0.83 can be calculated on the basis of the above nitrogen isotope effects.

The above conclusion is also supported by the deuterium isotope effect, although the quantitative analysis is difficult because of the lack of appropriate model data. Both $^{15}k_1/^{15}k_2$ and $^{15}k_1$ should be small secondary effects, probably slightly inverse due to the stiffer N-H bonds in $-^{+}NH_2-$ than in $-NH_2$. The isotope effect on k_3 should be large, as this step involves proton transfer. Thus, one would expect a small inverse isotope effect if the formation of the intermediate is rate determining and a large normal isotope effect if the decomposition is rate determining. These conclusions are supported by the observed isotope effects for ammonolysis of benzoates[10] and acetates[11] in D_2O: 0.8 and 1.0 for the uncatalyzed reactions, which proceed with rate-determining formation of the intermediate, and 1.6 and 1.5 for the catalyzed reactions, which proceed with rate-determining decomposition of the intermediate. Our observed deuterium isotope effect of 1.29 is intermediary and agrees well with the partitioning factor k_3/k_2 of about unity.

In conclusion, we find our results on kinetic isotope effects indicative of the stepwise reaction with the formation of a tetrahedral intermediate and its decomposition being nearly equally rate limiting. This is an interesting finding, since decomposition of the intermediate is usually assumed to control the overall reaction rate in analogous reactions.[12,13]

Registry No. 1, 3140-73-6; 2, 91889-76-8; 3, 6625-74-7; 4, 6625-74-7; Nitrogen-15, 14390-96-6; deuterium, 7782-39-0.

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Oxazoline-Directed Metalation of Unactivated Norbornenyl Olefinic CH: Application to an Attempted Synthesis of the Diterpenoid Mold Metabolite Sordaricin

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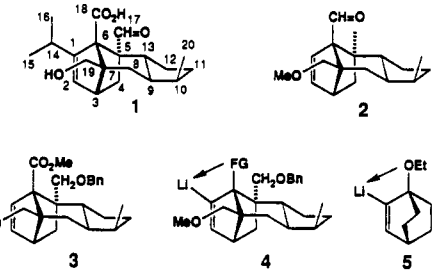
Heteroatom-directed ortho metalation of aromatic compounds is a highly developed technique,[2] but there are very few examples of the analogous deprotonation of unactivated vinyl compounds.[3,4] Having recently established efficient synthetic routes to the tetracyclic aldehyde **2** and ester **3**[5] as part of a project to elucidate the biogenesis of the unusual diterpenoid sordaricin (**1**),[6] we speculated about whether the unactivated norbornenyl double bond in **3** could be regioselectively deprotonated at C(1) with



1 **2** **3** **4** **5**

activation and direction by an appropriate derivative of the bridgehead carboxy group (cf. structure **4**). A metalation of this kind could then be expected to allow the selective introduction of the isopropyl group and facilitate a direct conversion of **3** into **1**.

The preparation of the alkenyllithium **5** by reaction of the parent alkene with *tert*-butyllithium[7] appeared to provide an encouraging precedent for obtaining the metalated ether **4** (FG = CH_2OCH_2OMe), but we were unable to detect any reaction of this kind, possibly because the inductive effect of the alkoxy function in this substrate is attenuated by an additional intervening carbon atom.[8] However, the oxazoline derivative **6** could be successfully lithiated by *n*-butyllithium at C(1) as demonstrated by deuteration to give **7** (Scheme I).[9]

Application of the metalation-based strategy to the synthesis of sordaricin (**1**) from the intermediate **3** was then explored as outlined in Scheme II. Ester **3** was very resistant to hydrolysis, but the oxazoline **8** could be obtained in an overall yield of 73% by heating **3** in a mixture of 2-amino-2-methylpropan-2-ol and its potassium salt at 140 °C and treating the amide with thionyl chloride. A significant amount of acid was also formed in the first step and was converted to amide in the usual way via the acyl chloride. Lithiation of oxazoline **8** proceeded as smoothly as for **6**, but attempts to effect the direct introduction of an isopropyl group[10] were not productive and it was necessary to resort to a progressive elaboration of this group. Thus, acylation of **9** with methyl chloroformate followed by in situ reaction with methyllithium afforded carbinol **10**.[11] Although simple dehydration was unsuccessful, treatment with HBr gave the cyclic ether **11**, which was readily converted by LDA into the isopropenyl derivative **12**. Selective hydrogenation of the more exposed double bond in this product could only be accomplished with a rhodium catalyst,[12] but unfortunately, concomitant satu-

