Biomimetic Cyclization of Enamide-Containing Polyenes as a New Route to Azapolycycles†

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Enamide **4** was studied for its effectiveness as a polyene precursor in biomimetic cyclizations. While most conventional Lewis acids were poor cyclization promoters, $FeCl_3 \cdot 6H_2O$ initiated the conversion of **4** into tricycles **6** and **7** in excellent yield. The two isomeric products result from the cyclization of intermediate aldehyde **5** by either a chair or boat B-ring transition state. These results suggest that enamides may be incorporated into polyene precursors for the construction of larger azapolycycles such as azasteroids.

Introduction

Biomimetic polyene cyclizations provide an elegant and efficient means of preparing polycycles with stereochemical control at several ring fusion centers.[1] Carbocation-stabilizing (CS) auxiliaries, such as the isobutenyl[2] and fluoride[3] moieties, have recently been shown to enhance both the yield and rate of polyene cyclizations. These functionalities apparently mimic a putative function of cyclase enzymes by lowering the energy of the cationic transition state(s) and/or intermediate(s) in the process.[4] We now report an extension of this methodology to the efficient synthesis of the ABC ring nucleus of a 7-azasteroid by inclusion of an enamide within the polyene chain as the CS auxiliary. Since azasteroids have been shown to be both potent enzyme inhibitors[5] and difficult compounds to synthesize,[6] new routes for their construction are expected to be of great utility in the development of new chemotherapeutic agents.

A general approach to the construction of nitrogen-containing polycycles by biomimetic polyene cyclization methodology is depicted in Scheme 1. Incorporating an appropriately positioned enamide functionality into a polyene chain was expected to provide a dual electronic benefit during the cyclization process. First, we anticipated that initial cyclization would be enhanced by the increased nucleophilicity of the β-carbon center. Next, once partial cyclization had proceeded, we envisioned that the resulting *N*-acyliminium ion would function as a stabilized cation/initiation site for further cyclization processes. Because monocyclizations of transient iminium and *N*-acyliminium ions are well-known,[7] it seemed likely that the reaction, once initiated, would proceed as planned. To determine the possible utility of the enamide moiety as a CS auxiliary in biomimetic polyene cyclizations, the tricyclization of enamide **4** was examined.

Results and Discussion

Enamide **4** was constructed in nine steps from geraniol in a 33% overall yield, as outlined in Scheme 2. The acetal initiator was introduced by conversion of the Δ-6,7 olefin into the corresponding trisnoraldehyde **1** by *m*-CPBA epoxidation of TBDPS-protected geraniol, followed by periodic acid cleavage.[8] Subsequent Wittig homologation and reaction of the resulting enol ether with ethylene glycol/TsOH gave, after silyl deprotection, alcohol **2** (67% overall yield, three steps). The allylic alcohol was converted to amine **3** under mild conditions *via* conversion to the allylic phthalimide and subsequent phthalimide removal with methylamine.[9] Enamide **4** was prepared by a one-pot procedure involving condensation of allylic amine **3** with cyclohexanone (benzene, K_2CO_3, reflux for 12 h), followed by reaction of the resulting unisolated imine with acetyl chloride and pyridine.[10]

† This paper is dedicated to the memory of William Summer Johnson.

