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A Novel Cyclopentene Annulation Method Based on Conjugate Addition Reactions of α-Cyano Carbanion Species

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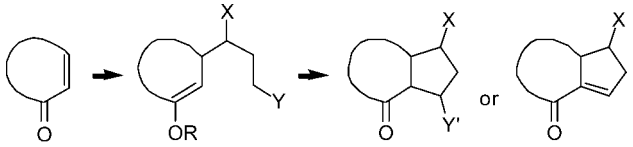
A new cyclopentene annulation method based on a conjugate addition reaction with 4-methoxybut-3-enenitrile was developed. Treatment of a cyclic enone with the potassium carbanion of the nitrile followed by acetic anhydride afforded an enol acetate, which underwent an HCl-mediated intramolecular cyclization reaction to yield a bicyclo[*n*.3.0]alkenone derivative in good yield. A lipase-mediated optical resolution of the annulation product provided a new chiral building block for steroids and other natural compounds.

Introduction

Annulation methods are of great importance for the construction of the polycyclic carbon frameworks widely found as the core structures of naturally occurring compounds.[1] The Robinson annulation reaction, one of the most useful methods for constructing a six-membered carbocycle, for example, has been employed in the synthesis of various terpenoids and steroids. There are also a number of annulation methods for the synthesis of five-membered carbocycles,[2] such as the Nazarov cyclization,[3] [3+2] cycloaddition reactions with trimethylenemethane[4] or oxyallyl cation species,[5] and the vinylcyclopropane-cyclopentene rearrangement.[6]

On the other hand, transformation of a cyclic α,β-unsaturated ketone by a conjugate addition reaction with a nucleophile containing an electrophilic moiety and subsequent intramolecular cyclization provides a general and flexible annulation method for the synthesis of five-membered carbocycles (Scheme 1).[7] A variety of nucleophiles, including organocopper reagents,[8] carbanions stabilized by an electron-withdrawing group,[9] and others,[10] have been developed for the synthesis of bicyclo[*n*.3.0]alkanone derivatives.



Scheme 1. Cyclopentane annulation through a conjugate addition reaction.

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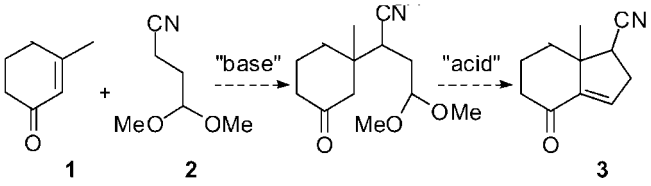
In the course of synthetic studies of natural products with polycyclic carbon frameworks, we became intrigued by a cyclopentene annulation reaction with a nitrile compound as a Michael donor (Scheme 2). We envisioned that the conjugate addition reaction of cycloalkenone **1** with the α-carbanion of nitrile **2**, followed by an intramolecular aldol condensation reaction, would yield bicyclic enone **3**, a useful precursor of the CD ring system of steroids. It is well known, however, that the α-carbanion generated from a simple alkanenitrile[11] usually undergoes a 1,2-addition reaction with an α,β-unsaturated ketone.



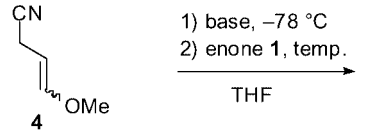
Scheme 2. Cyclopentene annulation with nitrile **2**.

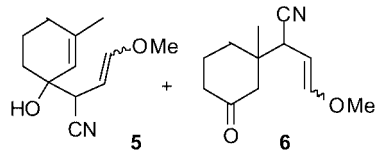
Results and Discussion

Indeed, an initial attempt at a conjugate addition reaction between enone **1** and the lithium carbanion generated from nitrile **2** merely resulted in formation of the 1,2 adduct. In the presence of HMPA at higher temperature, which would be expected to enhance the conjugate addition pathway under thermodynamic control, the reaction gave a complex mixture. Utilization of the corresponding organocopper species with or without TMSCl also failed to effect the desired transformation.

These results prompted us to design a new derivative of nitrile **2**, through the introduction of an appropriate functional group. Although 2-lithio-2-(phenylthio)acetonitrile[12] had been reported to undergo the conjugate ad-

