Bicyclic Lactams as Chiral Homoenolate Equivalents: Synthesis of (−)-Penienone

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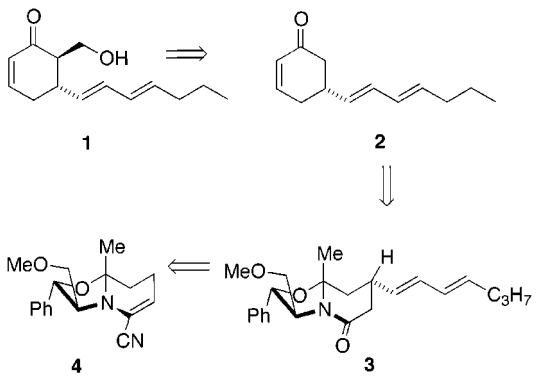
The synthesis of substituted chiral 2-cyclohexenones remains a challenging objective in organic chemistry. Often, when such compounds are needed as building blocks, they are derived from naturally occurring sources, such as carvone,[1] pinene,[2] pulegone,[3] or quinic acid.[4] In recent years, however, several methods for the synthesis of chiral 2-cyclohexenones in enantiomerically pure form have been reported.[5] Chiral 2-cyclohexenones with substituents in the 5-position are particularly difficult to construct stereoselectively. Indeed, very few methods are available which can be considered at all general. Among the most useful comes from the work of Sato,[6] which involves the addition of a cuprate to an optically active siloxy-substituted cyclohexenone. The latter is prepared from a chiral, nonracemic starting material. Also useful is the method of Takano, which involves the desymmetrization of Diels−Alder cycloadducts.[7]

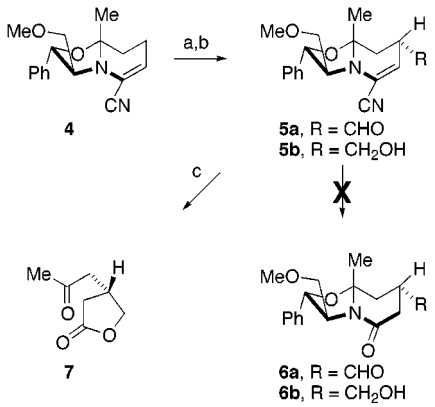
Bicyclic lactams have been shown over the past 10 years to be powerful tools for the construction of optically active carbocycles and heterocycles.[8] Recently, we have reported the utilization of α-cyanoenamines, prepared from chiral, nonracemic bicyclic lactams, as homoenolate equivalents, via a diastereoselective alkylation.[9] These alkylated lactams may then be employed for the preparation of a number of 5-substituted 2-cyclohexenones or functionalized piperidines.[10] Herein, we wish to report the further application of this methodology to the asymmetric synthesis of (−)-penienone (**1**), which was first isolated in 1997 and was shown to exhibit regulatory activities concerning plant growth.[11] Only one previous synthesis of penienone has been reported to date; an efficient synthesis (26% overall yield) by Sato using a cuprate addition to a siloxy-containing chiral 2-cyclohexenone.[6]

Retrosynthetically, penienone (**1**) was envisioned as arising from the 5-substituted 2-cylcohexenone **2** (Scheme 1). This compound, in enantiomerically pure form, would in turn be constructed from the reduction and hydrolysis of lactam **3**, which would be available from a homoenolate alkylation of the bicyclic lactam-derived cyanoenamine **4**. We have previously reported cyanoenamine **4**,[9] and it was efficiently prepared for this synthesis using the published method, from a commercially available bicyclic lactam.[12]

Scheme 1



Scheme 2[a]



[a] Conditions: (a) LiTMP, HMPA, THF, −78 °C; (b) ethereal formaldehyde, −78 °C; (c) THF/1 M HCl, 65 °C.