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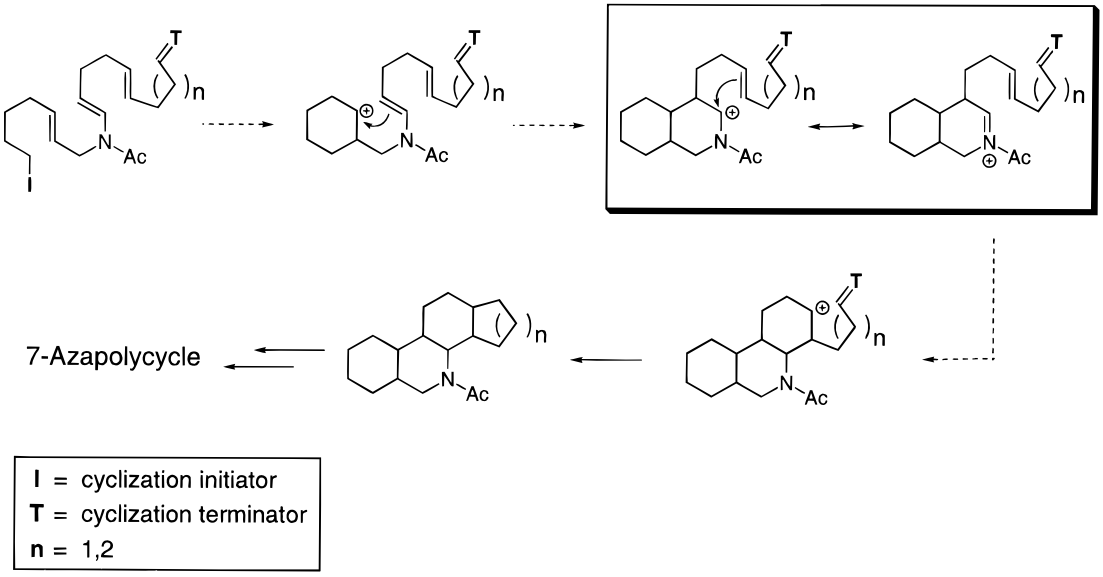
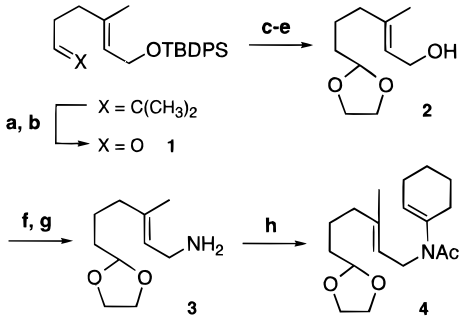
Scheme 1



Scheme 2. Synthesis of Enamide 4[a]



[a] (a) *m*-CPBA, $NaHCO_3$; (b) H_5IO_6, THF/H_2O; (c) $MeOCH{=}PPh_3$; (d) ethylene glycol, TsOH; (e) TBAF; (f) DIAD, PPh_3, phthalimide; (g) $MeNH_2$, EtOH, reflux; (h) cyclohexanone, benzene, reflux; followed by AcCl, pyridine.

To determine conditions for the cyclization of enamide **4**, small-scale (3−5 mg) cyclization studies were performed. Reactions with standard Lewis acid promoters, such as $SnCl_4$, $TiCl_4$, $EtAlCl_2$, and Me_2AlCl, at several different temperatures resulted in either no reaction or decomposition of the starting material (Table 1). $BF_3{\cdot}Et_2O$ was a more effective cyclization promoter, yielding a small (18%) amount of cyclic product, with the remaining material consisting of unreacted polyene and aldehyde **5** which results from Lewis acid promoted acetal hydrolysis. We attribute these results to strong coordination of the metals to the amide functionality of **4**, which inhibits the ability of the nitrogen to participate in the cyclization process. In contrast, enamide **4** was effectively cyclized with the use of the iron-based Lewis acid $FeCl_3{\cdot}6H_2O$.

A more detailed examination of the $FeCl_3{\cdot}6H_2O$-promoted cyclization of enamide **4** showed that the reaction is sensitive to small changes in reaction conditions. Efficient cyclization is only achieved at higher temperatures; thus, reaction of **4** with $FeCl_3{\cdot}6H_2O$ at 0 °C resulted in no reaction, even with prolonged (6 h) reaction times (Table 1). However, after the solution was warmed to room temperature, rapid cyclization proceeded within 1 h to yield up to 95% cyclic products. GLC analysis of preparative-scale reaction mixtures revealed complete consumption of starting material and the presence of a 5.7:1 mixture of two new components with retention times approximately 1 min shorter than that of enamide **4**. ^1H NMR analysis (500 MHz NMR COSY) of the purified components established that these major products are the *trans-anti* and *trans-syn* tricycles (**6** and **7**, respectively, Scheme 3) resulting from either a chair or boat transition state for B-ring formation upon attack by the cyclohexene enamide terminator.