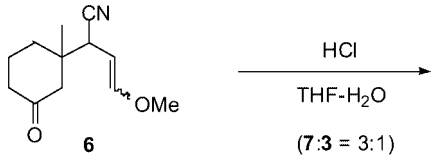
dition reactions with cycloalkenones, the carbanion generated from the corresponding α-(phenylthio) derivative of nitrile **2** exhibited no reactivity towards enone **1**. There are also several reports involving the use of an α-aryl nitrile[13,14] or a 2-alkoxy-3-alkenenitrile[15] as Michael donors. It is noteworthy that these conjugate addition reactions involve benzyl or allyl anion intermediates, which can be classified as a "soft nucleophiles".[16] Accordingly, we chose 4-methoxybut-3-enenitrile (**4**, Scheme 3), which possesses an enol ether moiety as a masked aldehyde, with a view to generating a soft allyl anion species. Nitrile **4** was readily prepared from nitrile **2** as a mixture of geometrical isomers by the reported $Ca(H_2PO_4)_2$-promoted flash thermolysis reaction.[17]

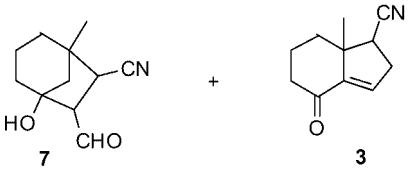


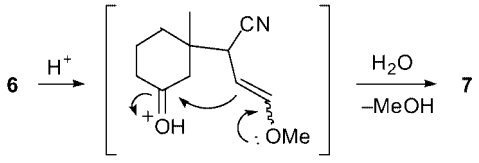


base	temp.	**5** (%)	**6** (%)	diastereomeric ratio of **6**
LDA	–78 °C	72	9	-
LDA	–78 ~ r.t.	0	92	57:43
KHMDS	–78 °C	0	100	81:19

Scheme 3. Conjugate addition reactions between enone **1** and nitrile **4**.







Scheme 4. Cyclization reaction of keto nitrile **6**.

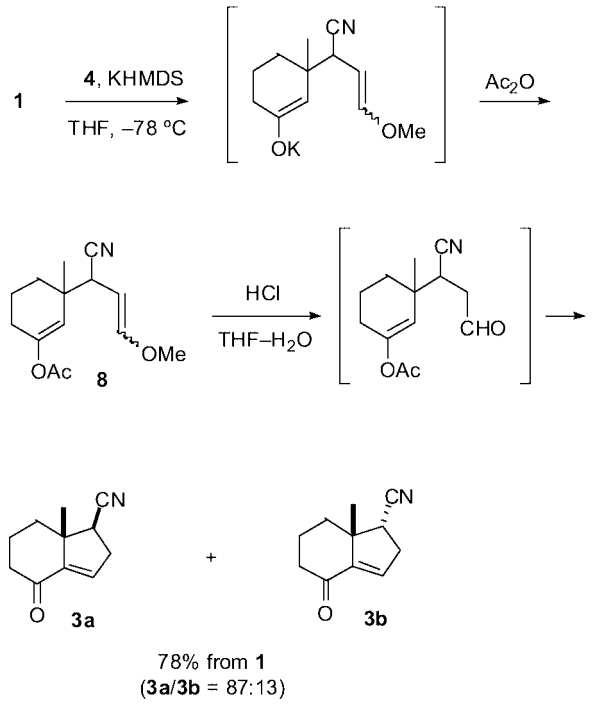
Treatment of enone **1** with the lithium carbanion of nitrile **4** was initially performed in THF at –78 °C for 1 h and provided the 1,2 adduct **5** in 72% yield along with 9% of the 1,4 adduct **6** (Scheme 3). On the other hand, alcohol **5** was not detected when the reaction mixture was allowed to warm up gradually to room temperature, the desired ketone **6** then being obtained in 92% yield. Because ketone **6** cannot be produced by the oxy-Cope rearrangement reaction of the lithium alkoxide of **5**, these results indicate that the kinetically favored 1,2-addition pathway had been superceded by a thermodynamically favored pathway at higher temperature. Interestingly, the use of potassium bis(trimethylsilyl)amide (KHMDS) instead of LDA effected selective formation of the conjugate addition product quantitatively even at –78 °C.

As ketone **6** was produced as a mixture of four stereoisomers including the (*E*) and (*Z*) isomers of the enol ether moiety, the diastereomeric ratio of the contiguous stereogenic centers was estimated after hydrogenation of the double bond. Whilst ketone **6** arising from the lithium carbanion of nitrile **4** was shown to be a 57:43 mixture of the diastereomers, the reaction promoted by KHMDS at lower temperature exhibited higher diastereoselectivity (*syn*/*anti* = 81:19). The *syn* relationship between the methyl group and the cyano group of the major product was confirmed after conversion into enone **3** (vide infra).

The stage was now set for the conversion of ketone **6** into bicyclic enone **3**. In the hope of achieving hydrolysis of the enol ether and subsequent intramolecular aldol condensation in one-pot style, ketone **6** was treated with dilute hydrochloric acid in THF (Scheme 4). The major product, however, was aldehyde **7** with a bicyclo[3.2.1]octane skeleton, arising from the intramolecular addition reaction of the enol ether moiety to the carbonyl group.