Initially, we planned to install the dienyl side chain of lactam **3** via a Horner−Emmons olefination, using an aldehyde (**6a**) formed from the direct formylation of cyanoenamine **4**. However, the γ-anion of the cyanoenamine proved to be unreactive toward a variety of standard formylating reagents, including DMF, various formates, and the pyridine-based "Meyers−Comins reagent".[13] Reasoning that the desired aldehyde **6a** might be obtained from oxidation of the corresponding alcohol **6b**, we attempted hydroxymethylation of the cyanoenamine. Treatment of cyanoenamine **4** with lithium tetramethylpiperidine (LiTMP) in the presence of HMPA at −78 °C resulted in a dark orange solution of the α,γ-delocalized anion. This anion was then treated with cold ethereal formaldehyde (Scheme 2).[14] Upon attempted acidic hydrolysis or silica gel purification of the crude product **5b**, the desired lactam **6b** was not observed.

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(2) Chapuis, C.; Brauchli, R.; Thommen, W. *Helv. Chim. Acta* **1993**, *76*, 535.
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(5) (a) Amino acid-catalyzed aldol-type reactions: Terishima, S.; Sato, S.; Koga, K. *Tetrahedron Lett.* **1979**, 3469. (b) Asymmetric Diels−Alder reactions: Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637. Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (c) Enantioselective deprotonations: O'Brien, P.; Poumelle, P. *Tetrahedron Lett.* **1996**, *37*, 8057.
(6) (a) Hareau, G. P−J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (b) Hareau, G.; Koiwa, M.; Hanazawa, T.; Sato, F. *Tetrahedron Lett.* **1999**, *40*, 7493.
(7) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948.
(8) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.
(9) Schwarz, J. B.; Devine, P. N.; Meyers, A. I. *Tetrahedron* **1997**, *53*, 8795.

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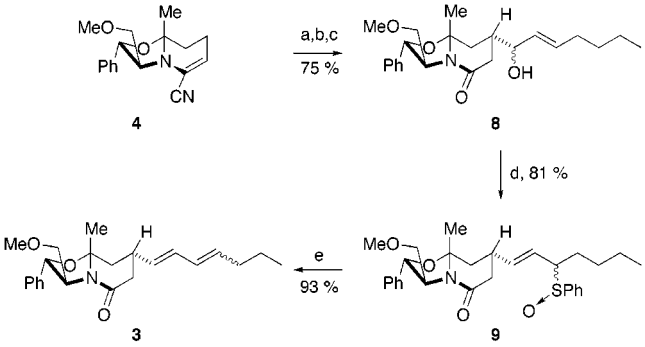
Scheme 3[a]



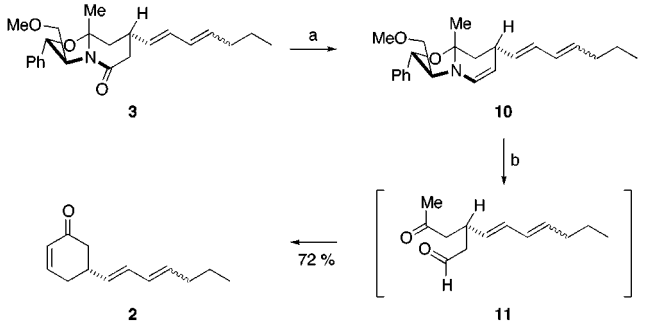
[a] Conditions: (a) LiTMP, HMPA, THF, −78 °C; (b) *trans*-2-heptenal, −78 °C; (c) THF/1 M HCl, 25 °C; (d) PhSCl, Et_3N, THF, 25 °C; (e) THF, 65 °C.

Instead, lactone **7** was isolated in very low yield. It was found that the lactone product **7** could be obtained in an improved 44% yield if the crude product **5b** was heated to reflux for 12 h in a 1:1 mixture of THF and 1 M HCl. It is unclear whether lactone formation is the result of initial hydrolysis of the cyanoenamine to lactam **6b** followed by rearrangement or if rearrangement proceeds directly from the hydroxymethylated cyanoenamine **5b**. Similar bicyclic lactams, bearing subtituents adjacent to the hydroxyl group, have previously been prepared in our group without competition from lactone formation.[9] At present, we choose not to suggest a possible pathway leading to **7** until more information becomes available.