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(9) The oxazoline function was chosen because it had been established as one of the more effective activating groups[2] and has a relatively low steric demand. TMEDA was employed as an activating ligand in early metalation experiments, but did not appear to affect the outcome.
(10) In an exploratory investigation, the isopropyl group was introduced into a simple norbornenyl oxazoline analogue of **8**, i.e., 2-[bicyclo[2.2.1]hept-2'-en-1'-yl]-4,4-dimethyloxazoline, by bromination of the lithiated derivative followed by a coupling reaction of the resulting vinyl bromide with isopropyl zinc chloride catalyzed by dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II): Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.*, **1984**, *106*, 158-163. Although the 1-bromo derivative of **8** was readily prepared, the coupling reaction failed on this substrate, presumably because of steric hindrance.
(11) The intermediate **9** could be converted directly into **10** by treatment with acetone, but in only ca. 25% yield, presumably because of competing enolization.
(12) Hydrogenation of **12** over platinum black, for example, afforded mainly the isopropylidene derivative (retention of benzyl). The use of 10% palladium on carbon similarly afforded largely the isopropylidene product, but with hydrogenolysis of the benzyl group as well. Variable results were obtained with soluble hydrogenation catalysts.

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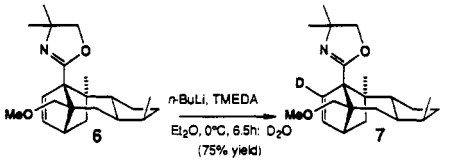
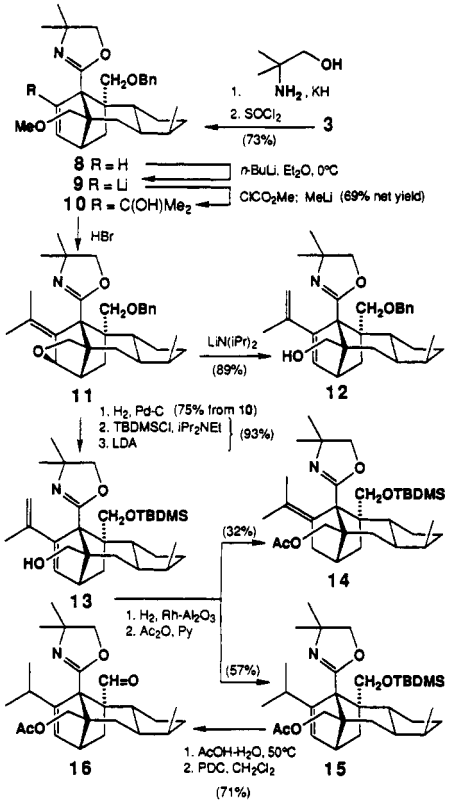
Scheme I



Scheme II



ration of the benzyl protecting group also occurred. The benzyl group was therefore replaced with *tert*-butyldimethylsilyl before the LDA treatment, affording **13**, but then hydrogenation over rhodium–alumina gave a 2:1 mixture of endocyclic and exocyclic alkenes. These were separated as their derived acetates **14** and **15**, respectively, and the latter converted into aldehyde **16** as indicated. The skeleton was now complete and all of the functional groups in this compound were at the same oxidation level as those in sordaricin (**1**), but all attempts to remove the oxazoline group from **16** or from selected precursors have so far failed.[13] Nevertheless, the strategy shows considerable promise and an examination of alternative pathways to **1** using more readily removed activating groups is in progress. Details of further studies that establish the scope of the metalation methodology will be published elsewhere.

Experimental Section[14]

2-[18′-(19′-Methoxy-14′,15′,16′-trinorsordaric-1′-enyl)]-4,4-dimethyloxazoline (6). A stirred solution of aldehyde **2** (26 mg) in acetone (2 mL) was treated dropwise with Jones' reagent until TLC indicated complete consumption of starting material. The excess of reagent was quenched with propan-2-ol, the filtered solution evaporated to dryness and extracted with EtOAc, and the resulting solution washed with brine and dried and solvent removed to leave a semicrystalline solid: ν_{max} 2650–3200 br, 1730 cm^{-1}; ^1H NMR δ 0.47 (d, 1 H, J = 12.4 Hz, H-4′α), 0.82 (d, 3 H, J = 6.8 Hz, 10′-Me), 1.25 (s, 3 H, 5′-Me), 2.54 (br t, 1 H, J = ~3 Hz, H-3′), 3.29 (s, 3 H, OMe), 3.44, 3.53 (ABd, 2 H, J = 9.0 Hz, CH_2OMe), 5.99 (d, 1 H, J = 5.6 Hz, H-1′), 6.34 (dd, J = 5.6, 3.4 Hz, H-2′). A portion of this material (17 mg) dissolved in benzene (2 mL) and thionyl chloride (40 μL) was heated at 70 °C for 4 h, the volatiles were removed, and the residue was dissolved in dichloromethane. 2-Amino-2-methyl-1-propanol (40 mg) was added, the mixture stirred under argon for 2 h and reduced to dryness, and then the residue extracted with Et_2O to give the desired amide. A solution of this product in benzene (2 mL) was treated with thionyl chloride (40 μL) and the solution stirred at 25 °C for 2 h. After dilution with ether and washing with dilute NaOH, the product was flash chromatographed with 7% EtOAc/hexane to afford oxazoline **6** (12 mg, 61% yield): ν_{max} 1645 cm^{-1}; ^1H NMR δ 0.49 (d, 1 H, J = 12.4 Hz, H-4′α), 0.82 (d, 1 H, J = 6.5 Hz, 10′-Me), 0.94 (s, 3 H, 5′-Me), 1.24, 1.28 (2 × s, 2 × 3 H, 4,4-diMe), 2.60 (m, 1 H, H-3′), 3.26 (s, 3 H, OMe), 3.28, 3.60 (ABd, 2 H, J = 8.7, CH_2OMe), 3.85 (s, 2 H, CH_2OC=N), 5.99 (d, 1 H, J = 5.9 Hz, H-1′), 6.29 (dd, 1 H, J = 5.9, 3.4, H-2′).