The result suggested that the keto group of **6** should be protected prior to hydrolysis of the enol ether, and so we designed enol acetate **8** (Scheme 5) as a new cyclization precursor in view of several advantageous features of the method: 1) enol esters are generally more stable than enol ethers towards acidic conditions, 2) the enol ester moiety of the resulting aldehyde should serve as a good nucleophile, and 3) ester **8** should be obtainable in one-pot fashion. Indeed, acetate **8** was prepared simply by adding acetic anhydride to a solution of the potassium enolate anion generated by the conjugate addition reaction between enone **1** and nitrile **4**. Treatment of the crude acetate **8** with hydrochloric acid afforded the desired enone in 78% overall yield and as an 87:13 mixture of diastereomers **3a** and **3b**. The stereochemistry of enone **3b** was determined by NOE measurements, which indicated a *syn* relationship between the angular methyl group and the α-methyne proton of the cyano group.

The scope of the cyclopentene annulation method was investigated by using several cycloalkenones as Michael acceptors (Table 1). While cyclohex-2-en-1-one and cyclohept-2-en-1-one afforded the corresponding bicyclic enones **9**



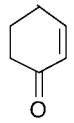
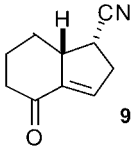
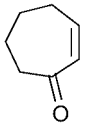
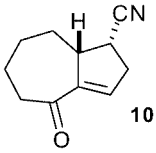
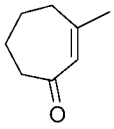
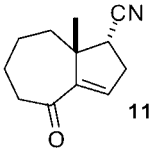
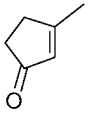
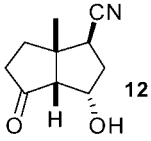
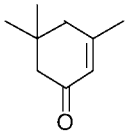
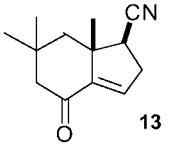
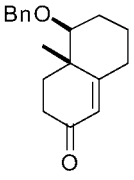
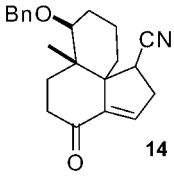
Scheme 5. Cyclopentene annulation via enol acetate **8**.

and **10**, respectively, in good yield, the diastereomeric ratios in the products were lower than that in enone **3** (Entries 1 and 2). Entries 3 and 4 indicated that use of a cycloalkenone with a methyl group at the β-position does not always provide high stereoselectivity. Accordingly, it is difficult to assume a common transition state model for these conjugate addition reactions at this stage. Use of a five-membered enone resulted in formation of β-hydroxy ketone **12**, because dehydration of **12** suffers from high strain energy of the enone possessing a bicyclo[3.3.0]octene skeleton (Entry 4).

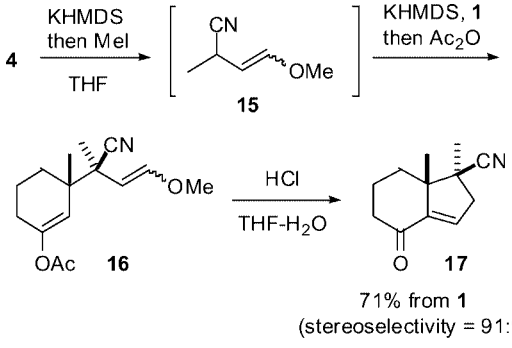
It is noteworthy that this annulation method is applicable to sterically demanding enones, as shown by Entries 5 and 6. These results prompted us to examine the construction of more highly hindered contiguous quaternary carbon atoms (Scheme 6). A solution of the carbanion generated from nitrile **4** and KHMDS was thus treated with methyl iodide to afford nitrile **15**, which was then subjected to the conjugate addition reaction with enone **1** in a one-pot operation. The subsequent cyclization reaction of the crude enol acetate **16** gave the desired enone **17** in 71% yield as a 91:9 mixture of the diastereomers. The new annulation method thus proved to be highly effective for the construction of an indenone skeleton containing two contiguous quaternary asymmetric carbon centers in a stereoselective manner.

Finally, optical resolution of enone **3a** was investigated with a view to providing a new chiral building block for the synthesis of steroids and other natural products. After several attempts, acetate **18** was chosen as a suitable substrate for this particular reaction, mediated by a lipase[18] (Scheme 7). It is noteworthy that the four-step synthesis of ester **18** from enone **1** needs no purification of the intermediates, which allowed us to perform the experiments on

Table 1. Cyclopentene annulation reactions of cyclic enones.