On the basis of this unexpected difficulty in synthesizing the desired aldehyde **6a**, we sought an alternative method for the construction of the dienyl side chain. The method that eventually proved useful involved the direct installation of the entire seven carbon chain present in penienone (**1**) by treatment of the anion of cyanoenamine **4** with commercially available *trans*-2-heptenal (Scheme 3). Without purification, the crude product was hydrolyzed at room temperature, affording lactam **8** in good yield as the exclusively endo alkylated compound. The reaction furnished a readily separable 1.4:1 mixture of diastereomeric alcohols. The lack of selectivity at this position has been previously observed[9] and was of no concern in the present synthesis since the alcohol was to be eventually transformed into an olefin. Attempts to directly eliminate the hydroxyl group in conjugate fashion failed to deliver the desired diene **3** in good yield. Thus, transposition of the alkene was carried out by reaction of the alcohol **8** with benzene sulfenyl chloride. The resulting sulfenate ester underwent spontaneous [2,3]-sigmatropic rearrangement to give sulfoxide **9** directly. As dictated by the cyclic transition state of the rearrangement, the sulfoxides **9** were formed in a 1.4:1 ratio of two inseparable diastereomers, as observed by proton NMR integration. This ratio is identical to the ratio observed with the alcohols **8**. Indeed, when only a single hydroxyl isomer was used, a single sulfoxide diastereomer was obtained. Complete selectivity for the *trans*-alkene was also observed in all cases, again as a result of the cyclic transition state. Thermal elimination of sulfoxide **9** then produced the desired diene **3** in 93% yield as a 9.5:1 mixture of *E*,*E* and *E*,*Z* isomers. These isomers proved to be inseparable, so the completion of the synthesis was performed with the mixture of dienes.

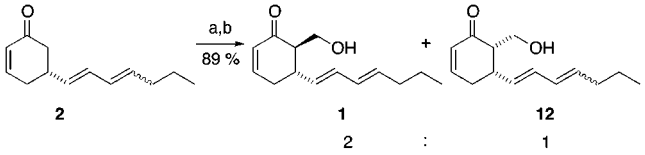
Lactam **3** was converted to the desired enone **2** using the previously developed protocol (Scheme 4).[9] Reduction

Scheme 4[a]



[a] Conditions: (a) DiBAL-H·*n*-BuLi, THF, −78 °C; (b) *p*-TsOH, THF/H_2O, Δ.

Scheme 5[a]



[a] Conditions: (a) LDA, THF, −78 °C; (b) ethereal formaldehyde, −78 °C.

of the lactam with the "ate" complex derived from DiBAL-H and *n*-BuLi afforded enamine **10**, which was subsequently treated with *p*-toluenesulfonic acid in a THF/water mixture. Hydrolysis of the enamine to keto aldehyde **11** was followed by intramolecular condensation to give enone **2** in 72% yield over the three-step sequence. The synthesis of **1** was completed by hydroxymethylation of enone **2** with formaldehyde[14] in 57% yield (Scheme 5). Interestingly, *epi*-penienone (**12**) was also formed in 32% yield. Attempts with a number of variations in the reaction conditions failed to significantly improve this 2:1 ratio. We noted that the undesired diastereomer **12** of the hydroxyenone can be epimerized using sodium or potassium carbonate in THF/water or methanol. In either case, epimerization afforded no better than a 1:1 mixture of the two compounds, along with some deformylated product, reaffirming the lack of induced stereocontrol in the hydroxymethylation reaction. The 9.5:1 *E*,*E* to *E*,*Z* diene mixture formed earlier upon sulfoxide elimination (Scheme 3), was readily purified at this point by simple crystallization, giving pure (−)-penienone (**1**). The compound thus obtained showed spectroscopic data identical to that reported by Kimura[11] for the original isolated compound.

In conclusion, the total asymmetric synthesis of penienone (**1**) has been achieved in 24% yield from a previ-

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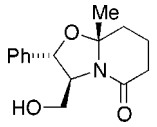
(11) Kimura, Y.; Mizuno, T.; Shimada, A. *Tetrahedron Lett.* **1997**, *38*, 469.
(12) The bicyclic 5,6-lactam is available from Aldrich and Ultrafine, U.K.



