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Zeolite NaY-Promoted Cyclization of Farnesal: A Short Route to Nanaimoal

Constantinos Tsangarakis, Ioannis N. Lykakis, and Manolis Stratakis*

Department of Chemistry, University of Crete, Voutes 71003, Iraklion, Greece

stratakis@chemistry.uoc.gr

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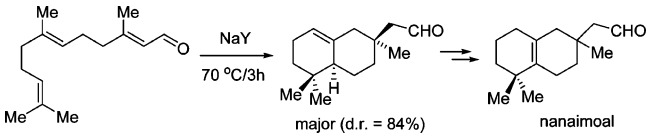


The sesquiterpene nanaimoal was synthesized in 21% overall yield and in a biomimetic manner. As a key step, the acid-catalyzed cyclization of farnesal under zeolite NaY confinement conditions was used. The intrazeolite cyclization of farnesal affords as major product a double-bond isomer of nanaimoal, via a novel diastereoselective tandem 1,5-diene cyclization/Prins-type reaction.

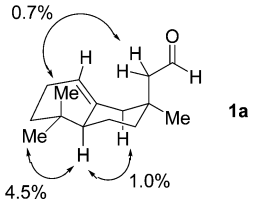
Nature constructs cyclic terpenes using a variety of enzymes called cyclases.[1] Those enzymes provide a delicate balance of an acidic initiator, a basic amino acid residue to terminate the cyclization sequence, and the perfect conformational control of the confined substrate that allows stereocontrol. As a result, synthetic chemists expend a great deal of effort attempting to mimic the work done by enzymes, as they strive for ever-greater efficiency in their own syntheses.[2]

We anticipated that by adsorbing an acyclic terpene within the cavities of an acidic zeolite, the confined environment would provide stereocontrolled cyclization through conformational control. Zeolites, which are mixed silicon/aluminum-based porous materials, catalyze reactions by confining the substrates within "active site" cavities.[3] We have reasoned that acidic zeolites with appropriate cage dimensions of ca. 10 Å,[4] such as faujasites (MX, MY, M = cation), would be particularly well suited for our purpose.

Our initial studies have revealed that the slightly acidic[5] zeolite NaY is a perfect catalyst and host medium, as well, to achieve the clean and good-yielding biomimetic cyclization of small acyclic terpenoids, such as geraniol and its derivatives.[6] The cyclization is catalyzed by Bronsted acidic sites[7] (bridging hydroxyl groups, Al−OH−Si), and since such sites appear only within the cavities of zeolites,[8] we consider the cyclization as occurring intrazeolite. In addition, we reported later on epoxy polyene terpenes undergo under NaY confinement conditions a fast and selective monocyclization,[9] allowing thus a short and good-yielding synthesis of elegansidiol and farnesiferols B−D.

We report in this manuscript a novel tandem bi-cyclization pathway promoted by zeolite NaY, which allows the fast and efficient synthesis of the sesquiterpene nanaimoal in a relatively few steps from the naturally occurring farnesal (**1**). Adsorption of 60 mg of farnesal per 1 g of dry NaY in a hexane slurry and heating to 70 °C for 3 h afforded a mixture of **1a**−**1c** in 82% yield (Scheme 1). The loading level of **1** within NaY was kept low to ensure its quantitative confinement within the zeolite cavities.[10] It is important to emphasize herein, that identical results were obtained by performing the intrazeolite cyclization reaction starting with a mixture of farnesal isomers, either at the C2−C3 or at the C6−C7 double bond.

The major product (50% relative yield; 30% isolated yield after column chromatography) was the bicyclic aldehyde **1a**[11] obtained as a 92/8 mixture of diastereomers (GC−MS), with the major one shown in Scheme 1. Aldehyde **1a** is a double-bond isomer of the naturally occurring nanaimoal (**2**),[12] a sesquiterpene with a unique carbon skeleton, isolated from the nudibranch *Acanthodoris nanaimoensis*. The monocyclized **1b** (*E*) and **1c** (*Z*) were formed in 50% relative yield and in ∼4/1 ratio. The relative stereochemistry of the major diastereomer **1a** was established by combined DEPT, COSY, HMQC, and NOESY experiments (some representative NOEs for the more stable conformer of the major diastereomer of **1a** are shown below).