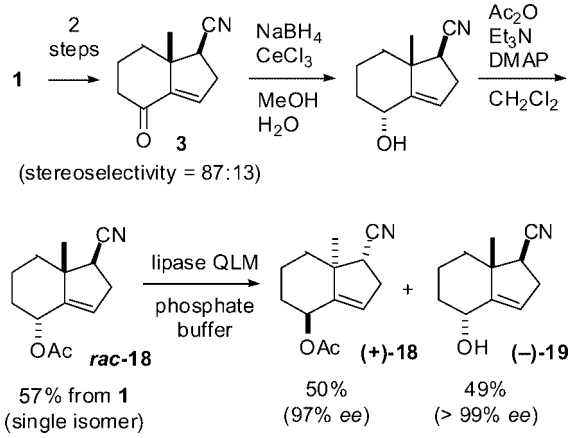
Entry	Enone	Product[a]	Yield[b]	Ratio[c]
1		 **9**	85%	60:40
2		 **10**	71%	72:28
3		 **11**	74%	53:47
4		 **12**	92%	68:24[d]:8
5		 **13**	88%	69:31
6		 **14**	68%	95: 5[e]

[a] The structure of the major diastereomer is depicted. [b] Isolated yield for two steps from the enone. [c] Diastereomeric ratio determined by ^{1}H NMR analysis. [d] Derived from the minor isomer of the conjugate addition step. [e] The stereochemistry of the product was not determined. Bn = benzyl.



Scheme 6. Stereoselective construction of contiguous quaternary asymmetric carbon centers.

multi-gram scales. The corresponding stereoisomer arising from enone **3b** was easily removed by recrystallization at the final step, and ester **18** was obtained in 57% overall yield. Treatment of the racemate with lipase QLM in a phosphate buffer solution afforded both ester (+)-**18** and alcohol (–)-β-**19** in almost optically pure forms.



Scheme 7. Optical resolution by use of a lipase.

Conclusions

In conclusion, we have developed a new cyclopentene annulation method based on a conjugate addition reaction with 4-methoxybut-3-enenitrile (**4**). Treatment of a cyclic enone with the potassium carbanion of nitrile **4** followed by acetic anhydride afforded an enol acetate, which underwent an intramolecular cyclization reaction to yield a bicyclo[*n*.3.0]alkenone derivative in good yield. This annulation method is highly useful for the construction of sterically hindered bicyclic carbon frameworks. A lipase-mediated optical resolution of the annulation product provided a new chiral building block that showed promise for the synthesis of steroids and other natural compounds.

Experimental Section

General Methods: All reactions were carried out under a positive pressure of dry argon. Tetrahydrofuran, pyridine, and triethylamine were distilled immediately before use. All other reagents and solvents were used as received. Flash chromatography was performed with 40–100 μm mesh (Kanto Chemical silica gel 60*N*, spherical, neutral). ^{1}H and ^{13}C NMR spectra were recorded with a JMN ECA-500 or a JMN AL-270 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. IR spectra were measured in a KBr cell with a Shimadzu spectrometer (FT-IR 8200A).

Typical Procedure for the Cyclopentene Annulation Reaction: A solution of 4-methoxybut-3-enenitrile (**4**, 5.34 g, 55.0 mmol) in tetrahydrofuran (25 mL) was added at –78 °C to a solution of potassium bis(trimethylsilyl)amide (11.0 g, 55.0 mmol) in tetrahydrofuran (200 mL). After the mixture had been stirred for 1 h at –78 °C, a solution of 3-methylcyclohex-2-en-1-one (**1**, 5.7 mL, 50.0 mmol) in tetrahydrofuran (25 mL) was added. After the mixture had been stirred for 1 h, acetic anhydride (9.4 mL, 100 mmol) was added, and the reaction mixture was allowed to warm slowly to –45 °C for 1 h. A saturated aqueous NH_4Cl solution was added and the mixture was separated. The aqueous layer was extracted with diethyl ether, and the combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure afforded crude enol acetate **8**, which was used for the next step without purification.

A mixture of the crude product, tetrahydrofuran (100 mL), and hydrochloric acid (3 M, 100 mL) was heated at 80 °C for 3 h. After cooling to room temperature, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure, followed by purification by silica gel column chromatography, afforded the desired enone (6.8 g, 78% from enone **1**) as an 87:13 mixture of diastereomers **3a** and **3b**. An analytically pure sample of **3a** was obtained by repeating the column chromatography.

Compound 3a: M.p. 38–39 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 1.53–1.68 (m, 1 H), 1.93–2.06 (m, 2 H), 2.06–2.16 (m, 1 H), 2.32–2.16 (m, 1 H), 2.55 (dtd, J = 17.3, 3.5, 1.6 Hz, 1 H), 2.90–2.70 (m, 2 H), 3.00 (dd, J = 10.7, 8.1 Hz, 1 H), 6.39 (t, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 19.97, 20.03, 33.49, 36.31, 39.36, 41.62, 48.94, 118.69, 131.89, 1146.89, 197.05 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1690, 1630 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{13}NO$ $[M]^+$ 175.0997; found 175.1003.

