arylpropionic ester using polyphosphoric acid first at 65 °C then at 91–93 °C for 8 h. Reaction of **3** in dry dimethoxyethane (DME) with potassium *tert*-butoxide and tosylmethyl isocyanide[7] at 0 °C for 20 min and 25 °C for 1 h followed by acidification with glacial acetate acid and isolation afforded the nitrile corresponding to **4** (as a mixture of two diastereomers) (52% yield) which was then transformed into the methyl ester **4** (as a mixture of diastereomers) by hydrolysis ($KOH-H_2O_2-H_2O$–ethanol[8]) to the acid and methylation (CH_2N_2). Methylation of the ester **4** was effected by deprotonation with 1 equiv of lithium diisopropylamide at −78 °C in THF followed by reaction with methyl iodide (4 equiv) and hexamethylphosphoric amide (1.3 equiv) at −78 °C for 3 h to give after chromatography on silica gel (8:1 pentane–ether) in 90% yield the ester **5** admixed with ~15% of the diastereomer (methyl and isopropyl cis) which could be removed conveniently at a later stage (intermediate **7**). The stereochemistry of **5** is assigned on the expectation that steric shielding by isopropyl will favor the formation of this geometry over the diastereomeric structure. Treatment of **5** with boron tribromide (2.1 equiv) in methylene chloride at −78 °C for 0.5 h and then at −10 ± 5 °C for an additional 4 h resulted in cleavage of the methyl ester and methyl ether functions to give the corresponding phenolic acid (82% after purification by rough chromatography on silica gel), which was then hydrogenated over Nishimura's catalyst[9] (20% by weight) in acetic acid containing 7% perchloric acid under 200 atm of hydrogen at 25 °C for 47 h to yield after chromatography on silica gel (25:1 hexane–ethylene acetate) the δ-lactone **6** as major product (IR max 1705 cm^{-1} in $CHCl_3$; R_f 0.48 on silica gel with 2:3 ether–petroleum ether as compared with starting phenolic acid R_f 0.41 with 100:20:1 benzene–dioxane–HOAc; yield 37%). The isolation of a saturated δ-lactone from the hydrogenation indicates that the aromatic ring has been fully reduced in the hydrogenation step to form the required cis fusion with a trans relationship between the hydrogens at the fusion atoms and the lactone bridge.

Reduction of the lactone **6** with lithium aluminum hydride in THF at 0 °C for 1 h produced a diol which, upon treatment with 1 equiv of tosyl chloride in pyridine at 0 °C for 2.5 h, isolation, and subsequent oxidation with pyridinium chlorochromate[10] (2 equiv) in methylene chloride at 25 °C for 2 h, furnished the keto tosylate **7** (68% overall). Addition of a solution of **7** in dry *tert*-butyl alcohol to a solution of potassium *tert*-butoxide in *tert*-butyl alcohol and reaction at 25 °C for ~30 min resulted in internal alkylation to form the desired tricyclic ketone **8** (70–75% isolated yield after chromatography on silica gel) along with an isomeric minor byproduct which is presumably **9**, the result of alkylation at the methylene α to carbonyl. Interestingly, this unexpected byproduct becomes the major cyclization product when lithium diisopropylamide in THF is used as the reagent, providing an unusual example of preferential formation of a four- rather than a six-membered ring by internal enolate alkylation.

The synthetic tricyclic ketone **8** was identical by spectral (IR, ^1H NMR, ^{13}C NMR, mass) and chromatographic comparison with a sample[11] of this constitution obtained as described previously[1] from naturally derived 9-isocyanopupukeanane. Reaction of **8** with hydroxylamine hydrochloride in pyridine–ethanol at 25 °C for 12 h yielded cleanly the corresponding oxime (**10**) which upon reduction with Nishimura's catalyst[9] and hydrogen (1 atm) in acetic acid afforded the amine **11**, further transformed in 80% overall yield into the formamide **12** by reaction with formic–acetic anhydride (−10 °C for 1.5 h). The ^1H NMR and IR spectra of synthetic **12** and naturally derived **12** were identical. Finally, reaction of the formamide **12** with methanesulfonyl chloride–pyridine[12] at 25 °C for 0.5 h produced synthetic (±)-9-isocyanopupukeanane (**1**), spectroscopically and chromatographically identical with naturally derived **1**.[13] Thus, the synthesis of this unusual natural product has been realized in a relatively simple way.