2-[18′-(2′-^2H-19′-Methoxy-14′,15′,16′-trinorsordaric-1′-enyl)]-4,4-dimethyloxazoline (7). To a stirred solution of oxazoline **6** (5.4 mg, 15.7 μmol) and TMEDA (40 μL) in ether (0.6 mL) at 0 °C under argon was added 1.6 M *n*-BuLi in hexane (0.20 mL, 320 μmol). The solution was stirred at 0 °C for 6.5 h and quenched with deuterium oxide (0.1 mL) and the product extracted into ether. Deuterium incorporation was estimated to be ca. 75%. ^1H NMR identical with that obtained for **6**, except for reduction of signal at δ 5.99 to 25% intensity, and signal at 6.29 simplified to a doublet (J = 3.4 Hz).

2-[18′-(17′-(Benzyloxy)-19′-methoxy-14′,15′,16′-trinorsordaric-1′-enyl)]-4,4-dimethyloxazoline (8). To a mixture of the ester **3** (200 mg, 0.487 mmol) and 2-amino-2-methyl-1-propanol (6 mL, 62.9 mmol) was added KH powder (200 mg, 4.99 mmol). The mixture was heated under argon in an oil bath at 150–160 °C for 5 h and then cooled and quenched with an excess of saturated NH_4Cl. Most of the water and amino alcohol were removed by distillation under reduced pressure. The residue was taken up in ether and washed with 1 N HCl, the aqueous layer being back-extracted with ether. The product was obtained as a yellow oil (228 mg) consisting of two products, amide and acid. These were not separated, but were dissolved in benzene (10 mL) and treated with thionyl chloride (0.6 mL, 8.3 mmol). The solution was stirred under argon for 1.5 h and then quenched with 10% NaOH. After dilution with H_2O, the mixture was extracted with ether to afford an oily mixture of the oxazoline **8** and the parent carboxylic acid. Chromatography on silica gel (2.5 × 16 cm) using 3:1 hexane/ether as eluant gave the oxazoline **8** (126 mg, 58%): $[\alpha]^{20}_D$ −52.8° (*c* 1.68). This was followed by the acid, which was treated sequentially with thionyl chloride and the aminopropanol to afford further amide and then oxazoline (31 mg, 15%) as above: ν_{max} 1645 cm^{-1}; ^1H NMR δ 0.58 (d, 1 H, J = 12.4 Hz, H-4′α), 0.86 (d, 1 H, J = 6.5 Hz, 10′-Me), 1.18, 1.20 (2 × s, 2 × 3 H, 4,4-diMe), 2.60 (m, 1 H, H-3′), 3.23 (s, 3 H, OMe), 3.17, 3.58 (ABd, 2 H, J = 8.7 Hz, CH_2OMe), 3.32 (ABd, 1 H, J = 9.4 Hz, CH_2OBn, upfield d obscured), 3.74, 3.79 (ABd, 2 H, CH_2OC=N), 4.40 (s, 2 H, OBn), 6.08 (d, 1 H, J = 5.9 Hz, H-1′), 6.29 (dd, 1 H, J = 5.9, 3.4, H-2′), 7.29 (m, 5 H, ArH); ^{13}C NMR δ 17.6, 27.1, 28.2, 28.4, 29.7, 32.1, 41.2, 41.3, 47.6, 49.4, 59.2, 60.0, 66.7, 66.9, 73.0, 75.9, 77.8, 78.0, 127.0, 127.2, 128.0, 131.8, 138.4, 139.2, 164.4; MS m/z 449 (M^+, 14), 404 (30), 358 (100). Anal. Calcd for $C_{29}H_{39}NO_3$: C, 77.47; H, 8.74. Found: C, 77.40; H, 8.55.