Compound 9a: This compound was obtained from cyclohex-2-en-1-one as the major diastereomer of the annulation product. M.p. 56–57 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.72–1.93 (m, 2 H), 2.09–2.38 (m, 3 H), 2.52–2.63 (m, 1 H), 2.87–2.81 (m, 2 H), 3.07–3.22 (m, 1 H), 3.50 (dt, J = 9.0, 3.9 Hz, 1 H), 6.61 (q, J = 2.7 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 23.14, 30.13, 35.18, 35.95, 39.79, 50.13, 120.60, 134.89, 142.44, 196.75 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1690, 1620 cm^{-1}. HRMS (EI) calcd. for $C_{10}H_{11}NO$ $[M]^+$ 161.0841; found 161.0847.

Compound 9b: This compound was obtained from cyclohex-2-en-1-one as the minor diastereomer of the annulation product. M.p. 74–75 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.36 (dq, J = 3.1, 12.7 Hz, 1 H), 1.90–1.70 (m, 1 H), 2.04–2.43 (m, 3 H), 2.49–2.63 (m, 1 H), 2.67–2.96 (m, 3 H), 3.13–3.28 (m, 1 H), 6.52–6.59 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 23.14, 30.13, 35.18, 35.95, 39.79, 50.13, 120.60, 134.89, 142.44, 196.75 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1680, 1620 cm^{-1}. HRMS (EI) calcd. for $C_{10}H_{11}NO$ $[M]^+$ 161.0841; found 161.0847.

Compound 10a: This compound was obtained from cyclohept-2-en-1-one as the major diastereomer of the annulation product. M.p. 84–85 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.33–1.57 (m, 4 H), 1.74–1.85 (m, 2 H), 1.86–2.10 (m, 3 H), 2.49 (ddd, J = 16.4, 12.8, 2.4 Hz, 1 H), 2.56–2.69 (m, 1 H), 2.73 (ddd, J = 17.9, 9.1, 2.6 Hz, 1 H), 2.83 (ddd, J = 17.9, 8.2, 2.6 Hz, 1 H), 2.98 (dd, J = 9.1, 8.2 Hz, 1 H), 6.42 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 24.63, 30.15, 33.12, 33.61, 35.81, 44.62, 46.32, 119.83, 137.56, 147.03, 199.03 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2240, 1680, 1610 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{13}NO$ $[M]^+$ 175.0997; found 175.0989.

Compound 10b: This compound was obtained from cyclohept-2-en-1-one as the minor diastereomer of the annulation product. M.p. 56–57 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33–1.49 (m, 2 H), 1.56–1.66 (m, 2 H), 1.99–2.11 (m, 2 H), 2.15–2.21 (m, 1 H), 2.48 (td, J = 13.0, 1.9 Hz, 1 H), 2.59–2.65 (m, 1 H), 2.72–2.80 (m, 2 H), 2.90 (ddt, J = 20.7, 11.6, 2.6 Hz, 1 H), 3.22–3.28 (m, 1 H), 6.67 (q, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 25.01,

30.02, 34.81, 35.90, 36.09, 44.86, 50.61, 121.36, 138.26, 146.22, 198.64 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1690, 1630 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{13}NO$ $[M]^+$ 175.0997; found 175.0988.

Compound 11a: This compound was obtained from 3-methylcyclohept-2-en-1-one as the major diastereomer of the annulation product. M.p. 87–88 °C. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.33–1.57 (m, 4 H, including a singlet at 1.36), 1.74–1.85 (m, 2 H), 1.86–2.10 (m, 3 H), 2.49 (ddd, J = 16.4, 12.8, 2.4 Hz, 1 H), 2.56–2.69 (m, 1 H), 2.73 (ddd, J = 17.9, 9.1, 2.6 Hz, 1 H), 2.83 (ddd, J = 17.9, 8.2, 2.6 Hz, 1 H), 2.98 (dd, J = 9.1, 8.2 Hz, 1 H), 6.42 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 23.41, 24.46, 25.68, 34.20, 37.34, 42.49, 43.40, 49.89, 119.46, 135.58, 151.85, 201.57 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2240, 1680, 1610 cm^{-1}. HRMS (EI) calcd. for $C_{12}H_{15}NO$ $[M]^+$ 189.1154; found 189.1141.