The lactone **6** has also been transformed (via an intramolecular aldol reaction) into the hydroxy ketone **13** and thence into **2**. Details of the synthesis of 2-isocyanopupukeanane (**2**) will be reported separately.[14,15]

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(2) Absolute configuration not established.
(3) Personal communication from Professor Paul Scheuer.
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(9) S. Nishimura, *Bull. Chem. Soc. Jpn.*, **33**, 566 (1960); **34**, 32 (1961).
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(13) Although synthetic 1 was in hand some time ago (March 1978), neither spectra of pure 1 nor samples of 1 were available for comparison until recently. We are indebted to Professor Paul Scheuer for kindly arranging for the collection of more material which was purified and supplied to us through the courtesy of Professor Hisashi Yamamoto. Our work has been submitted for simultaneous publication with results from Professor Yamamoto's laboratory through mutual agreement: H. Yamamoto and H. L. Sham, *J. Am. Chem. Soc.*, following paper in this issue.
(14) *Tetrahedron Lett.*, in press.
(15) We are grateful to the National Science Foundation for a research grant and to Dr. Stephen D. Hurt for experimental assistance.

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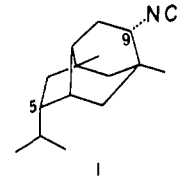
Total Synthesis of (±)-9-Isocyanopupukeanane

Sir:

An off-white sponge, *Hymeniacidon* sp., elaborates a novel sesquiterpene isocyanide, which is utilized by a nudibranch predator, *Phyllidia varicosa*, as a defensive secretion.[1] The structure of this marine invertebrate allomone was characterized recently by Scheuer and his collaborators as 1,3-dimethyl-9-isocyano-5-isopropyl[4.3.1.$0^{3,7}$]decane (**1**),[1] and this new ring system was named pupukeanane after the place where the mollusk and sponge were collected.[1] A highly stereose-



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lective synthesis of this unique compound is the subject of the present communication. The synthesis heavily depends on an intramolecular Diels–Alder reaction[2] as the skeleton-forming transformation.

The preparation of the key Diels–Alder substrate **2** was achieved as outlined in Scheme I. Reduction of commercially available 3,5-dimethyl-2-cyclohexen-1-one with diisobutyl-

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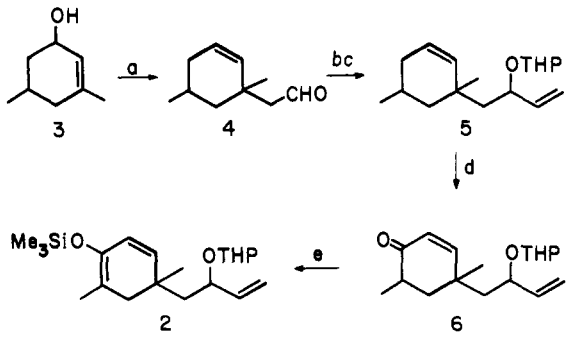
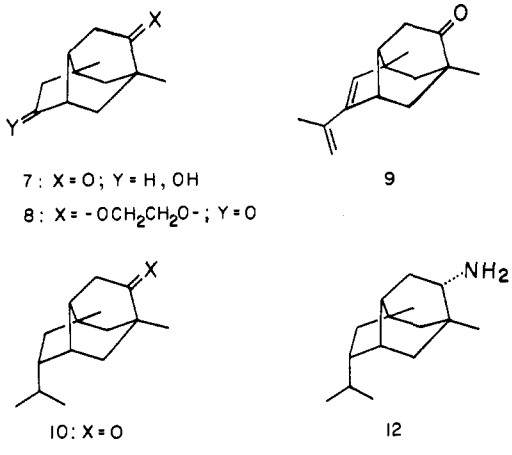
Scheme I[a]



[a] a, $EtOCH{=}CH_2$, Hg^{2+}, 210 °C (15 h). b, $CH_2{=}CHMgBr$, THF, 0 °C (1 h). c, dihydropyran, CH_2Cl_2, TsOH, 0 °C (1 h) → 25 °C (2 h). d, $CrO_3 \cdot py_2$ (20 equiv), CH_2Cl_2, 25 °C (15 h). e, LDA (1.5 equiv), THF, 0 → 25 °C (2 h), Me_3SiCl (1.5 equiv), 25 °C (30 min).