(13) Comins, D.; Meyers, A. I. *Synthesis* **1978**, *19*, 403.
(14) The formaldehyde solution was generated by predrying paraformaldehyde and cracking according to the method of Stork: Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114.

ously reported bicyclic lactam-derived starting material. The synthesis uses a cyanoenamine **4** derived from a chiral, nonracemic bicyclic lactam as a diastereoselective homoenolate equivalent to construct the cyclohexenone core of the molecule and to install the hydrocarbon side chain. In addition, a heretofore unobserved bicyclic lactam rearrangement was discovered, leading to the formation of a chiral, substituted lactone **7**.

Experimental Section

General Methods. Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Solvents were dried according to established procedures by distillation from an appropriate drying agent under an inert atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone ketyl under argon immediately prior to use. Reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been flame-dried. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM).

4-Acetonyltetrahydrofuran-2-one (7). To a solution containing 0.09 mL (0.528 mmol) of 2,2,6,6-tetramethylpiperidine (TMP) and 4 mL of THF at −78 °C was added 0.28 mL (0.528 mmol) of 1.86 M *n*-BuLi in hexanes and then 0.09 mL (0.528 mmol) of HMPA. The reaction mixture was allowed to stir for 15 min at −78 °C and then raised to 0 °C for 5 min. At the end of this time, the bright yellow solution was cooled to −78 °C and a solution containing 100 mg (0.352 mmol) of cyanoenamine **4**[9] and 1 mL of THF was added dropwise. The dark orange solution was stirred at −78 °C for 20 min, and an excess of ethereal formaldehyde[14] was added. The reaction mixture was allowed to stir at −78 °C for 2.0 h and was quenched by the addition of aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was taken up in 5 mL of THF. To this solution was added 5 mL of 1 M aqueous HCl, and the mixture was heated at reflux for 12 h. The THF was removed under reduced pressure, and the mixture was partitioned between CH_2Cl_2 and water. The phases were separated and the aqueous phase was further extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 44 mg (44%) of lactone **7** as a colorless oil: $[\alpha]^{23}_D$ −30.8 (*c* 1.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (dd, 1H, J = 17.7 and 7.8 Hz), 2.22 (s, 3H), 2.65−2.82 (m, 3H), 2.97−3.05 (m, 1H), 3.95 (dd, 1H, J = 9.3 and 6.6 Hz), and 4.58 (dd, 1H, J = 9.3 and 7.2 Hz); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 30.2, 30.8, 34.1, 46.6, 73.0, 176.6, and 206.0; IR (neat) 2917, 1774, 1711, 1173, and 1017 cm $^{-1}$; HRMS (*m*/*e*) calcd for $C_7H_{11}O_3$ (M + H^+) 143.1640, found 143.1635.

Lactam 8. To a solution containing 1.39 mL (8.23 mmol) of 2,2,6,6-tetramethylpiperidine (TMP) and 40 mL of THF at −78 °C was added 3.40 mL (8.23 mmol) of 2.40 M *n*-BuLi in hexanes and then 1.43 mL (8.23 mmol) of HMPA. The reaction mixture was allowed to stir for 15 min at −78 °C and then raised to 0 °C for 5 min. At the end of this time, the bright yellow solution was cooled to −78 °C and a solution containing 1.56 g (0.352 mmol) of cyanoenamine **4**[9] and 10 mL of THF was added dropwise. The dark orange solution was stirred at −78 °C for 20 min, and a solution containing 0.94 mL (7.15 mmol) of *trans*-2-heptenal and 5 mL of THF was added slowly. The reaction mixture was allowed to stir at −78 °C for 2.5 h and was quenched by the addition of aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was taken up in 20 mL of THF. To this solution was added 20 mL of 1 M aqueous HCl, and the mixture was allowed to stir at room temperature for 13 h. The THF was removed under reduced pressure, and the mixture was partitioned between EtOAc and water. The phases were separated, and the aqueous phase was further extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.60 g (75%) of lactam **8** as a 1.4:1 mixture of diastereomers.