Table 1. Cyclization Study of Enamide 4, Using Several Different Lewis Acids

Lewis acid[a]	equiv	temp (°C)	result[b]
$SnCl_4$	5	−40	no reaction
$SnCl_4$	5	0	<7% cyclization[c]
$SnCl_4$	5	23	decomposition[d]
$TiCl_4$	6	−78	no reaction
$TiCl_4$	6	0	no reaction
$TiCl_4$	6	23	decomposition[d]
$EtAlCl_2$	5	−78	decomposition[e]
Me_2AlCl	5	−78	no reaction
Me_2AlCl	5	0	no reaction
Me_2AlCl	5	23	no reaction
$BF_3{\cdot}Et_2O$	5	−78	no reaction
$BF_3{\cdot}Et_2O$	5	23	<20% cyclization[f]
$FeCl_3{\cdot}6H_2O$	3.5	0	no reaction
$FeCl_3{\cdot}6H_2O$	3.5	23	84% cyclization

[a] All reaction were performed under an inert atmosphere in anhydrous solvent. [b] GLC yield. [c] Composition: 6% **6** and **7**, 6% enamide **4**, 11% aldehyde **5**, remaining mass consists of monocyclic material and unidentified decomposition products. [d] No starting material recovered. [e] 20% enamide **4** remained. [f] Composition: 18% **6** and **7**, 60% enamide **4**, 16% aldehyde **5**.

Changes in both the amount of Lewis acid present and type of solvent used had a pronounced effect on the outcome of the reaction (Tables 2 and 3, respectively). Excess Lewis acid was required for efficient cyclization to proceed; on the basis of these findings, 3.5 equiv of $FeCl_3{\cdot}6H_2O$ was used for subsequent cyclization studies. As observed with other reactions involving the use of $FeCl_3$,[11] CH_2Cl_2 was found to be the best solvent for the cyclization of enamide **4** (Table 3). In contrast, coordinating solvents (e.g., THF) strongly inhibited the cyclization process, resulting in almost complete recovery of starting material. The use of benzene and acetonitrile resulted in a complex mixture of materials that has been

Scheme 3. Proposed Pathway for $FeCl_3 \cdot 6H_2O$-Promoted Cyclization of 4

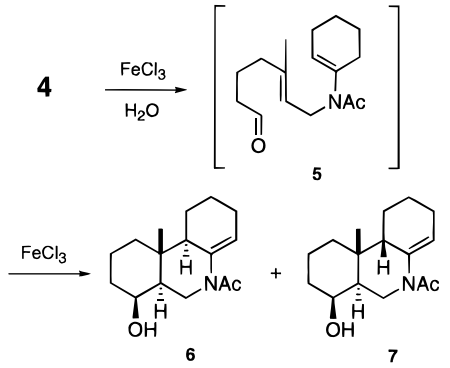


Table 2. Effect of Increasing Amount of $FeCl_3 \cdot 6H_2O$ on the Cyclization of 4[a]

equiv of $FeCl_3 \cdot 6H_2O$	tricycles **6** and **7** (%)[b]	enamide **4** (%)	aldehyde **5** (%)
1.0	4	89	7
2.0	20	1	61[c]
3.5	83	0	5[c]
7.0	67	2	7[c]

[a] Reaction conditions: 2−3 mg of **4** in CH_2Cl_2 (3 mM), rt for 2 h. [b] GLC yield. [c] Remaining mass consists of unidentified cyclic material and decomposition products.

Table 3. Effect of Different Solvents on the $FeCl_3 \cdot 6H_2O$-Promoted Cyclization of 4[a]

solvent	tricycles **6** and **7** (%)[b]	enamide **4** (%)	aldehyde **5** (%)
benzene	12	7	25[c]
acetonitrile	7	4	28[c]
tetrahydrofuran	1	96	3
methanol	0	72	24
methylene chloride	83	0	5

[a] Reaction conditions: 2−3 mg of **4** (3 mM), 3.5 equiv of $FeCl_3 \cdot 6H_2O$, rt for 2 h. [b] GLC yield. [c] Remaining mass consists of unidentified cyclic material and decomposition products.

tentatively assigned as monocyclic and polymeric products (determined by ^1H NMR analysis of the crude reaction mixture).