aluminum hydride (Dibah, 1.5 equiv)[3] at 0 °C for 1 h afforded the allylic alcohol **3** (90%).[4] The olefinic aldehyde **4**[4,5] was obtained from the alcohol **3** in 78% yield by Claisen rearrangement using mercuric acetate in excess ethyl vinyl ether at 210 °C for 15 h.[6] The aldehyde **4** was converted to the diene **5** (91%)[4] by treatment with vinylmagnesium bromide in tetrahydrofuran at 0 °C followed by protection of the resulting alcohol by the tetrahydropyranyl group. Selective allylic oxidation of **5** was accomplished using chromium trioxide–dipyridine complex (20 equiv)[7] in methylene chloride at 25 °C for 12 h to form the enone **6** (65%).[4,8,9] Sequential treatment of the enone **6** with lithium diisopropylamide (1.5 equiv) and trimethylsilyl chloride (1.5 equiv)[10] provided the silyl enol ether **2**[4,11] in pure form after column chromatography on silica gel (85%).

The desired tricyclic skeleton of pupukeanane was constructed highly efficiently from the triene **2** by an intramolecular cyclization. Specifically, **2** was heated in benzene at 160 °C for 30 min in a sealed tube and the product was isolated after acid hydrolysis (AcOH–H_2O, 3:1, 50 °C, 3 h) to yield the keto alcohol **7**[4,12] quantitatively as a colorless oil. Ketalization of **7** with ethylene glycol in the presence of methyl orthoformate–*p*-toluenesulfonic acid[13] followed by oxidation of the alcohol by the Corey–Kim method[14] furnished the single ketone **8**[15] in 60% overall yield from **2**. Conversion of **8** to the diene **9**[16] was effected by the following sequence: (1) reaction of **8** with 2-propenyllithium in ether at −78 °C (89%), (2) deprotection of the ethylene ketal (3:1 AcOH–H_2O, 60 °C, 3 h) (91%), (3) dehydration of the tertiary allylic alcohol by treatment with methanesulfonyl chloride (4 equiv) and triethylamine (8 equiv) in methylene chloride at −20 °C (1 h) → 25 °C (40 min) (60%).



Completion of the synthesis requires introduction of two appendages of **1** (C(5) isopropyl and C(9) isocyano) with the correct configurations. This was accomplished as described below. Although hydrogenation of **9** with palladium on charcoal, Raney nickel, or a number of other standard catalysts affords a mixture of stereoisomers, the selective hydrogenation was realized with remarkable stereoselectivity (>98%) using iridium black as a catalyst[17] in ethanol at 25 °C and 1 atm of H_2. The ketone **10** so produced was identical in all respects with an authentic specimen derived from natural (+)-**1**.[1,18,19] Reaction of **10** with hydroxylamine in ethanol at reflux for 1 h produced the oxime **11**[18] quantitatively. Treatment of the oxime with low-valent titanium,[20] derived from titanium trichloride–Dibah (1:3), in dry tetrahydrofuran at 25 °C for 15 min, gave the corresponding imine[21] which was concentrated in vacuo and directly exposed to excess Dibah in hexane[22] at −78 °C to furnish the desired amine **12** as a sole product.[23] Thus, the addition of hydride to the imine group was effectively stereoselective generating only one of the two possible configurations at C(9). The conversion of **12** to the final isocyanide **1** was straightforward. Thus, reaction of **12** with excess acetic–formic anhydride[24] in methylene chloride at 25 °C for 2 h produced cleanly the corresponding formamide (60% yield from **10**).[18,25] The amide was converted to (±)-**1** by exposure with 1.5 equiv of *p*-toluenesulfonyl chloride in pyridine at 25 °C for 1.5 h (89%).[26] The synthetic isocyanide was chromatographically and spectrally indistinguishable with the authentic naturally occurring material.[27]

Acknowledgment. Support for this research from the Research Corporation and the University of Hawaii at Manoa is gratefully acknowledged. We thank Professor P. J. Scheuer and Dr. F. Woolard of our department for a generous supply of a crude extract of isocyanides and spectral data for **1** and **10.** We also thank Professor E. J. Corey for generous comparisons of our synthetic intermediates with theirs.