2-[18′-(17′-(Benzyloxy)-14′-hydroxy-19′-methoxysordaric-1′-enyl)]-4,4-dimethyloxazoline (10). To a solution of oxazoline **8** (323 mg, 0.72 mmol) in ether (5 mL) cooled to 0 °C under argon was added 1.6 M *n*-BuLi in hexane (0.5 mL, 0.80 mmol). The solution was stirred at 0 °C for 1 h 20 min and cooled to −45 °C (dry ice/PhCl bath), methyl chloroformate (62 μL, 0.80 mmol) added, and stirring at −45 °C continued for 0.25 h then at room temperature for 0.75 h; during this period a white precipitate formed. After the solution was cooled to 0 °C, MeLi in ether (1.5 M, 1.3 mL, 1.95 mmol) was injected into the reaction flask. The mixture was stirred at 0 °C for 80 min and at room temperature

(13) N-Methylation to activate the oxazoline group toward nucleophilic attack in **16** and selected precursors failed (cf. Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611–4624), as did direct hydrolysis (3 N HCl, reflux). Reduction of **8** with Li/NH_3/*t*-BuOH followed by hydrolysis afforded the debenzylated 18-carboxaldehyde, but the oxazoline group in **11** and later intermediates was resistant to reduction.

(14) For general directions see ref 5.

for an additional 40 min. While being cooled in an ice bath the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with ether. The mixture was washed with H_2O and brine. The product was dried under vacuum, again dissolved in dry ether (4 mL), and cooled to 0 °C under argon and further MeLi in ether (1.5 M, 1.0 mL, 1.5 mmol) added. The mixture was stirred at room temp for 1 h, cooled to 0 °C and quenched with saturated NH_4Cl solution. Chromatography on silica gel (2.5 × 17 cm) using 3:2 hexane/ether as eluant afforded recovered 8 (149 mg) followed by **10** (135 mg, 37%; 69% net): $[\alpha]^{20}_D$ −73.3° (*c* 2.06); ν_{max} 3300, 1640 cm^{-1}; ^1H NMR δ 0.78 (d, 3 H, *J* = 6.8 Hz, 10′-Me), 0.84 (d, 1 H, *J* = 12.7 Hz, H-4′α), 1.19, 1.28, 1.31, 1.35 (4 × s, 4 × 3 H, 4 × Me), 2.50 (t, 1 H, *J* = 3.7 Hz, H-3′), 3.25 (s, 3 H, OMe), 3.30, 3.55 (ABd, 2 H, *J* = 8.7 Hz, CH_2OMe), 3.66, 3.68 (ABd, 2 H, *J* = 9.6 Hz, CH_2OBn), 3.91 (s, 2 H, $CH_2OC{=}N$), 4.40, 4.43 (ABd, 2 H, *J* = 11.7 Hz, OCH_2Ph), 6.07 (d, 1 H, *J* = 3.7 Hz, H-2′), 7.28 (m, 5 H, ArH); ^{13}C NMR δ 17.7, 27.6, 27.7, 28.4, 29.5, 31.0, 31.5, 31.7, 32.4, 41.2, 43.2, 45.2, 50.5, 59.3, 63.8, 66.6, 68.0, 69.3, 73.0, 76.6, 78.3, 78.6, 127.0, 127.6, 128.0, 131.9, 139.3, 150.0, 166.9; MS *m/z* 507 (M^+,10), 492 (100), 489 (18). Anal. Calcd for $C_{32}H_{45}NO_4$: C, 75.70; H, 8.93. Found: C, 75.92; H, 8.83.

2-[18′-(17′-(Benzyloxy)-2′,19′-epoxysordaric-1′(14′)-enyl)]-4,4-dimethyloxazoline (11). A solution of the alcohol **10** (129 mg, 0.254 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. Gaseous HBr was bubbled through the solution for 3 min, and stirring at 0 °C was continued for 1.25 h. Argon was bubbled through the solution for a few min to remove most of the excess of HBr. The mixture was then quenched with 10% aqueous NaOH (10 mL) and stirred vigorously. The mixture was diluted with ether, and the organic phase was washed once with H_2O and once with brine. The cyclic ether **11** was obtained as an oil (127.5 mg): ν_{max} 1645 cm^{-1}; ^1H NMR δ 0.77 (d, 3 H, *J* = 6.8 Hz, 10′-Me), 0.96 (d, 1 H, *J* = 13.5 Hz, H-4′α), 1.25 (s, 6 H, 4,4-diMe), 1.52, 1.74 (2 × s, 2 × 3 H, $=CMe_2$), 2.15 (dd, 1 H, *J* = 2.8, 1.6 Hz, H-3′), 3.36, 3.86 (ABd, 2 H, *J* = 8.7 Hz, CH_2O), 3.48, 4.44 (ABd, 2 H, *J* = 8.2 Hz, CH_2OBn), 3.79, 3.81 (ABd, 2 H, *J* = 8.2 Hz, $CH_2OC{=}N$), 4.31, 4.53 (ABd, 2 H, *J* = 12.4 Hz, OCH_2Ph), 4.46 (d, 1 H, *J* = 2.8 Hz, H2′), 7.29 (m, 5 H, ArH).