Analysis of several crude reaction mixtures showed the presence of aldehyde **5** resulting from hydrolysis of the acetal functionality of enamide **4**. This result, in addition to the observed exclusive recovery of C-4 hydroxy (steroid numbering) azapolycycles, prompted us to establish that formation of **5** is a prerequisite for cyclization (Scheme 3). If aldehyde **5** is a true intermediate in the reaction, one would expect that $FeCl_3$-promoted cyclization of this material would also yield polycycles **6** and **7** and that the presence of water is essential for the initial acetal hydrolysis.

An examination of the effect of water on the cyclization process showed that an optimum water content was necessary for efficient cyclization (Figure 1).[12] In sharp contrast to conventional Lewis acid promoted transformations which require the rigorous exclusion of moisture,

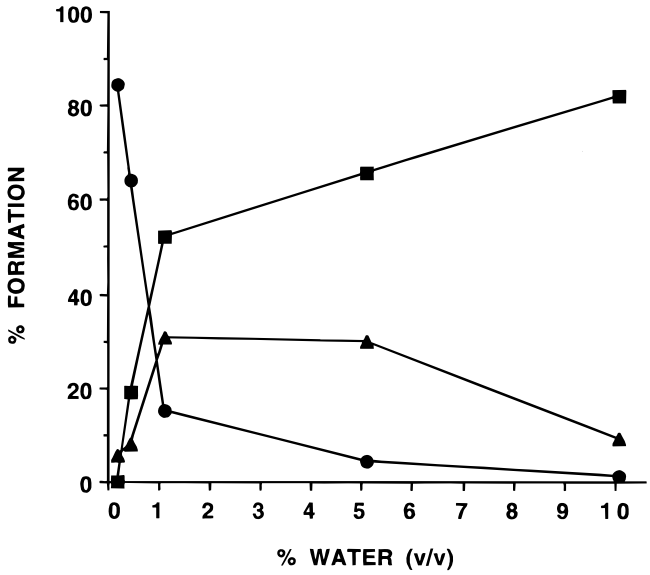


Figure 1. Effect of water content (v/v) on the cyclization of enamide **4**: ■, enamide **4**; ●, tricycles **6** and **7**; ▲, aldehyde **5**. Reaction conditions: 2−3 mg of **4** in CH_2Cl_2 (3 mM), rt for 2 h.

the reaction of **4** with $FeCl_3$ containing 0.1% (v/v) water provided azapolycycles **6** and **7**, with negligible amounts of starting material and aldehyde remaining. Conversely, under anhydrous conditions a complex mixture of unidentified cyclic and decomposition products was obtained, whereas addition of more water (1−5%) led to an accumulation of aldehyde and a decrease in cyclization products. The latter is most likely due to competitive complexation of $FeCl_3$ by water, resulting in a less active cyclization promoter. Thus, formation of the C-4 hydroxy tricycles is the result of a two-step sequence, acetal deprotection followed by Lewis acid activation of the corresponding aldehyde derivative of **4** (Scheme 3). This conclusion was supported by the observed efficient cyclization of aldehyde **5** (obtained by deprotection with pyridinium *p*-toluenesulfonate) to azapolycycles **6** and **7** by reaction with $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 at room temperature. The ratio of the products formed was identical to that obtained in the reaction of **4** with $FeCl_3 \cdot 6H_2O$, supporting the likelihood that **5** is a true intermediate in this process.

Conclusion

The preparation of azapolycycles by biomimetic polyene cyclization methodology has been demonstrated with the efficient cyclization of **4** by $FeCl_3 \cdot 6H_2O$. The reaction is selective, yielding a mixture of 4-hydroxy-7-aza (steroid numbering) tricycles **6** and **7** that results from initial hydrolysis of the acetal functionality followed by cyclization of the corresponding aldehyde. These results suggest that other azapolycycles, such as azasteroids, may be prepared by similar methodology with appropriate positioning of the enamide functionality within a polyene precursor chain. The application of this chemistry to higher-order cyclizations is currently under investigation.