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(4) A mixture of stereoisomers. Separation was unnecessary since all of them turn out to be the same ketone **10**.
(5) NMR ($CDCl_3$) δ 9.75 ppm (1 H, t, J = 3 Hz, CHO); IR (liquid film) 2760, 1730, 1660 cm^{-1}.
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(7) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).
(8) Some starting material was recovered under these conditions and the yield given here is corrected for such recovery (usually ~20%). Less satisfactory results were obtained with longer reaction times or more excess reagents.
(9) IR (liquid film) 1690 cm^{-1} (C=O). None of the regioisomer was isolated from this reaction; see ref 7.
(10) G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **43**, 1599 (1978).
(11) Two components by TLC assay. The more polar fraction: R_f 0.40 (silica gel, benzene); NMR ($CDCl_3$) δ 1.07 and 1.09 (3 H, 2 s, CH_3), 1.64 (3 H, s, allylic CH_3), 5.54 ppm (2 H, br s, olefinic protons of cyclohexadiene). The less polar fraction: R_f 0.53 (silica gel, benzene); NMR ($CDCl_3$) δ 1.04 (3 H, s, CH_3), 1.64 (3 H, s, allylic CH_3), 5.51 ppm (2 H, AB, olefinic protons of cyclohexadiene).
(12) NMR ($CDCl_3$) δ 0.85, 0.92, 1.00, 1.08, 2.36 (2 H, m, $CH_2C{=}O$), 3.1 (1 H, br s, OH), 4.0 ppm (1 H, br m, C*H*OH).
(13) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ournnes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).
(14) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972); *J. Org. Chem.*, **38**, 1233 (1973).
(15) NMR ($CDCl_3$) δ 0.72 (3 H, s, CH_3), 1.14 (3 H, s, CH_3), 3.7–4.0 (4 H, m, CH_2CH_2); IR (liquid film) 1740 cm^{-1} (C=O of five-membered ketone).
(16) NMR ($CDCl_3$) δ 0.94 (3 H, s, CH_3), 1.09 (3 H, s, CH_3), 1.87 (3 H, s, allylic CH_3), 1.42 (2 H, d, J = 3 Hz, $CH_2C{=}O$), 2.72 (1 H, ddd, J = 1, 5, and 8 Hz, allylic CH), 4.85 (2 H, br d, J = 5 Hz, $=CH_2$), 5.72 ppm (1 H, s, olefinic CH of ring); IR (liquid film) 1722 (C=O), 1630 and 1598 cm^{-1} (C=C).
(17) Iridium black (Alfa, Ventron) is a highly selective hydrogenation catalyst; see S. Nishimura, F. Mochizuki, S. Kobayakawa, *Bull. Chem. Soc. Jpn.*, **43**, 1919 (1970); S. Nishimura, H. Sakamoto, and T. Ozawa, *Chem. Lett.*, 855 (1973); S. Nishimura, *J. Synth. Org. Chem., Jpn.*, **36**, 268 (1978).
(18) Identical with the synthetic sample prepared by Professor Corey and his collaborators using entirely different approach; see E. J. Corey, M. Beh-

forouz, and M. Ishiguro, *J. Am. Chem. Soc.*, preceding paper in this issue.
(19) NMR ($CDCl_3$) δ 0.90 (9 H, br s, CH_3), 1.04 (3 H, s, CH_3), 1.49, 1.56, 1.61, 2.32 (2 H, d, J = 3 Hz, $CH_2C{=}O$); IR (liquid film) 2980, 2950, 2890, 1722 (C=O), 1470, 1452, 1407, 1393, 1383, 1367, 1347, 1190, 1147, 1096, 1047, 1007 cm^{-1}.
(20) As a review of low-valent titanium reagent, see J. E. McMurry, *Acc. Chem. Res.*, **9**, 281 (1974).
(21) An attempted isolation of the intermediary imine was unsuccessful because of its extreme lability in protic solvent.
(22) Hexane was found to be the best solvent for the stereoselective reduction of imines; see ref 23.
(23) The details of this new procedure will be published elsewhere.
(24) C. D. Hurd and A. S. Roe, *J. Am. Chem. Soc.*, **61**, 3355 (1939); C. W. Hoffman, *J. Org. Chem.*, **23**, 727 (1958); G. G. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945).
(25) NMR ($CDCl_3$, XL-100) δ 0.72, 0.79, 0.84, 0.96, 0.97, 1.22, 3.81 (1 H, br m, CHNC=O), 5.5 (1 H, br m, NH), 7.92, 8.04, 8.18 ppm; IR (CCl_4) 1695 cm^{-1}.
(26) W. R. Hertler and E. J. Corey, *J. Org. Chem.*, **23**, 1221 (1958).
(27) A crude extract of *Hymeniacidon* sp., kindly provided from Professor P. J. Scheuer and Dr. F. Woolard, was purified by thin layer chromatography on silica gel using 1–2% ether in hexane as a developing solvent (five developments). 9-Isocyanopupukeanane thus obtained as a pale yellow liquid of reasonable purity was used for the comparison: NMR ($CDCl_3$, XL-100) of synthetic 1, δ 0.80, 0.83, 0.86, 0.90, 1.03, 1.24, 3.26 ppm (1 H, br d, CHNC); NMR of the natural **1** contaminated by small peaks at δ 0.86, 0.95, 1.06, 1.54 ppm; IR (CCl_4) 2150 cm^{-1} (isocyanide); TLC (silica gel, 5% ether in hexane) R_f 0.45; LC, Altex 4.6 × 250 10 μ-Lichrosorb column, 5% ether in hexane, t_r 78 min.