1a

After much experimentation, by monitoring the reaction at several stages, we found that the optimum conditions favoring **1a** were 3 h at refluxing hexane. Upon shorter reaction times,

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(10) Under these low loading level conditions ($n \approx 0.2$), neither the reacting farnesal nor any of the products was detected by GC on the supernatant hexane, indicative that all substrate was adsorbed within the zeolite cavities.

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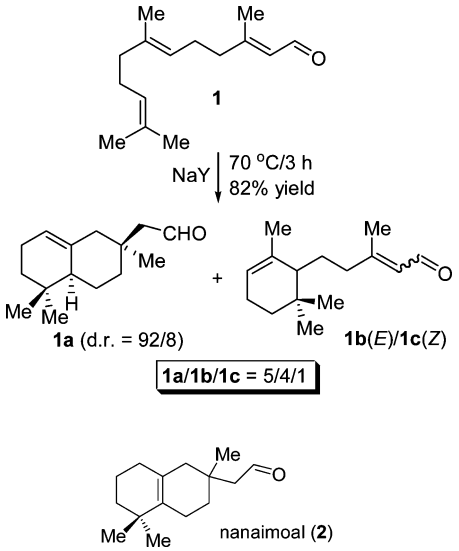
SCHEME 1. Cyclization of Farnesal (1) under NaY Confinement

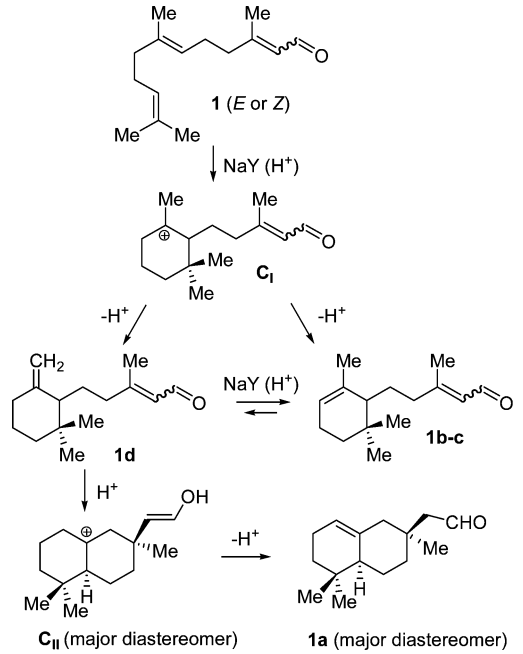


the relative yield of **1a** drops substantially. On the other hand, prolonged reaction times (up to 12 h) increase the relative yield of **1a** to 55−60% and decrease that of **1b**/**1c**. However, this result led to the gradual formation of a non-conjugated aldehyde byproduct (up to 10−15% relative yield), which proved extremely difficult to separate from **1a** by column chromatography and characterize properly, despite several careful attempts. This compound was neither nanaimoal nor a fused tricyclic aldehyde produced during the cyclization of **1d** promoted by Lewis acids.[11] We postulate that the byproduct arises from further acid-catalyzed transformation(s) of **1b**/**1c**. Indeed, treatment of the mixture **1b**/**1c** within NaY, under identical conditions as applied to the cyclization of farnesal, resulted after 4 h (15% conversion) in an almost equimolar formation of **1a** and the unknown byproduct.

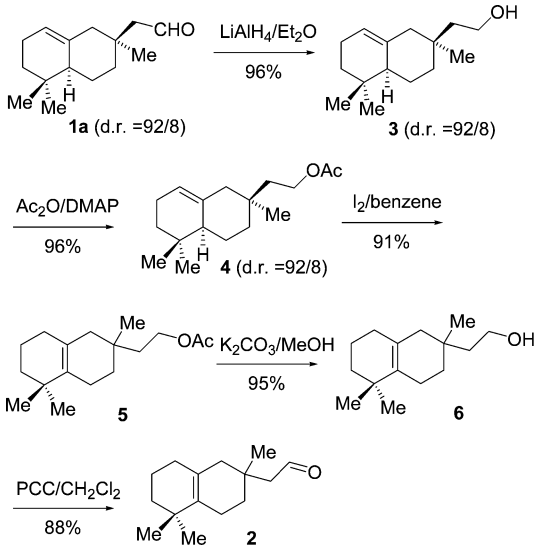
From the mechanistic point of view (Scheme 2), formation of **1a** could be envisioned as occurring through a tandem[13] 1,5-diene cyclization of farnesal to form mainly at the initial reaction stages the monocyclized product **1d** (not detected), which undergoes an intramolecular Prins-type reaction between the exocyclic double bond and the enal moiety to form **1a** in one step and in a highly diastereoselective manner. The deprotonation of the bicyclic carbocation $\mathbf{C_{II}}$ is highly regioselective in favor of the formation of the trisubstituted double bond, without forming the thermodynamically more stable nanaimoal (**2**). This is in accordance with previous intrazeolite cyclization results, such as with geranyl derivatives, which provide mainly the less thermodynamically stable cyclo-isomers, as deprotonation of the cyclized carbocations by the basic O atoms of the zeolite interior is kinetically driven.[6b,9]