Experimental Section

General Methods. Unless otherwise stated, all chemicals obtained from commercial sources were used without further purification. THF was distilled from benzophenone sodium ketyl, Et_3N and C_5H_5N were distilled from KOH, and AcCl was

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distilled from PCl_5. $CH_3OCH_2PPh_3Cl$ was recrystallized from CH_2Cl_2/hexane and dried *in vacuo* overnight prior to use. Routine ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent. Proton δ and J assignments of cyclic products **6** and **7** were based on 500 MHz COSY studies using a standard pulse experiment. Flash chromatography was performed using silica gel 60 (230−400 mesh, EM Science). Gas−liquid chromatography was performed using a DB5-HT 30 m capillary column (J & W Scientific), and retention times (t_R) are given in minutes. Elemental analyses were performed by Desert Analytics Laboratory, Tucson, AZ.

1-((*tert*-Butyldiphenylsilyl)oxy)-3-methyl-7-methoxy-2(*E*),6(*E*/*Z*)-heptadiene. To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (3.9 g, 11.4 mmol) in 50 mL of THF at −78 °C was added 7.2 mL of *n*-BuLi (1.6 M in hexanes, 11.5 mmol). After 15 min of stirring, the temperature was raised to 0 °C and the reaction mixture was stirred for 1 h, after which time a red solution was obtained. The reaction was cooled to −78 °C, and trisnoraldehyde **1** (2.8 g, 7.7 mmol, prepared as previously described)[8] dissolved in 10 mL of THF was added dropwise. The solution was stirred an additional 1 h and quenched with 60 mL of H_2O. The aqueous layer was extracted three times with 60 mL of hexanes, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Cold hexane (20 mL) was added to precipitate triphenylphosphine oxide, which was removed by filtration. The filtrate was concentrated *in vacuo*, and the resulting oil was chromatographed using EtOAc/hexanes (5:95) as the eluent to yield 2.6 g of the enol ether (6.6 mmol, 86%, 6(*Z*):6(*E*) = 53:47): MS *m*/*z* (rel intensity) 394.2 (0.34), 337.1 (20.9), 213.2 (16.3), 199.2 (100), 183.2 (10.4), 81.0 (9.4), 153.1 (11.4), 107.1 (10.5), 71.2 (24.5); IR (neat) cm^{-1} 3112, 2960, 1658, 1432, 1110, 1054; ^1H NMR δ 1.06 (s, 9 H), 1.45 (s, 3 H), 2.01−2.12 (m, 4 H), 3.49 (s, OMe(*E*)), 3.57 (s, OMe(*Z*)), 4.24 (d, 2 H, J = 6 Hz), 4.32 (m, 6(*Z*)), 4.72 (m, 6(*E*)), 5.39 (t, 1 H, J = 7 Hz), 5.86 (d, 7(*Z*), J = 6 Hz), 6.30 (d, 7(*E*), J = 12 Hz), 7.40 (m, 6 H), 7.68 (m, 4 H); ^{13}C NMR δ 16.25, 19.18, 26.88, 39.40, 40.69, 55.85, 61.14, 104.57, 124.23, 124.51, 127.51, 129.56, 134.29, 136.61, 146.11, 147.20.