2-[18-(17′-(Benzyloxy)-19′-hydroxysordaric-1′,14′-dienyl)]-4,4-dimethyloxazoline (12). A solution of ether **11** (10.3 mg, 22 μmol) in Et_2O (1.0 mL) was cannulated into a solution of LDA in Et_2O at 0 °C prepared from *n*-BuLi (1.6M in hexane, 0.13 mL, 0.21 mmol) and diisopropylamine (30 μL, 0.21 mmol) in Et_2O (0.5 mL). The mixture was stirred at room temp for 1.5 h, cooled in an ice bath, and quenched with saturated NH_4Cl (1.0 mL). The product was obtained as an oil (9.5 mg): ν_{max} 3260, 1645 cm^{-1}; ^1H NMR δ 0.79 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.25, 1.31 (2 × s, 2 × 3 H, 4,4-diMe), 1.84 (s, 3 H, =CMe), 2.25 (t, 1 H, *J* = 3.5 Hz, H-3′), 3.18, 4.13 (d, 1 H, *J* = 11.7 Hz, CH_2OH), 3.28, 3.94 (ABd, 2 H, *J* = 8.9 Hz, CH_2OBn), 3.97, 4.06 (ABd, 2 H, *J* = 8.4 Hz, $CH_2OC{=}N$), 4.33, 4.38 (ABd, 2 H, *J* = 12.1 Hz, OCH_2Ph), 4.81, 4.91 (2 × s, 2 H, $=CH_2$), 6.40 (d, *J* = 3.5 Hz, H-2′).

2-[18′-(2′,19′-Epoxy-17′-hydroxysordaric-1′(14′)-enyl)]-4,4-dimethyloxazoline. A solution of **11** (127.5 mg, 0.27 mmol) in absolute EtOH (3 mL) containing Pd on charcoal (10%, 300 mg) was stirred at room temperature under an atmosphere of H_2 (balloon) for 2.25 h. The mixture was filtered through Celite, concentrated in vacuo, and then chromatographed on silica gel (2.5 × 13 cm) using 1:1 hexane/ether as eluant to obtain pure carbinol (73.6 mg, 75%) as a crystalline solid: mp 145–148 °C; $[\alpha]^{20}_D$ −251.7° (*c* 1.09); ν_{max} 3240, 1645 cm^{-1}; ^1H NMR δ 0.39 (d, 1 H, *J* = 13.2 Hz, H-4′α), 0.77 (d, 3 H, 10′-Me), 1.30, 1.32 (2 × s, 2 × 3 H, 4,4-diMe), 1.78, 1.83 (2 × s, 2 × 3 H, $=CMe_2$), 3.22, 3.58 (ABd, 2 H, *J* = 11.5 Hz, CH_2OH), 3.49, 4.48 (ABd, 2 H, *J* = 8.2 Hz, CH_2OCH_3), 3.98, 4.02 (ABd, 2 H, *J* = 8.4 Hz, $CH_2OC{=}N$), 6.61 (br s, 1 H, OH); ^{13}C NMR δ 17.7 (Me), 28.4 (Me), 22.0 (Me), 24.1 (CH_2), 24.6 (CH_2), 26.5 (CH_2), 26.8 (Me), 29.4 (Me), 31.3 (CH_2), 32.4 (CH), 38.4 (CH), 42.3 (CH), 48.4 (CH), 53.3 (C), 60.4 (C), 63.7 (C), 64.3 (CH_2), 66.2 (C), 72.7 (CH_2), 79.2 (CH_2), 82.7 (CH), 132.2 (C), 133.9 (C), 168.1 (C); MS *m/z* 385 (M^+, 100), 354 (80); HRMS calcd for $C_{24}H_{35}NO_3$ 385.2617, found 385.2618.

