solution of citric acid. The

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(11) For ^{1}H, ^{77}Se, and ^{13}C NMR spectra of this adduct, see the Supporting Information (S5−7). The ^{77}Se NMR shows a single doublet at 550.2 ppm (the apparent minor doublet at 680 ppm has J = 140 Hz and cannot be from a selenocarbonyl). Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543.

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product was extracted with CH_2Cl_2 and dried over Na_2SO_4. Evaporation of the solvent offered 0.170 g of the crude product. Unreacted selenium (29 mg, 39%) was recovered. Silica gel flash chromatography with first CH_2Cl_2 and then 10% EtOAc/CH_2Cl_2 gave 100 mg (84% based on recovered Se) of **5** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.60 (s, br, 1H), 4.73 (td, J = 9.3, 2.6[J_{H-C}] Hz, 1H), 4.42 (ddd, J = 9.3, 6.5, 3.4[J_{H-C}] Hz, 1H), 3.93−3.85 (m, J = 13.4, 9.3, 6.5, 3.2[J_{H-C}] Hz, 1H), 1.92−1.81 (m, J = 13.4, 6.7 Hz, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 187.1 (d, J = 232 Hz), 74.7, 63.5, 31.9, 16.6 (2C); ^{77}Se NMR ($CDCl_3$) δ 112 (d, J = 233 Hz); MS + 1 192.1, MS^2 + 1 86.1, 69.0; HRMS calcd for $C_5{}^{13}CH_{11}NO^{77}Se$ 191.0073, obsd 191.0069.

Phenylmethoxy-[2-^{13}C]-acetyl Chloride (6). Phenylmethoxy-[2-^{13}C]-acetic acid was first synthesized using a procedure modified from Gravestock et al.[11a] A typical example is as follows. To a suspension of NaH (1 g, 60% dispersion in mineral oil, 25.0 mmol) in dry THF (35 mL) under Ar at 0 °C was added a solution of benzyl alcohol (1.17 mL, 11.3 mmol) in THF (5 mL). After the mixture was stirred for 1 h, a solution of bromo-[2-^{13}C]-acetic acid (1.0 g, 7.1 mmol) in THF (20 mL) was added and the mixture was refluxed overnight. The mixture was quenched with methanol (20 mL), diluted with water, and washed with ether. The aqueous layer was then acidified with concd HCl to pH 4 and extracted with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated to give 1.14 g (96% yield) of crude product as a slightly yellow oil. NMR spectra were analogous to unlabeled commercial samples and showed sufficient purity for subsequent reactions: ^{1}H NMR ($CDCl_3$) δ 7.44−7.37 (m, 5H), 4.70 (d, J = 4.3 Hz, 2H), 4.20 (d, J = 144.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 175.5 (d, J = 61 Hz), 136.6, 128.6, 128.2, 128.1, 127.7, 127.1, 73.4, 66.5; MS + 1 166.5, 148.3.

The acid chloride was obtained using the procedure of Miller et al.[11b] The acid (8.0 g, 48.0 mmol) was dissolved in dry CH_2Cl_2 (150 mL) and chilled to 0 °C under Ar. A solution of $(COCl)_2$ (50.0 mL, 2 M in CH_2Cl_2, 100.0 mmol) was added, and the solution was stirred 4 h and then allowed to gradually warm to ambient overnight. The solvent was coevaporated with toluene, and the product was distilled under reduced pressure (0.65 mmHg, bp[14] 88−90 °C) to give 5.65 g (63%) of acid chloride **6** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.48−7.38 (m, 5H), 4.72 (d, J = 4.0 Hz, 2H), 4.50 (d, J = 148.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 171.9 (d, J = 57 Hz), 136.1, 134.0, 130.1, 128.7, 128.5, 128.2, 74.8, 73.6; MS 184.5.

(14) For the unlabeled compound, lit. bp 81−83 °C, 0.6 mm: Bennington, F.; Morin, R. D. *J. Org. Chem.* **1961**, *26*, 194.

4-(*S*)-(−)-(1-Methylethyl)-3-[(phenylmethoxy)-[2-^{13}C]-acetyl]-[2-^{13}C]-oxazolidine[^{77}Se]-selone (7). To the previous seleno compound **5** (44.7 mg, 0.234 mmol) in 2.5 mL of CH_2Cl_2, in an ice bath, was added acetyl chloride **6** (52.2 mg, 0.281 mmol) in 0.5 mL of CH_2Cl_2 and triethylamine (0.742 g, 0.304 mmol). The bright yellow reaction was stirred for 15 min at 0 °C and then 1 h at rt. When TLC showed disappearance of the starting material, the reaction was filtered over a pad of silica gel and rinsed with CH_2Cl_2. After solvent evaporation in vacuo, the yellow oil was purified by flash chromatography with 15% ethyl acetate/hexanes to offer 64 mg (80%) of **7**: ^{1}H NMR ($CDCl_3$) δ 7.48−7.32 (m, 5H), 5.26 (d, J = 147.8 Hz, 2H), 4.82−4.76 (m, 1H), 4.72 (d, J = 4.1 Hz, 2H), 4.54−4.42 (m, 2H), 2.48−2.38 (m, 1H), 0.99 (d, J = 7 Hz, 3H), 0.93 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 188.5 (d, J = 241.2 Hz), 72.3 (d, J = 16.3 Hz) [unlabeled **7**: δ 188.5, 170.9, 137.0, 128.5, 128.2, 128.0, 73.6, 72.2, 70.3, 64.3, 28.8, 18.1, 14.9]; ^{77}Se NMR ($CDCl_3$) δ 447.35 (dd, J = 16.3, 241.2 Hz); MS + 1 341.1, MS^2 + 1 282.1

4-(*S*)-(−)-(1-Methylethyl)-3-(1-oxopropyl)-[2-^{13}C]-oxazolidineselone (8): 70%; ^{1}H NMR ($CDCl_3$) δ 4.72−4.65 (m, 1H), 4.41−4.29 (m, 2H), 3.53−3.26 (ABX3, J = 17.9, 7.3 Hz, 2H), 2.33−2.21 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 189.3 (apparent doublet, J = 242 Hz, is from 7% ^{77}Se natural abundance), 154.4, 69.4, 64.1, 32.2, 28.8, 18.1, 14.9, 8.6.

4-(*S*)-(−)-(1-methylethyl)-3-[(phenylmethoxy)-[2-^{13}C]-acetyl]-[2-^{13}C]-oxazolidineselone (9): 72%; ^{1}H NMR ($CDCl_3$) δ 7.48−7.32 (m, 5H), 5.26 (d, J = 147.8 Hz, 2H), 4.82−4.76 (m, 1H), 4.72 (d, J = 4.1 Hz, 2H), 4.54−4.42 (m, 2H), 2.48−2.38 (m, 1H), 0.99 (d, J = 7 Hz, 3H), 0.93 (d, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 188.6, 72.2.

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Supporting Information Available: Spectral data for compounds **5**−**9**, α-^{13}C benzyloxyacetic acid, and α-^{13}C benzyloxyacetyl chloride. This material is available free of charge via the Internet at http://pubs.acs.org.

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