Having **1a** (dr 92/8) in our hands, we attempted the isomerization of the trisubstituted double bond to the tetrasubstituted one, thus forming nanaimoal (**2**). The isomerization was achieved in five consecutive steps, yet in 70% overall isolated yield (Scheme 3). The aldehyde **1a** was reduced with $LiAlH_4$ to alcohol **3** (dr 92/8), which was acetylated to form acetate **4** (dr 92/8). The acetate was isomerized exclusively to the

SCHEME 2. Mechanistic Arguments for the Tandem Formation of 1a from Farnesal



SCHEME 3. Isomerization of 1a to (±)-Nanaimoal (2)



tetrasubstituted isomerized acetate **5** by reacting with I_2 in refluxing benzene.[14] Finally, **5** was hydrolyzed (K_2CO_3 in MeOH), and the resulting alcohol **6**[15] was oxidized with PCC to form nanaimoal as a racemate.

Despite the five steps required for the isomerization of **1a** to **2**, we emphasize that the reactions are almost quantitative; no byproducts are formed, and there is no essential need for chromatographic purification in any of the intermediate steps. Attempts to isomerize the trisubstituted double bond directly on **1a** or at the stage of alcohol **3** with I_2 or HI were unsuccessful. Complex mixtures of products were formed

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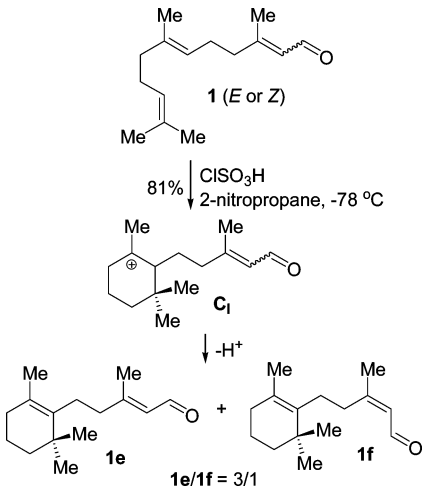
SCHEME 4. Cyclization of Farnesal (1) under $ClSO_3H$ Catalysis



without obtaining any of the desired products. Furthermore, a shorter approach for the isomerization of **1a** to **2** by an attempted I_2-promoted isomerization of acetal **7** (obtained from **1a** and ethylene glycol) also failed, as the acetal undergoes deprotection by the iodine. In addition, treatment of **1a** with Lewis acids such as BBr_3 or $MeAlCl_2$, which were efficient in catalyzing the cyclization of a suitable precursor to β-georgywood,[16] a terpenoid structurally similar to **2**, were disappointing. The aldehyde disappeared, with accompanying formation of a polymeric material. Finally, the attempted isomerization of **1a** to **2** using $RhCl_3$[17] as catalyst also failed. A tricyclic dimethoxy product (**8**, see Supporting Information) was formed almost quantitatively, probably though a solvent (methanol) intercepted intramolecular carbonyl-ene reaction. Further research is currently in progress[18] to explore this novel reaction pathway.

We consider the current synthesis of nanaimoal as biomimetic. In our opinion, nanaimoal might arise through the direct isomerization of farnesal to **2** via a tandem reaction sequence, such as the one provided by the zeolite environment. In addition, the current synthesis is very fast and the overall yield is quite acceptable (21%). There are four known literature syntheses of nanaimoal,[11,19−21] however, applying significantly more steps compared to our approach. Engler and co-workers[11] prepared **1d** and attempted its cyclization upon treatment with several Lewis acids, with varying degrees of success. Nanaimoal was formed, among two other isomeric products, in up to 19% yield.