2-[18′-[17′-[(*tert*-Butyldimethylsilyl)oxy]-19′-hydroxysordaric-1′,14′-dienyl]]-4,4-dimethyloxazoline (13). *tert*-Butyldimethylsilyl chloride (28 mg, 186 μmol) was added to a solution of the alcohol prepared above (38 mg, 99 μmol) and *N*-ethyldiisopropylamine (35 μL, 201 μmol) in DMF (1.3 mL). The mixture was stirred at room temperature under argon for 1 h and then quenched with an excess of saturated $NaHCO_3$. The mixture was diluted with ether and washed twice with H_2O and once with brine. The oily product (54 mg) was dried under high vacuum, dissolved in ether (0.5 mL) and cannulated into a solution of LDA in Et_2O (1.0 mL) at 0 °C prepared from *n*-BuLi in hexane (1.6 M, 0.60 mL, 0.96 mmol) and diisopropylamine (0.14 mL, 1.0 mmol). The mixture was stirred at room temperature for 0.75 h, cooled in an ice bath, and quenched with saturated NH_4Cl (2 mL). Following dilution with ether, the mixture was washed with H_2O and brine, dried, and concentrated to leave an oil. Chromatography on silica gel (1 × 12 cm) using 1:1 hexane/ether as eluant provided pure **13** (45.7 mg, 93%) as an oil: ν_{max} 3300, 1645 cm^{-1}; ^1H NMR δ −0.10, −0.06 (2 × s, 2 × 3 H, $SiMe_2$), 0.78 (d, 3 H, *J* = 7.0 Hz, 10′-Me), 0.76 (s, 9 H, Si-*t*-Bu), 1.24, 1.30 (2 × s, 2 × 3 H, 4,4-diMe), 1.80 (s, 3 H, =CMe), 2.22 (t, 1 H, *J* = 3.5 Hz, H-3′), 3.13, 4.13 (d, 1 H, *J* = 11.8 Hz, CH_2OH), 3.30, 4.19 (ABd, 2 H, *J* = 9.6 Hz, CH_2OSi), 3.96, 4.18 (ABd, 2 H, *J* = 8.4 Hz, $CH_2OC{=}N$), 4.81, 4.90 (2 × s, 2 H, $=CH_2$), 6.39 (d, *J* = 3.5 Hz, H-2′); ^{13}C NMR δ −5.4, 18.1, 18.2, 22.4, 25.9, 27.9, 28.1, 28.2, 28.0, 31.8, 32.0, 32.5, 41.0, 44.3, 48.1, 51.5, 65.6, 66.4, 67.5, 68.3, 59.1, 79.0, 111.2, 138.2, 140.4, 144.8, 167.0. Anal. Calcd for $C_{30}H_{49}NO_3Si$: C, 72.09; H, 9.88. Found: C, 72.31; H, 9.69.

2-[18′-[19′-Acetoxy-17′-[(*tert*-butyldimethylsilyl)oxy]sordaric-1′(14′)-enyl]]-4,4-dimethyloxazoline (14) and 2-[18′-[19′-Acetoxy-17′-[(*tert*-butyldimethylsilyl)oxy]sordaric-1′-enyl]]-4,4-dimethyloxazoline (15). A solution of the diene **13** (42.1 mg, 84.2 μmol) in THF (1 mL) containing 5% Rh on alumina (5%, 150 mg) was stirred under an atmosphere of H_2 (balloon) for 2.5 h. After filtration through Celite, the solvent was evaporated in vacuo and the residue dissolved in pyridine (1 mL) and treated with Ac_2O (0.5 mL) at 0 °C. The mixture was stirred overnight at room temperature, and then the excess of Ac_2O was destroyed by addition of saturated $NaHCO_3$ at 0 °C. The product was chromatographed on silica gel (1.5 × 19 cm) using 4:1 hexane/ether as eluant and afforded **15** (23.9 mg, 52%), a small mixed fraction (ca. 1:1) (6.1 mg, 13%), and then isomer **14** (12.2 mg, 27%).

14: ν_{max} 1740, 1645 cm^{-1}; ^1H NMR δ −0.05, −0.03 (2 × s, 2 × 3 H, $SiMe_2$), 0.74 (d, 3 H, *J* = 6.8 Hz, 10′-Me), 0.84 (s, 9 H, Si-Bu), 1.24, 1.25 (2 × s, 2 × 3 H, 4,4-diMe), 1.58, 1.61 (2 × s, 2 × 3 H, $=CMe_2$), 2.04 (s, 3 H, OAc), 3.58, 4.05 (ABd, 2 H, *J* = 9.6 Hz, CH_2OSi), 3.78, 3.80 (ABd, 2 H, *J* = 8.2 Hz, $CH_2OC{=}N$), 4.04, 4.17 (ABd, 2 H, *J* = 11.8 Hz, CH_2OAc).

15: ν_{max} 1740, 1645 cm^{-1}; ^1H NMR δ −0.05, −0.03 (2 × s, 2 × 3 H, $SiMe_2$), 0.75 (d, 3 H, *J* = 6.8 Hz, CH*Me*), 0.83 (s, 9 H, Si-*t*-Bu), 0.93, 1.05 (2 × d, 2 × 3 H, *J* = 6.8 Hz, $CHMe_2$), 1.24, 1.26 (2 × s, 2 × 3 H, 4,4-diMe), 2.01 (s, 3 H, OAc), 2.50 (t, 1 H, *J* = 3.4 Hz), 3.14, 4.03 (ABd, 2 H, *J* = 9.6 Hz, CH_2OSi), 3.79, 3.87 (ABd, 2 H, *J* = 7.9 Hz, $CH_2OC{=}N$), 4.26, 4.34 (ABd, 2 H, *J* = 10.7 Hz, CH_2OAc), 5.95 (d, 1 H, *J* = 3.4 Hz, H-2′); ^{13}C NMR δ −5.3, 18.0, 21.0, 21.1, 23.2, 26.0, 28.4, 28.7, 29.0, 31.1, 31.8, 32.8, 41.6, 44.6, 45.8, 51.5, 63.5, 65.5, 67.3, 68.8, 70.9, 78.1, 130.0, 149.8, 163.2.