Compound 11b: This compound was obtained from 3-methylcyclohept-2-en-1-one as the minor diastereomer of the annulation product. M.p. 88–90 °C. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.40–1.58 (m, 5 H, including a singlet at 1.40), 1.71–2.09 (m, 4 H), 2.53–2.94 (m, 5 H), 6.70 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 20.09, 25.03, 25.17, 33.70, 41.51, 42.68, 44.09, 48.95, 119.41, 138.50, 150.04, 198.18 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2240, 1680, 1600 cm^{-1}. HRMS (EI) calcd. for $C_{12}H_{15}NO$ $[M]^+$ 189.1154; found 189.1124.

Compound 12: This compound was obtained from 3-methylcyclopent-2-en-1-one as the major diastereomer of the annulation product. M.p. 84–85 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.88 (dt, J = 13.7, 9.2 Hz, 1 H), 2.10 (dt, J = 13.7, 6.9 Hz, 1 H), 2.20 (dt, J = 5.2, 12.6 Hz, 1 H), 2.29 (ddd, J = 13.2, 6.3, 1.7 Hz, 1 H), 2.41–2.51 (m, 4 H), 3.14 (dd, J = 12.0, 6.9 Hz, 1 H), 4.56–4.61 (m, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.02, 33.48, 37.96, 39.80, 40.08, 50.07, 64.39, 71.90, 119.65, 217.62 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3490, 2240, 1740 cm^{-1}. HRMS (EI) calcd. for $C_{10}H_{13}NO_2$ $[M]^+$ 179.0946; found 179.0957.

Compound 13a: This compound was obtained from isophorone as the major diastereomer of the annulation product. M.p. 68–69 °C. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.08 (s, 3 H), 1.31 (s, 3 H), 1.74 (dd, J = 14.3, 1.3 Hz, 1 H), 1.82 (d, J = 14.3 Hz, 1 H), 2.20 (dd, J = 16.5, 1.3 Hz, 1 H), 2.32 (d, J = 16.5 Hz, 1 H), 2.73 (ddd, J = 17.6, 10.7, 2.1 Hz, 2 H), 2.83 (ddd, J = 17.6, 7.9, 3.3 Hz, 2 H), 3.00 (dd, J = 10.7, 7.9 Hz, 1 H), 6.54 (dd, J = 3.3, 2.1 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 25.35, 29.04, 31.42, 32.97, 34.32, 44.44, 47.45, 49.44, 52.21, 119.16, 133.55, 146.80, 196.80 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1690, 1620 cm^{-1}. HRMS (EI) calcd. for $C_{13}H_{17}NO$ $[M]^+$ 203.1310; found 203.1297.

Compound 13b: This compound was obtained from isophorone as the minor diastereomer of the annulation product. M.p. 81–82 °C. ^1H NMR (270 MHz, $CDCl_3$): δ = 1.04 (s, 3 H), 1.12 (s, 3 H), 1.25 (s, 3 H), 1.71 (d, J = 14.3 Hz, 1 H), 2.19–2.38 (m, 3 H), 2.81 (ddd, J = 18.4, 3.3, 1.5 Hz, 1 H), 2.96 (ddd, J = 18.4, 7.1, 2.2 Hz, 1 H), 3.11 (dd, J = 7.1, 1.5 Hz, 1 H), 6.60 (dd, J = 3.3, 2.2 Hz, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 29.41, 29.46, 31.59, 32.84, 35.45, 44.20, 46.54, 48.43, 52.17, 121.09, 133.79, 145.96, 197.28 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1690, 1620 cm^{-1}. HRMS (EI) calcd. for $C_{13}H_{17}NO$ $[M]^+$ 203.1310; found 203.1301.

Synthesis of Tricyclic Enone 14 by the Cyclopentene Annulation Reaction: The reaction was performed with a 93:7 mixture of (*Z*)- and (*E*)-4-methoxybut-3-enenitrile (**4**). A toluene solution of potassium bis(trimethylsilyl)amide (0.50 M, 0.48 mL, 0.24 mmol) was added at –78 °C to a solution of nitrile **4** (27 μL, 0.26 mmol) in tetrahydrofuran (0.6 mL). After the mixture had been stirred for 30 min at –78 °C, the bicyclic enone (54 mg, 0.20 mmol) in tetrahydrofuran (0.5 mL) was added. The mixture was warmed up to ca. –50 to –40 °C and was stirred for 1 h. Acetic anhydride (38 μL, 0.40 mmol) was added, and the mixture was stirred at –45 °C for 10 min and then at 0 °C for 10 min. A saturated aqueous $NaHCO_3$ solution was added, and the mixture was separated. The aqueous layer was extracted with diethyl ether, and the combined organic layer was dried with $MgSO_4$. Concentration under reduced pressure afforded the crude enol acetate, which was used without purification for the next step.