High-R_f diastereomer (**8a**): 0.93 g (44%) as a colorless oil; $[\alpha]^{23}_D$ +26.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.0 Hz), 1.28−1.42 (m, 5H), 1.66 (s, 3H), 2.07−2.22 (m, 5H), 2.54 (t, 2H, J = 11.7 Hz), 3.42 (s, 3H), 3.65 (dd, 1H, J = 10.2 and 3.0 Hz), 3.85 (dd, 1H, J = 10.2 and 4.8 Hz), 3.95 (t, 1H, J = 6.6 Hz), 4.10 (ddd, 1H, J = 9.9, 5.1, and 3.3 Hz), 5.30 (d, 1H, J = 8.1 Hz), 5.49 (ddt, 1H, J = 15.3, 7.5, and 1.5 Hz), 5.57 (dt, 1H, J = 15.3 and 6.6 Hz), and 7.34−7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.3, 24.4, 31.2, 32.0, 34.0, 35.7, 38.1, 59.3, 63.2, 70.4, 76.0, 78.3, 91.7, 99.9, 126.6, 128.3, 128.5, 129.7, 134.8, 139.01, 160.9, and 168.9; IR (neat) 3400, 2922, 1627, 1455, 1394, and 1122 cm $^{-1}$; HRMS (*m*/*e*) calcd for $C_{23}H_{34}NO_4$ (M + H^+) 388.2488, found 388.2485.

Low-R_f diastereomer (**8b**): 0.66 g (31%) as a colorless oil: $[\alpha]^{23}_D$ +27.6 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.0 Hz), 1.28−1.44 (m, 5H), 1.65 (s, 3H), 1.69 (brs, 1H), 2.10 (q, 2H, J = 7.0 Hz), 2.17−2.29 (m, 2H), 2.35 (t, 1H, J = 10.5 Hz), 2.71 (dd, 1H, J = 17.4 and 5.7 Hz), 3.42 (s, 3H), 3.64 (dd, 1H, J = 10.2 and 3.0 Hz), 3.85 (dd, 1H, J = 10.2 and 5.1 Hz), 4.02 (t, 1H, J = 6.6 Hz), 4.10 (ddd, 1H, J = 7.2, 4.8, and 3.0 Hz), 5.30 (d, 1H, J = 7.8 Hz), 5.50 (ddt, 1H, J = 14.4, 7.8, and 1.5 Hz), 5.76 (dt, 1H, J = 15.6 and 6.6 Hz), and 7.34−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.3, 24.4, 31.2, 32.0, 33.5, 35.7, 38.3, 59.3, 63.2, 70.4, 76.1, 78.2, 93.6, 99.9, 126.3, 128.3, 128.5, 129.6, 135.1, 138.9, 166.9, and 169.1; IR (neat) 3406, 2927, 1629, 1458, 1399, and 1117 cm $^{-1}$; HRMS (*m*/*e*) calcd for $C_{23}H_{34}NO_4$ (M + H^+) 388.2488, found 388.2477.

Sulfoxide 9. To a solution containing 1.40 g (3.61 mmol) of lactam **8** and 30 mL of THF was added 0.75 mL (5.42 mmol) of triethylamine. The solution was allowed to stir at room temperature for 15 min, and 0.57 g (3.97 mmol) of freshly prepared benzene sulfenyl chloride was added dropwise. The reaction mixture was allowed to stir at room temperature for 1.5 h and then poured into brine and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography to give 1.45 g (81%) of sulfoxide **9** as a 1.4:1 mixture of inseparable diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88−0.93 (m, 6H), 1.23−1.46 (m, 10H), 1.56 (s, 3H major), 1.60 (s, 3H minor), 1.75−1.80 (m, 2H), 1.88−2.15 (m, 6H), 2.33−2.70 (m, 4H), 2.98 (ddd, 1H major, J = 8.7, 8.7, and 5.8 Hz), 3.22 (ddd, 1H minor, J = 10.4, 10.4, and 3.8 Hz), 3.34 (s, 3H major); 3.35 (s, 3H minor), 3.55−3.60 (m, 2H), 3.75−3.81 (m, 2H), 3.95−4.06 (m, 2H), 5.00−5.13 (m, 2H), 5.21−5.37 (m, 2H), 7.30−7.35 (m, 10H), and 7.45−7.54 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.0, 21.0, 22.4, 24.4, 24.5, 27.7, 27.8, 28.6, 28.7, 29.0, 29.1, 32.8, 32.9, 32.95, 33.0, 36.9, 37.0, 37.1, 37.2, 41.4, 41.6, 41.7, 41.8, 59.2, 63.2, 63.3, 67.8, 69.1, 69.4, 70.4, 78.1, 93.0, 93.1, 122.1, 122.2, 122.6, 122.7, 124.5, 125.5, 125.6, 128.3, 128.5, 128.6, 128.7, 130.7, 131.3, 131.4, 138.8, 138.9, 139.0, 139.1, 140.0, 141.2, 141.8, 141.9, 167.9, and 168.0; IR (neat) 2929, 1649, 1443, 1396, and 1043 cm $^{-1}$; HRMS (*m*/*e*) calcd for $C_{29}H_{38}NSO_4$ (M + H^+) 496.2522, found 496.2523.