1-((*tert*-Butyldiphenylsilyl)oxy)-3-methyl-7,7-(ethylenedioxy)-2(*E*)-heptene. To a solution of 1-((*tert*-butyldiphenylsilyl)oxy)-3-methyl-7-methoxy-2(*E*),6(*E*/*Z*)-heptadiene (1.3 g, 3.3 mmol) in 150 mL of dry benzene were added 3.7 mL of ethylene glycol (66.0 mmol) and a catalytic amount of TsOH. The reaction was stirred vigorously and refluxed for 5 h. After the addition of 100 mL of H_2O, the aqueous layer was extracted two times with 100 mL of Et_2O. The combined ether layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography of the crude oil using EtOAc/hexanes (4:96) provided 1.1 g of the acetal (2.7 mmol, 82%) as a clear oil: IR (neat) cm^{-1} 3075, 2950, 1450, 1110, 1070; ^1H NMR δ 1.05 (s, 9 H), 1.43 (s, 3 H), 1.51−1.65 (m, 4 H), 2.01 (t, 2 H, J = 7 Hz), 3.84−3.96 (m, 4 H), 4.22 (d, 2 H, J = 6 Hz), 4.85 (t, 1 H, J = 5 Hz), 5.40 (t, 1 H, J = 6 Hz), 7.40 (m, 6 H), 7.71 (m, 4 H); ^{13}C NMR δ 16.04, 19.14, 22.01, 26.85, 33.47, 39.19, 61.10, 64.79, 104.57, 124.44, 127.47, 127.63, 129.38, 134.24, 135.58, 136.71. Anal. Calcd for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54. Found: C, 73.50; H, 8.37.

3-Methyl-7,7-(ethylenedioxy)-2(*E*)-hepten-1-ol (2). To a stirred solution of 1-((*tert*-butyldiphenylsilyl)oxy)-3-methyl-7,7-(ethylenedioxy)-2(*E*)-heptene (3.7 g, 9.1 mmol) in 30 mL of THF at 0 °C was added tetrabutylammonium fluoride (1.0 M in THF, 27 mmol). The reaction was allowed to warm to rt over 3 h and quenched by the addition of 20 mL of H_2O. The aqueous layer was extracted three times with 20 mL of Et_2O, and the combined ether layers were washed (saturated aqueous $NaHCO_3$, brine), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography using Et_2O/hexanes (60:40) yielded 1.6 g of **2** (8.6 mmol, 95%): IR (neat) cm^{-1} 3417, 2947, 2876, 1669, 1408, 1134; ^1H NMR δ 1.51−1.63 (m, 4 H), 1.65 (s, 3H), 2.05 (t, 2 H, J = 7 Hz), 3.80−4.14 (m, 4 H), 4.10 (d, 2 H, J = 7 Hz), 4.80 (t, 1 H, J = 5 Hz), 5.30 (t, 1 H, J = 7 Hz); ^{13}C NMR δ 16.01, 21.96, 33.39, 39.24, 59.32, 64.83, 104.49, 123.86, 139.28.

1-Phthalimido-3-methyl-7,7-(ethylenedioxy)-2(*E*)-heptene. Triphenylphosphine (742 mg, 2.8 mmol) and phthalimide (410 mg, 2.8 mmol) were added to a stirred solution of alcohol **2** (400 mg, 2.2 mmol) in 15 mL of THF. Diisopropyl azodicarboxylate (550 μL, 2.8 mmol) was added dropwise to the solution in the dark over 10 min. The reaction was stirred at rt for 6 h and quenched by the addition of 15 mL of water. The aqueous layer was extracted three times with 15 mL of hexanes, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude oil was purified by flash chromatography using MeOH/CH_2Cl_2 (5:95) to yield 588 mg of allylic phthalimide (1.8 mmol, 86%) as a white solid: IR (KBr) cm^{-1} 2947, 2876, 1720, 1706, 1549, 1381; ^1H NMR δ 1.56 (m, 4 H), 1.80 (s, 3 H), 2.05 (t, 2 H, J = 7 Hz), 3.78−3.94 (m, 4 H), 4.24 (d, 2 H, J = 7 Hz), 4.80 (t, 1 H, J = 4 Hz), 5.25 (t, 1 H, J = 6 Hz), 7.70 (m, 2 H), 7.79 (m, 2 H); ^{13}C NMR δ 16.16, 21.91, 33.30, 35.72, 39.19, 64.76, 104.35, 118.21, 123.08, 132.25, 133.73, 140.32, 168.06.