For comparison, we studied the cyclization of farnesal under Bronsted acid catalysis ($ClSO_3H$, 2-nitropropane, −78 °C).[22] The two isomeric monocyclized products[23] **1e** and **1f** were isolated in 81% yield, and in a ratio **1e**/**1f** of ∼3/1 (Scheme 4). Apparently, the mono-cyclized carbocation $\mathbf{C_I}$ (Scheme 4) does not react with the electron-deficient C2−C3 double bond but rather deprotonates to form the thermodynamically more stable **1e** and **1f**. The absence of **1a** or **2** indicates that any **1d** formed by deprotonation of $\mathbf{C_I}$ undergoes a faster isomerization to **1e**/**1f** than to give an intramolecular Prins-type reaction which leads to the nanaimoal carbon skeleton.

The current synthesis of nanaimoal, using as a key reaction a novel tandem cyclization promoted by NaY, exemplifies a new biomimetic application of terpene cyclization under zeolite confinement. To the best of our knowledge, we have presented herein the first example of a tandem 1,5-cyclization/Prins-type reaction that provides a direct access to 1,2,3,4,4a,5,6,7-octahydronaphthalenes, the core skeleton of several terpenes such as macfarlandins C and D[24] and przewalskin B.[25]

In conclusion, we have presented a novel, simple, mild, environmentally friendly and efficient biomimetic methodology for the di-cyclization of farnesal, which provides a direct route to nanaimoal. Further synthetic applications and mechanistic studies of terpene cyclization under zeolite confinement conditions are currently under investigation.

Experimental Section

Intrazeolite Cyclization of Nanaimoal. A slurry of 1 g of NaY (dried at 120 °C under vacuum for at least 6 h prior to use), 10 mL of hexane, and 60 mg (0.27 mmol) of farnesal (**1**) was heated to 70 °C for 3 h. The solvent was removed by filtration, and the solid residue was washed with methanol (2 × 10 mL) for 30 min each time. The combined solvents were evaporated under reduced pressure to afford 46 mg of **1a**−**c**, in a relative ratio of 50/38/12. The mixture was chromatographed using hexane/ethyl acetate = 50/1 to afford 18 mg of the less polar **1a**[11] and 17 mg of the mixture of **1b,c**. Under careful chromatographic conditions pure samples of **1b** and **1c** can be isolated. ^{1}H NMR of the major diastereomer of 2−2,5,5-trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)-acetaldehyde, 1a (500 MHz, $CDCl_3$): δ 9.81 (dd, J = 3.0 Hz, 1H), 5.33 (br. s, 1H), 2.29 (dd, J_1 = 14.5 Hz, J_2 = 3.0 Hz, 1H), 2.24 (dd, J_1 = 14.5 Hz, J_2 = 3.0 Hz, 1H), 2.09 (dd, J_1 = 13.0 Hz, J_2 = 2.0 Hz, 1H), 1.97 (m, 2H), 1.90 (dd, J_1 = 13.0 Hz, J_2 = 2.0 Hz, 1H), 1.58 (m, 1H), 1.65−1.73 (m, 2H), 1.30−1.36 (m, 2H), 1.20−1.27 (m, 2H), 1.07 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 136.6, 121.2, 49.3, 48.9, 47.1, 38.2, 35.5, 34.8, 31.3, 28.9, 28.5, 24.7, 23.8, 22.7. ^{1}H NMR of (*E*)-3-methyl-5-(2,6,6-trimethylcyclohex-2-enyl)pent-2-enal, **1b** (500 MHz, $CDCl_3$): δ 10.00 (d, J = 8.0 Hz, 1H), 5.88 (d, J = 8.0 Hz, 1H), 5.34 (br. s, 1H), 2.24 (m, 2H), 2.17 (s, 3H), 1.98 (m, 2H), 1.68 (s, 3H), 1.62 (m, 2H), 1.40 (m, 1H),1.27 (m, 1H), 1.17 (m, 1H), 0.93 (s, 3H), 0.88 (s, 3H). MS (EI): 220 (M^+, 2%), 206 (1%), 176 (3%), 138 (29%), 121 (27%), 81 (51%), 55 (26%), 41 (100%). ^{1}H NMR of (*Z*)-3-methyl-5-(2,6,6-trimethylcyclohex-2-enyl)pent-2-enal, **1c** (500 MHz, $CDCl_3$): δ 9.95 (d, J = 8.0 Hz, 1H), 5.85 (d, J = 8.0 Hz, 1H), 5.37 (br. s, 1H), 2.58 (m, 2H), 1.99 (s, 3H), 1.70 (s, 3H), 1.64 (m, 1H), 1.52 (m, 2H), 1.43−1.37 (m, 2H), 1.17−1.15 (m, 2H), 0.97 (s, 3H), 0.89 (s, 3H). MS (EI): 220 (M^+, <1%), 206 (1%), 176 (2%), 149 (5%), 138 (17%), 121 (18%), 95 (21%), 81 (52%), 55 (27%), 41 (100%).