2-[18′-(19′-Acetoxy-17′-oxosordaric-1′-enyl)]-4,4-dimethyloxazoline (16). A solution of the silyl ether **15** (23.5 mg, 43.2 μmol) in THF (1 mL), H_2O (0.83 mL), and AcOH (1.67 mL) was heated at 50 °C for 3 h. After the solution was cooled, the volatiles were removed in vacuo. The residue was taken up in ether and washed successively with saturated $NaHCO_3$ and brine. The crude alcohol (20 mg) was dissolved in CH_2Cl_2 (1 mL), powdered molecular sieves were added, and after stirring for a short time, PDC (150 mg) was added. After 2 h at room temperature ether was added and the mixture filtered through Celite. Following removal of the solvents in vacuo, the crude product was flash chromatographed on a column of silica gel (1.5 × 16 cm) using 5:1 hexane/ether as eluant to afford pure **16** (13.1 mg, 71%), as a crystalline solid: $[\alpha]^{20}_D$ −14.4° (*c* 0.66); ν_{max} 2740, 2710, 1740, 1725, 1655 cm^{-1}; ^1H NMR δ 0.78 (d, 3 H, 10′-Me), 0.94, 0.99 (2 × d, 2 × 3 H, *J* = 7.9 Hz, $CHMe_2$), 1.28 (s, 6 H, 4,4-diMe), 2.02 (s, 3 H, OAc), 2.69 (t, 1 H, *J* = 3.7 Hz, H-3′), 3.90, 3.91 (ABd, 2 H, *J* = 8.2 Hz, $CH_2OC{=}N$), 4.27, 4.29 (ABd, 2 H, *J* = 11.0 Hz, CH_2OAc), 6.03 (dd, 1 H, *J* = 3.7, 1.4 Hz, H-2′); ^{13}C NMR δ 17.5, 21.1, 21.4, 22.8, 26.4, 27.6, 28.5, 28.8 (2×), 29.1, 31.4, 32.3, 40.5, 41.5, 46.6, 59.4, 65.3, 65.5, 67.9, 70.0, 78.7, 130.7, 148.9, 162.3, 171.3, 204.9. MS *m/z* 427 (M^+, 40), 384 (2), 356 (70), 263 (100); HRMS calcd for $C_{26}H_{37}NO_4$ 427.2725, found 427.2725, calcd for $C_{24}H_{34}NO_4$ (M^+

– $COCH_3$) 384.2539 found 384.2538.

Registry No. 1, 51493-69-7; 2, 133349-39-0; 2 (18-acid), 135615-57-5; 3, 133372-88-0; 3 (acid), 135615-59-7; 3 (*N*-(1,1-dimethyl-2-hydroxyethyl)amide), 135615-58-6; 6, 135615-46-2; 7, 135615-47-3; 8, 135615-48-4; 8 (debenzylated 18-aldehyde), 133349-48-1; 9, 135615-49-5; 10, 135615-50-8; 11, 135615-51-9; 11 (17-alcohol), 135615-60-0; 11 (17-TBDMS ether), 135615-61-1; 12, 135615-52-0; 13, 135615-53-1; 14, 135615-54-2; 15, 135615-55-3; 15 (17-alcohol), 135615-62-2; 16, 135615-56-4.

Supplementary Material Available: Copies of ^1H NMR spectra for compounds 3, 6-8, 10-16, and unnumbered intermediates and ^{13}C NMR spectra for compounds 8, 10, 13, 15, and 16 (23 pages). Ordering information is given on any current masthead page.

Photoinitiated Addition of Diphenyl Diselenide to Acetylenes[1]

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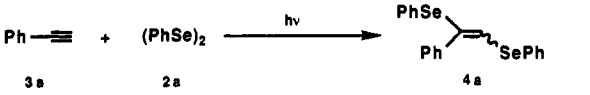
The addition to unsaturated compounds of heteroatom-centered radicals formed by the homolytic dissociation of a heteroatom–heteroatom bond is one of the most basic reactions in organic chemistry.[2] It is well known that, under UV irradiation, disulfides add to terminal alkynes via a radical chain mechanism.[3] However, similar additions of diselenides to acetylenes have not been reported except in cases where electron-deficient acetylenes like dimethyl acetylenedicarboxylate and methyl propiolate were reactants.[4] For example, the difficulty in realizing the addition of diphenyl diselenide to acetylenes is mainly due to the lower reactivity of the phenylseleno radical (1), compared to the phenylthio radical,[5] toward carbon–carbon multiple bonds and the tendency of phenylseleno radical to combine to re-form the starting diselenide, which results in a low concentration of 1 in the system.