A mixture of the crude product, water (0.13 mL), and acetic acid (0.38 mL) was heated at 100 °C for 6 h. After cooling to room temperature, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was dried with $MgSO_4$. Concentration under reduced pressure followed by purification by silica gel column chromatography afforded the desired enone **14** (46 mg, 68% from the enone) as an 95:5 mixture of diastereomers. M.p. 81–82 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.32 (m, 2 H), 1.51–1.82 (m, 7 H, including a singlet at 1.56), 1.89–1.91 (m, 1 H), 2.35–2.45 (m, 2 H), 2.49–2.57 (m, 1 H), 2.72 (dd, J = 3.4, 18.9 Hz, 1 H), 2.92 (ddd, J = 2.3, 7.4, 18.9 Hz, 1 H), 3.31–3.34 (m, 1 H), 3.38 (d, J = 7.4 Hz, 1 H), 4.57 (d, J = 12.0 Hz, 1 H), 4.64 (d, J = 12.0 Hz, 1 H), 6.73 (dd, J = 2.3, 3.4 Hz, 1 H), 7.28, (m, 1 H), 7.34–7.38 (m, 2 H), 7.45–7.48 (m, 2 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 17.58, 20.22, 22.81, 30.91, 32.36, 35.18, 37.27, 37.46, 40.33, 54.97, 71.94, 80.96, 124.19, 127.53, 128.10, 128.24, 136.91, 138.34, 146.28, 197.15 ppm. IR (neat): $\tilde{\nu}$ = 2230, 1680, 1620, 1250, 1060, 740, 700 cm^{-1}. HRMS (EI) calcd. for $C_{22}H_{25}NO_2$ $[M]^+$ 335.1885; found 335.1918.

Synthesis of Enone 17 by the Cyclopentene Annulation Reaction: A toluene solution of potassium bis(trimethylsilyl)amide (0.50 M, 0.56 mL, 0.28 mmol) was added at –78 °C to a solution of 4-methoxybut-3-enenitrile (**4**, 27 mg, 0.28 mmol) in tetrahydrofuran (1.5 mL). After the mixture had been stirred for 30 min at –78 °C, methyl iodide (17 μL, 0.28 mmol) was added. After the mixture had been stirred for 30 min, a toluene solution of potassium bis(trimethylsilyl)amide (0.50 M, 0.44 mL, 0.22 mmol) was added, and the mixture was stirred for an additional 1 h. A solution of 3-methylcyclohex-2-en-1-one (**1**, 23 μL, 0.20 mmol) in tetrahydrofuran (0.5 mL) was added, and the reaction mixture was allowed to warm slowly to –45 °C for 1 h. Acetic anhydride (26 μL, 0.28 mmol) was added, and the mixture was stirred at –45 °C for 30 min. A saturated aqueous NH_4Cl solution was added, and the mixture was separated. The aqueous layer was extracted with diethyl ether, and the combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure afforded crude enol acetate **16**, which was used without purification for the next step.

A mixture of the crude product, tetrahydrofuran (0.4 mL), and hydrochloric acid (3 M, 0.4 mL) was heated at 80 °C for 1 h. After cooling to room temperature, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure followed by purification by silica gel column chromatography afforded the desired enone **17** (27 mg, 71% from enone **1**) as an 91:9 mixture of diastereomers. M.p. 68–69 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.38 (s, 3 H), 1.68–1.73 (m, 1 H), 1.79–1.87 (m, 1 H), 1.96–2.03 (m, 2 H), 2.16–2.25 (m, 1 H), 2.45 (dd, J = 17.8, 3.4 Hz, 1 H), 2.50–2.56 (m, 1 H), 3.10 (dd, J = 17.8, 2.0 Hz, 1 H), 6.45 (dd, J = 3.4, 2.0 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 20.02, 22.08, 23.17, 29.41, 39.65, 43.17, 45.69, 51.64, 122.77, 132.39, 145.44,

198.02 ppm. IR (neat): $\tilde{\nu}$ = 2240, 1680, 1620 cm^{-1}. HRMS (EI) calcd. for $C_{12}H_{15}NO$ $[M]^+$ 189.1154; found 189.1171.

Preparation of a Steroid Precursor on a Large Scale: A solution of 4-methoxybut-3-enenitrile (**4**, 8.88 g, 91.4 mmol) in tetrahydrofuran (30 mL) was added at –78 °C to a solution of potassium bis(trimethylsilyl)amide (19.2 g, 91.4 mmol) in tetrahydrofuran (260 mL). After the mixture had been stirred for 1 h at –78 °C, a solution of 3-methylcyclohex-2-en-1-one (**1**, 9.60 mL, 84.5 mmol) in tetrahydrofuran (50 mL) was added. After the mixture had been stirred for 1 h, acetic anhydride (13.0 mL, 138 mmol) was added, and the reaction mixture was allowed to warm slowly to –45 °C for 1 h. A saturated aqueous NH_4Cl solution was added, and the mixture was separated. The aqueous layer was extracted with diethyl ether, and the combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure afforded crude enol acetate **8**, which was used without purification for the next step.