Diene 3. A solution containing 1.45 g (2.93 mmol) of sulfoxide **9** and 75 mL of THF was heated at reflux for 24 h. The reaction mixture was cooled, poured into brine, and extracted with EtOAc. The combined organic extracts were washed with 10% aqueous KOH, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography to give 1.00 g (93%) as a colorless oil as a 9.5:1 *E*:*E* to *E*:*Z* diene mixture: $[\alpha]^{23}_D$ +51.7 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.2 Hz), 1.44 (app. sextet, 2H, J = 7.2 Hz), 1.67 (s, 3H), 1.68−1.80 (m, 1H), 2.11 (app. q, 2H, J = 7.2 Hz), 2.23−2.32 (m, 2H), 2.68−2.84 (m, 2H), 3.42 (s, 3H), 3.66 (dd, 1H, J = 10.2 and 3.0 Hz), 3.86 (dd, 1H, J = 10.2 and 5.1 Hz), 4.12 (ddd, 1H, J = 8.1, 5.1, and 3.0 Hz), 5.30 (d, 1H, J = 8.4 Hz), 5.53 (dd, 1H, 14.7 and 6.6 Hz), 5.72 (dt, 1H, J = 13.8 and 7.5 Hz), 6.02−6.15 (m, 2H), and 7.34−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.7, 24.8, 33.2, 34.9, 37.8, 42.2, 59.5, 63.5, 70.7, 78.4, 93.6, 126.8, 128.5, 128.7, 129.8, 130.5, 132.8, 134.8, 139.2, and 168.8; IR (neat) 2928, 1651, 1396, 1124, and 989 cm $^{-1}$; HRMS (*m*/*e*) calcd for $C_{23}H_{32}NSO_3$ (M + H^+) 370.2382, found 370.2378.

Enone 2. To a solution containing 1.35 mL (2.03 mmol) of 1.5 M DiBAL-H in toluene and 10 mL of THF at 0 °C was added 0.86 mL (2.03 mmol) of 2.35 M *n*-BuLi in hexanes. The solution was stirred at this temperature for 30 min, and a solution containing 75 mg (0.203 mmol) of lactam **3** and 1 mL of THF was added. The reaction mixture was allowed to warm to room temperature, stirred for 13 h, and quenched by the dropwise addition of MeOH. The solvent was removed under reduced pressure, and the residue was taken up in 1:1 hexanes−Et_2O, washed with 10% aqueous KOH, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give crude enamine **10**, which was used in the next step without further purification.

To a solution containing crude enamine 10, 3.4 mL of THF, and 3.4 mL of water was added 0.19 g (1.02 mmol) of *p*-toluenesulfonic acid. The reaction mixture was heated at reflux for 36 h and cooled, and the THF was removed under reduced pressure. The residue was taken up in Et_2O, washed with saturated aqueous $NaHCO_3$, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was subjected to silica gel chromatography, using a pentane/Et_2O mixture as the eluent to give 28 mg (72%) of enone **2** as a slightly volatile oil: $[\alpha]_D^{23}$ −10.8 (*c* 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.5 Hz), 1.42 (tq, 2H, J = 7.5 and 7.5 Hz), 2.04 (dt, 2H, J = 7.5 and 7.5 Hz), 2.12−2.36 (m, 2H), 2.42−2.58 (m, 2H), 2.74−2.87 (m, 1H), 5.53 (dd, 1H, J = 13.8 and 6.3 Hz), 5.65 (dt, 1H, J = 13.8 and 7.5 Hz), 5.94−6.09 (m, 3H), and 6.95 (ddd, 1H, J = 8.2, 5.3, and 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.6, 32.3, 34.9, 38.2, 44.2, 129.8, 129.9, 130.4, 132.9, 134.7, 149.9, and 199.1; IR (neat) 2958, 1682, 1386, 1248, and 984 cm^{-1}; HRMS (*m*/*e*) calcd for $C_{13}H_{19}O$ (M + H^+) 191.1436, found 191.1432.