Results and Discussion

The presence of high initial concentrations of acetylene and diphenyl diselenide and the use of an efficient means of generating the phenylseleno radical (1) are believed to be critical to the success of the addition. Thus, three factors were examined: (a) the light source, (b) the initial concentrations of the reactants, and (c) the reaction temperature. With regard to (a), near ultraviolet light (λ = 300–400 nm) was expected to be most suitable for the efficient generation of 1, because diphenyl diselenide (**2a**) exhibits its absorption maximum in the near ultraviolet (λ_{max} = 330 nm, $\epsilon_{max} = 10^3$).[5] Thus, upon irradiation with monochromatic UV light (365 nm), the addition of **2a** to phenylacetylene (**3a**) proceeded with high efficiency (entry 1, Table I). Sunlight was also effective (entry 2). However, upon irradiation with UV light, the yield of the 1,2-adduct **4a** decreased and elemental selenium was deposited. Addition did not take place in the dark (entry 3). It was convenient to irradiate with a tungsten lamp through a Pyrex (entry 4), so this was done routinely.

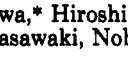
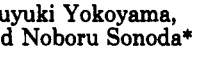
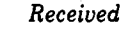
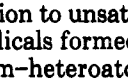
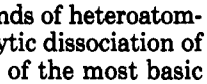
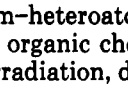
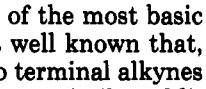
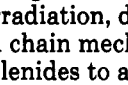
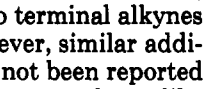
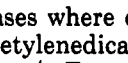
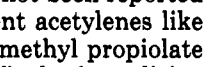
Table I. Addition of Diphenyl Diselenide to Phenylacetylene[a]



entry	radiation	solvent	T (°C)	time (h)	yield (%)	E/Z
1	hν (λ = 365 nm)	$CDCl_3$	25	10	80	86/14
2	sunlight (through Pyrex)	b	25	3	83	82/18
3	dark	b	40	24	c	
4	tungsten lamp (500 W, through Pyrex)	b	40	4	93	83/17

[a] Phenylacetylene (1 mmol), $(PhSe)_2$ (1 mmol). [b] In the absence of solvent. [c] No reaction.

Table II. Photoinitiated Addition of Diphenyl Diselenide to Acetylenes[a]

entry	substrate	conditions	product	yield (%)[b]	E/Z[c]
1		40 °C, 24 h[d]		83	82/18
2		40 °C, 24 h		91 (100)	95/5
3		40 °C, 24 h		81 (93)	73/27
4		40 °C, 24 h		73 (89)	28/72
4		40 °C, 24 h		69 (81)	95/5
6		70 °C, 24 h		18 (22)	90/10
7		40 °C, 0.5 h		87 (98)	17/83

[a] Acetylene (1 mmol), $(PhSe)_2$ (1 mmol), hν (tungsten lamp, 500 W, Pyrex), no solvent. [b] Isolated yield (NMR yield). [c] The E/Z ratio was determined by ^1H NMR. [d] $(n\text{-BuSe})_2$ (1 mmol) was used.

As to (b), reaction in the absence of solvent gave optimum results. In contrast, in the presence of solvent, longer reaction times were required to give high yields of product. As to (c), temperatures above 40 °C favored addition in the absence of solvent, because the diphenyl diselenide (mp 63 °C)/acetylene mixture becomes homogeneous above that temperature.

Representative results are shown in Table II. Quite high yields were obtained from a variety of acetylenes.[6] The sterochemistry of the adducts was determined from the results of NOE experiments[7] and the respective ^{77}Se NMR spectra.[8] The simple acetylenes **3a**, **3b**, **3c**, **3e**, and **3f** preferentially afforded the (*E*)-bis(phenylseleno)olefins **4a**, **4b**, **4c**, **4e**, and **4f**, respectively, whereas silylacetylene

(1) This work was first presented at the 56th Annual Meeting of Chemical Society of Japan, 1988 (April 4th).
(2) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973; Vol. II.
(3) Heiba, E. I.; Dessau, R. M. *J. Org. Chem.* **1967**, *32*, 3837.
(4) Back, T. G.; Krishna, M. V. *J. Org. Chem.* **1988**, *53*, 2533.
(5) It was reported that the rate constants for the addition of PhSe• to some vinyl monomers are smaller than those of PhS• by a factor of ~10–50. See: Ito, O. *J. Am. Chem. Soc.* **1983**, *105*, 850.
(6) The addition to such activated acetylenes as conjugated enyne **3g** was complete within 0.5 h, whereas longer reaction times were required for unactivated acetylenes (e.g., **3b**, **3c**, **3d**, **3e**, and **3f**).
(7) The stereochemistry was established unambiguously by an NOE experiment in which the vinyl singlet was enhanced upon irradiation of the signal due to the protons of the allylic methylene group.
(8) It is known that J_{Se-Se} of *vic*-bis(phenylseleno)olefins is in the range 2–25 Hz for *E* isomers and 77–117 Hz for *Z* isomers. See: (a) Johannsen, I.; Eggert, H. *J. Am. Chem. Soc.* **1984**, *106*, 1240. (b) Johannsen, I.; Henriksen, L.; Eggert, H. *J. Org. Chem.* **1986**, *51*, 1657.

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