1-Amino-3-methyl-7,7-(ethylenedioxy)-2(*E*)-heptene (3). To a solution of 1-phthalimido-3-methyl-7,7-(ethylenedioxy)-2(*E*)-heptene (320 mg, 1.0 mmol) in 10 mL of ethanol was added 700 μL of methylamine (7.9 mmol, 40% by wt solution). The reaction was refluxed for 7 h and quenched by the addition of 20 mL of ice-cold H_2O. The aqueous layer was basified (pH > 10) with solid KOH and extracted three times with 20 mL of Et_2O. The combined ether layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography using MeOH/CH_2Cl_2 (20:80) provided 170 mg of amine **3** (0.9 mmol, 91%): IR (neat) cm^{-1} 3289, 2949, 2873, 1558, 1457, 1136; ^1H NMR δ 1.44−1.54 (m, 4 H), 1.56 (s, 3H), 1.97 (t, 2 H, J = 7 Hz), 3.20 (d, 2 H, J = 6 Hz), 3.76−3.93 (m, 4 H), 4.79 (t, 1 H, J = 5 Hz), 5.20 (t, 1 H, J = 7 Hz); ^{13}C NMR δ 15.84, 22.05, 33.32, 39.28, 39.52, 64.81, 104.46, 126.10, 136.04. Anal. Calcd for $C_{10}H_{19}NO_2 \cdot {}^1/_4\, H_2O$: C, 64.05; H, 10.21; N, 7.47. Found: C, 64.05; H, 10.30; N, 7.77.

1-(*N*-1-Cyclohexenylacetamido)-3-methyl-7,7-(ethylenedioxy)-2(*E*)-heptene (4). To a stirred solution of amine **3** (30 mg, 0.16 mmol) in 10 mL of dry benzene were added 138 mg of K_2CO_3 (1.0 mmol) and 33 μL of cyclohexanone (0.32 mmol). The flask was equipped with a Dean−Stark apparatus whose side arm was filled with activated 4 Å molecular sieves and refluxed for 15 h.[13] The reaction was cooled to rt, and 13 μL of acetyl chloride (0.18 mmol) and 17 μL of pyridine (0.20 mmol) were added. After 20 min the reaction was quenched by the addition of 15 mL of H_2O. The aqueous layer was extracted three times with 15 mL of Et_2O, and the combined ether extracts were washed (saturated aqueous $NaHCO_3$, brine), dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography using MeOH/CH_2Cl_2 (1:99) provided 40 mg of enamide **4** (0.13 mmol, 81%) as a colorless oil: GLC (220 °C for 1 min, 10 °C/min to 325 °C) 7.98 min; MS *m*/*z* (rel intensity) 307.2 (3.6), 206.0 (12.6), 164.05 (100), 139.0 (30.6), 122.0 (29.2), 107.0 (13.6), 98.9 (16.4), 97.0 (50.5), 96.0 (19.2), 80.9 (58.5), 78.9 (34.8), 72.9 (51.4), 68.9 (15.5), 66.9 (19.5), 54.9 (24.5), 52.9 (15.6); IR (neat) cm^{-1} 2933, 2881, 1651, 1404, 1144, 1035; ^1H NMR δ 1.49−1.70 (m, 8 H), 1.61 (s, 3 H), 1.96−2.09 (m, 6 H), 1.98 (s, 3 H), 3.80−3.97 (m, 4 H), 4.01 (d, 2 H, J = 7 Hz), 4.82 (t, 1 H, J = 5 Hz), 5.17 (t, 1 H, J = 6 Hz), 5.56 (br s, 1 H); ^{13}C NMR δ 17.52, 23.11, 23.19, 23.65, 24.45, 26.38, 29.79, 34.99, 40.90, 44.89, 66.43, 106.10, 122.12, 128.95, 139.93, 140.77, 171.03. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.20; H, 9.22; N, 4.67.