Penienone (1). To a solution containing 20 μL (0.13 mmol) of diisopropylamine and 2 mL of THF at −78 °C was added 58 μL (0.13 mmol) of 2.35 M *n*-BuLi in hexanes. After the solution was stirred at this temperature for 30 min, a solution containing 15 mg (0.079 mmol) of enone **2** and 0.5 mL of THF was added slowly. The reaction mixture was allowed to stir at −78 °C for 45 min, and an excess of ethereal formaldehyde was added. After being stirred for 1 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The THF was removed under reduced pressure, and the residue was extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography using a pentane/Et_2O mixture as the eluent to give 10 mg (57%) of penienone (**1**) as a white solid, along with 5.6 mg (32%) of *epi*-penienone (**12**) as a colorless oil.

Penienone (**1**): mp: 60−62 °C (lit.[11] mp: 61−63 °C); $[\alpha]^{23}_D$ −42 (*c* 0.30, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.5 Hz), 1.45 (tq, 2H, J = 7.5 and 7.5 Hz), 2.09 (dt, 2H, J = 7.5 and 7.5 Hz), 2.37−2.49 (m, 2H), 2.66−2.78 (m, 1H), 2.94 (dd, 1H, J = 8.4 and 4.5 Hz), 3.77 (ddd, 1H, J = 11.7, 5.5, and 5.1 Hz), 3.95 (ddd, 1H, J = 11.7, 8.7, and 3.6 Hz), 5.49 (dd, 1H, J = 14.4 and 8.7 Hz), 5.71 (dt, 1H, J = 13.5 and 7.5 Hz), 6.00−6.19 (m, 3H), and 7.03 (ddd, 1H, J = 8.0, 5.0, and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.7, 33.3, 35.0, 40.4, 53.0, 61.0, 129.5, 129.7, 131.9, 132.8, 135.3, 150.1, and 202.4; IR (neat) 3463, 2958, 1672, 1391, and 990 cm^{-1}; HRMS (*m*/*e*) calcd for $C_{14}H_{21}O_2$ (M + H^+) 221.1542, found 221.1551.

epi-Penienone (12): $[\alpha]^{23}_D$ −84 (*c* 0.40, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3H, J = 7.4 Hz), 1.43 (tq, 2H, J = 7.4 and 7.4 Hz), 2.07 (dt, 2H, J = 7.4 and 7.4 Hz), 2.39−2.49 (m, 1H), 2.69 (dd, 9.5 and 2.8 Hz), 2.76−2.86 (m, 2H), 2.96−3.02 (m, 1H), 3.54 (ddd, 1H, J = 11.3, 9.6, and 5.4 Hz), 4.01 (ddd, 1H, J = 11.3, 8.1, and 2.0 Hz), 5.55 (dd, 1H, J = 14.6 and 8.8 Hz), 5.67 (dt, 1H, J = 14.6 and 6.4 Hz), 5.92−6.13 (m, 3H), and 6.97 (ddd, 1H, J = 9.3, 6.4, and 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.6, 32.9, 34.9, 40.8, 52.6, 62.5, 128.4, 129.7, 129.8, 133.2, 135.2, 148.6, and 202.3; IR (neat) 3436, 2944, 1669, 1388 and 992 cm^{-1}; HRMS (*m*/*e*) calcd for $C_{14}H_{21}O_2$ (M + H^+) 221.1542, found 221.1551.

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Supporting Information Available: Copies of ^{1}H or ^{13}C NMR spectra for all new compounds described in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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