2-2,5,5-Trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)-ethanol (3). Alcohol **5** was prepared in 96% yield by reacting 16 mg (0.073 mmol) of aldehyde **1a** with 25 μL (0.025 mmol) of $LiAlH_4$ (1 M in Et_2O). ^{1}H NMR of the major diastereomer of **3** (500 MHz, $CDCl_3$): δ 5.29 (m, 1H), 3.65 (m, 2H), 1.97−1.92 (m, 4H), 1.80 (br. s, 1H), 1.60−1.49 (m, 3H), 1.36−1.30 (m, 2H),

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1.24−1.21 (m, 3H), 0.91 (s, 6H), 0.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.4, 120.2, 59.6, 48.9, 47.2, 42.4, 38.6, 38.1, 35.3, 31.3, 29.0, 28.6, 24.5, 23.7, 22.7. MS (EI): 222 (M^+, 8%), 207 (19%), 177 (27%), 121 (72%), 105 (44%), 91 (42%), 79 (70%), 55 (39%), 41 (100%).

2-2,5,5-Trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)-ethyl Acetate (4). The acetate **4** was prepared in 96% yield by acetylation of alcohol **3** (15 mg, 0.068 mmol) in ethyl acetate (0.5 mL), with 10 μL (0.1 mmol) of Ac_2O in the presence of 14 mg (0.1 mmol) of K_2CO_3 and 2 mg of DMAP. ^{1}H NMR of the major diastereomer of **4** (500 MHz, $CDCl_3$): δ 5.30 (br. s, 1H), 4.04 (t, J = 7.5 Hz, 2H), 2.03 (s, 3H), 1.96 (m, 4H), 1.78 (br. d, 1H), 1.59 (m, 2H), 1.45 (m, 1H), 1.34 (m, 1H), 1.22 (m, 2H), 0.94 (m, 2H), 0.92 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 137.1, 120.4, 61.7, 48.9, 47.2, 42.6, 37.7, 35.3, 33.8, 31.3, 28.7, 28.6, 24.4, 23.6, 22.7, 21.1. MS (EI): 264 (M^+, 2%), 249 (1%), 204 (17%), 189 (21%), 175 (23%), 161 (12%), 133 (19%), 120 (35%), 105 (28%), 91 (23%), 79 (25%), 43 (100%).

2-(2,5,5-Trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-ethyl Acetate (5). The acetate **4** (16 mg, 0.061 mmol) was dissolved in 1 mL of benzene. Subsequently 55 mg of I_2[14] was added, and the reaction mixture was refluxed for 8 h. After workup, 14.5 mg of the isomeric acetate **5** was isolated (91% yield). ^{1}H NMR of **5** (500 MHz, $CDCl_3$): δ 4.12 (t, J = 7.0 Hz, 2H), 2.03 (s, 3H), 1.96 (m, 2H), 1.76 (m, 2H), 1.70 (br. s, 1H), 1.62−1.52 (m, 5H), 1.44−1.35 (m, 4H), 0.96 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 133.4, 125.4, 61.7, 43.7, 39.8, 39.1, 34.4, 33.5, 31.7, 30.7, 28.0, 27.8, 24.7, 21.3, 21.1, 19.4. MS (EI): 264 (M^+, 1%), 189 (21%), 175 (23%), 161 (12%), 148 (11%), 133 (19%), 120 (35%), 105 (28%), 91 (23%), 79 (25%), 55 (24%), 43 (100%).