1-(*N*-1-Cyclohexenylacetamido)-3-methyl-2(*E*)-hepten-7-al (5). To a solution of polyene **4** (8 mg, 0.03 mmol), dissolved in 7 mL of a 95:5 mixture of acetone:water, was added pyridinium *p*-toluenesulfonate (1 equiv, 7 mg). The reaction was refluxed for 7 h and then quenched by the addition of water. The aqueous layer was extracted three times with 10 mL of Et_2O, and the combined ether layers were washed (saturated aqueous $NaHCO_3$, brine), dried over $MgSO_4$, and concentrated *in vacuo*. GLC analysis of the reaction mixture revealed a 55:45 mixture of aldehyde **5** and starting material. Chromatography using *i*-PrOH/hexane (5:95) provided 3 mg of aldehyde **5** (0.01 mmol, 38%) as a colorless oil: GLC (220 °C for 1 min, 10 °C/min to 325 °C) 5.97 min; IR (neat) cm^{-1} 2938, 2719, 1721, 1646, 1392; ^1H NMR δ 1.64 (s, 3 H),

1.66−1.78 (m, 6 H), 2.01 (s, 3 H), 2.03−2.12 (m, 6 H), 2.39 (t, 2 H, J = 7 Hz), 4.02 (d, 2 H, J = 7 Hz), 5.19 (t, 1 H, J = 6 Hz), 5.57 (br s, 1 H), 9.76 (br s, 1H).

Tricycles 6 and 7. To a solution of enamide **4** (20 mg, 0.06 mmol) in 3 mL of CH_2Cl_2 at rt was added $FeCl_3 \cdot 6H_2O$ (61 mg, 3.5 equiv). The mixture was stirred at rt for 2 h, and then washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The crude residue (15 mg, 88% mass recovery) was purified by flash chromatography using *i*-PrOH/hexane (5:95) to give a mixture of tricycles **6** and **7** (11 mg, 65%, **6**:**7** = 85:15): GLC (220 °C for 1 min, 1 °C/min to 250 °C) 10.26 min (**6**), 10.10 min (**7**). Anal. Calcd for $C_{16}H_{27}NO_2 \cdot {}^4/_3H_2O$: C, 66.87; H, 9.70; N, 4.88. Found: C, 66.74; H, 9.86; N, 4.69.

The tricycles were separated by MPLC (10% *i*-PrOH/hex) and further purified by recrystallization from hexane/CH_2Cl_2 to give fine needles. Tricycle **6**: IR (KBr) cm^{-1} 3402, 2936, 2867, 2363, 2332, 1652, 1620, 1558; ^{1}H NMR δ 1.36 (s, C10-Me, 3 H), 1.42−1.68 (m, 4 H), 1.75 (m, 4 H), 1.95 (m, 3 H), 2.09 (s, 3 H), 2.15 (m, 2 H), 2.26 (m, 1 H), 3.21 (dd, H_{6eq}, 1 H, J = 13.7 Hz, J = 3.2 Hz), 3.79 (ddd, H_4, 1 H, J = 3.5 Hz, J = 3.1 Hz, J = 6.2 Hz), 4.19 (dd, H_{6ax}, 1 H, J = 13.7 Hz, J = 12.1 Hz), 4.63 (dd, OH, 1 H, J = 3.5 Hz, J = 1.6 Hz), 5.5 (dd, 1 H, J = 2.2 Hz, J = 2.6 Hz); ^{13}C NMR δ 19.21, 21.50, 22.70, 23.90, 24.73, 27.27, 29.72, 31.87, 41.85, 43.67, 48.97, 65.18, 72.04, 127.91, 138.66, 172.15. Tricycle **7**: ^{1}H NMR δ 1.12, (s, C10-Me, 3H), 1.21−1.80 (m, 6 H), 1.90−2.29 (m, 8 H), 2.08 (s, 3 H), 3.07 (dd, H_{6eq}, 1 H, J = 14.3 Hz, J = 4.2 Hz), 3.81 (br m, H_4, 1 H), 4.40 (dd, H_{6ax}, 1 H, J = 13.9 Hz, J = 12.5 Hz), 4.74 (br s, H_2O), 5.34 (br m, OH, 1 H), 5.51 (br m, 1 H).

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