A mixture of the crude product, tetrahydrofuran (140 mL), and hydrochloric acid (3 M, 140 mL) was heated at 80 °C for 3 h. After cooling to room temperature, the mixture was poured into a saturated aqueous $NaHCO_3$ solution. The mixture was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure afforded the crude enone as an 87:13 mixture of diastereomers **3a** and **3b**, which was used without purification for the next step.

Sodium borohydride (9.60 g, 254 mmol) was added at –55 °C to a mixture of the crude enone, cerium(III) chloride heptahydrate (8.88 g, 91.4 mmol), methanol (760 mL), and water (85 mL), and the mixture was gradually warmed up to 0 °C for 1 h. The mixture was diluted with water, and most of the methanol was removed under reduced pressure. Tartaric acid was added until the mixture becomes clear, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure afforded the crude alcohol as a mixture of diastereomers, which was used without purification for the next step.

Acetic anhydride (16.0 mL, 169 mmol) was added at 0 °C to a solution of the crude alcohol, 4-(dimethylamino)pyridine (1.0 g, 8.5 mmol), and triethylamine (35 mL, 254 mmol) in dichloromethane (280 mL). After the mixture had been stirred for 1 h, water was added and the mixture was separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure afforded the crude acetate, which was treated with charcoal in ether. Recrystallization from ethanol at –78 °C afforded acetate *rac*-**18** (7.0 g). The mother liquid was concentrated, and the residue was subjected to silica gel column chromatography followed by recrystallization from ethanol at –78 °C to give additional *rac*-**18** (3.6 g, 10.6 g in total, 57% from enone **1**) as a single diastereomer.

Lipase-Mediated Optical Resolution of Ester *rac*-18: A phosphate buffer solution was prepared from KH_2PO_4 (0.29 g), $Na_2HPO_4{\cdot}7H_2O$ (2.25 g), and water (50 mL). A mixture of ester *rac*-**18** (1.10 g, 5.0 mmol), lipase QLM (Meito Co., 250 mg), tetrahydrofuran (5 mL), and phosphate buffer solution (25 mL) was vigorously stirred for 2 days at 23 °C. After addition of an excess amount of sodium chloride with vigorous stirring, the mixture was filtered through a pad of celite, and the residue was washed with diethyl ether. The filtrate was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine and dried with $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography afforded (+)-**18** (543 mg, 50%) and (–)-**19** (438 mg, 49%). The enantiomeric purity of (+)-**18** (97% *ee*) was determined by HPLC analysis on a DAICEL CHIRALCEL AS-H column with 20% propan-2-ol in hexane as the eluent. The enantiomeric purity of (–)-**19** (>99%ee) was also determined by HPLC on a DAICEL CHIRALCEL OD-H column with the same eluent.

Compound (+)-18: M.p. 111–112 °C. $[\alpha]_D^{30}$ = +13.0 (*c* = 0.20, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21–1.31 (m, 5 H), 1.63–1.83 (m, 2 H), 1.93–1.98 (m, 1 H), 2.08–2.15 (m, 4 H), 2.60–2.75 (m, 2 H), 2.85 (t, *J* = 9.5 Hz, 1 H), 5.29–5.37 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 19.77, 21.09, 21.15, 32.65, 34.42, 39.94, 41.93, 50.04, 70.08, 116.67, 120.06, 146.38, 169.92 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2250, 1730, 1250 cm^{-1}. HRMS (EI) calcd. for $C_{13}H_{17}NO_2$ $[M]^+$ 219.1259; found 219.1281.

Compound (–)-19: Colorless oil. $[\alpha]_D^{30}$ = –21.2 (*c* = 0.20, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.14–1.27 (m, 5 H, including a singlet at 1.22), 1.51–1.70 (m, 2 H), 1.74–1.82 (m, 1 H), 1.91–1.98 (m, 1 H), 2.08–2.16 (m, 1 H), 2.60–2.77 (m, 2 H), 2.84 (dd, *J* = 10.4, 8.4 Hz, 1 H), 4.19–4.28 (m, 1 H), 5.44–5.46 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 19.95, 21.38, 34.41, 36.58, 40.16, 42.05, 49.85, 68.47, 115.98, 120.33, 151.39 ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3430, 2240, 820 cm^{-1}. HRMS (EI) calcd. for $C_{11}H_{15}NO$ $[M]^+$ 177.1154; found 177.1151.

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