2-(2,5,5-Trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-ethanol (6).[15] The acetate **5** (14 mg, 0.053 mmol) was hydrolyzed in 95% yield upon treatment at room temperature for 2 h with 17 mg of K_2CO_3 (0.12 mmol) in 0.5 mL of methanol. ^{1}H NMR of **6** (500 MHz, $CDCl_3$): δ 3.72 (t, J = 7.0 Hz, 2H), 1.96 (m, 2H), 1.78 (m, 2H), 1.72 (br. s, 1H), 1.60−1.48 (m, 6H), 1.44−1.33 (m, 5H), 0.97 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.8, 125.5, 59.7, 44.0, 43.9, 39.8, 34.7, 33.5, 31.7, 30.8, 28.0, 27.8, 24.9, 21.4, 19.4. MS (EI): 222 (M^+, 13%), 207 (61%), 204 (17%), 189 (26%), 177 (24%), 161 (30%), 91 (62%), 55 (60%), 41 (100%).

2-(2,5,5-Trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)-acetaldehyde (2). The alcohol **6** (11 mg, 0.050 mmol) was oxidized with 18 mg of PCC (0.081 mmol) in 0.5 mL of dichloromethane. After 2 h the solvent was removed, and the residue was passed through a short pad of silica gel with diethyl ether as eluent to afford 9.4 mg of nanaimoal (**2**) in pure form (yield 88%). The spectral data are in perfect agreement with those of the natural product.[11,12a] ^{1}H NMR of **2** (500 MHz, $CDCl_3$): δ 9.85 (t, J = 3.0 Hz, 1H), 2.27 (dd, J_1 = 3.0 Hz, J_2 = 14.5 Hz, 2H), 2.00 (m, 2H), 1.86−1.74 (m, 4H), 1.60 (m, 3H), 1.44 (m, 3H), 1.05 (s, 3H), 0.97 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 133.7, 125.3, 53.6, 43.6, 39.7, 34.8, 33.6, 32.1, 31.6, 27.9, 27.8, 25.9, 21.3, 19.3. MS (EI): 220 (M^+, 3%), 176 (38%), 161 (100%), 105 (31%), 177 (24%), 161 (30%), 105 (54%), 41 (42%).

Cyclization of Farnesal Catalyzed by $ClSO_3H$. A solution of farnesal (0.1 g, 0.45 mmol) in 2 mL of 2-nitropropane was cooled to −78 °C. Subsequently 0.075 mL (1.1 mmol) of $ClSO_3H$[22] was syringed, and stirring was continued for 30 min. Then, 0.5 mL of Et_3N dissolved in 5 mL of diethyl ether was added, and the organic layer was washed with brine. After removal of the solvents a mixture of the monocyclized products[23a] **1e** and **1f** (82 mg) was isolated in 82% yield and in a ∼3/1 ratio. Under careful chromatographic conditions (hexane/ethyl acetate = 25/1), the separation of **1e** and **1f** was possible. The relative stereochemistry of **1e** and **1f** was assigned on the basis of NOE experiments (irradiation of the olefinic hydrogen atom of the enal moiety). ^{1}H NMR of **1e** (500 MHz, $CDCl_3$): δ 10.01 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 8.0 Hz, 1H), 2.25 (m, 2H), 2.20 (s, 3H), 2.15 (m, 2H), 1.91 (t, J = 6.5 Hz, 2H), 1.59 (s, 3H), 1.56 (m, 2H), 1.43 (m, 2H), 1.00 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.4, 164.5, 135.9, 128.2, 126.8, 41.2, 39.7, 35.0, 32.7, 28.5, 26.7, 19.8, 19.4, 17.6. ^{1}H NMR of **1f** (500 MHz, $CDCl_3$): δ 9.99 (d, J = 8.0 Hz, 1H), 5.86 (d, J = 8.0 Hz, 1H), 2.61 (m, 2H), 2.19 (m, 2H), 2.04 (s, 3H), 1.94 (t, J = 6.5 Hz, 2H), 1.65 (s, 3H), 1.59 (m, 2H), 1.44 (m, 2H), 1.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.7, 164.7, 136.0, 128.6, 128.1, 39.7, 35.0, 33.4, 32.8, 28.6, 28.3, 25.0, 20.0, 19.4.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR and MS spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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