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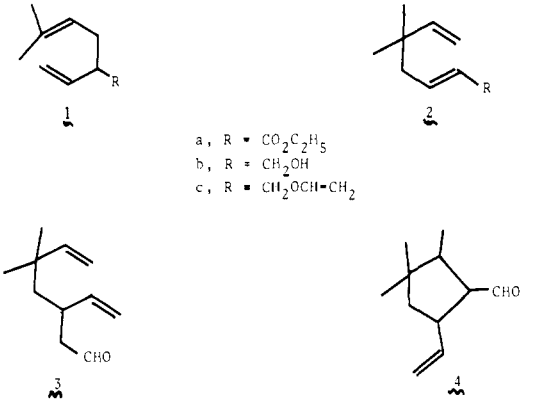
Tandem Cope–Claisen Rearrangement: A Contrathermodynamic [3,3] Sigmatropic Sequence

Sir:

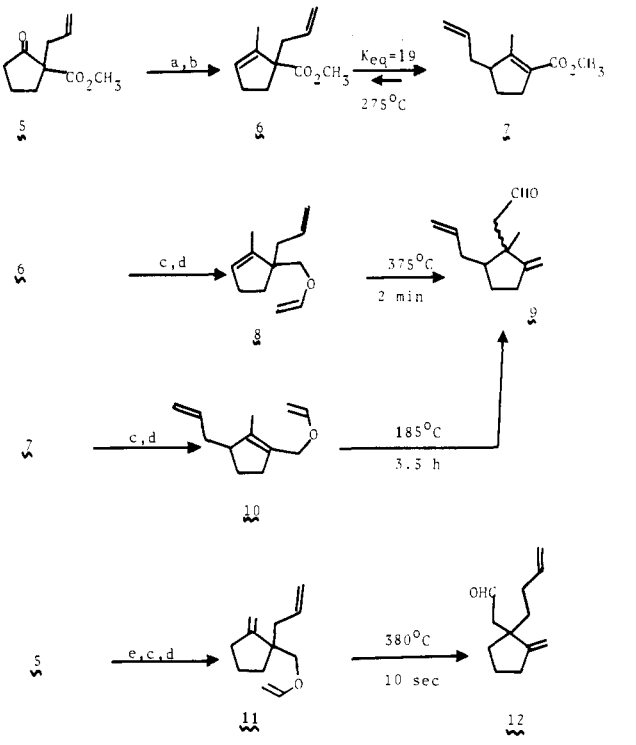
The Claisen rearrangement and to a lesser extent the Cope rearrangement have found substantial utility in the methodology of synthetic organic chemistry.[1] These rearrangements have been exploited in tandem (Claisen–Cope rearrangement[2]) in such a manner that the lower activation energy, irreversible Claisen rearrangement generates a 1,5-hexadiene which permits a subsequent, higher activation energy, reversible Cope rearrangement to proceed. The aldehyde produced (in the case of vinyl ether rearrangements) depends upon the position of the Cope equilibrium and, in general, is the 1,5-hexadiene with the more highly substituted double bonds.

To our knowledge this tandem sequence has not been practiced in the opposite sense, whereby the Cope triggers the Claisen rearrangement. We report here that this reaction sequence is *viable and that it serves to shift unfavorable Cope equilibria by an irreversible Claisen rearrangement.*

Thermolysis[3] of ester **1a**[4,5] at 275 °C provided an equilibrium mixture of esters **1a** and **2a** (K_{eq}(**2a**/**1a**) = 0.25). Although well suited for eventual Claisen rearrangement via the sequence **1a** → **2a** → **2b** → **2c** → **3**, ester **2a** is the minor component in the equilibrium. This difficulty was circumvented by transforming ester **1a** into vinyl ether **1c** by sequential $LiAlH_4$ reduction and vinylation. Rearrangement of **1c** in a flow system (hexane, N_2, 525 °C, 10 s) gave rise to the aldehyde **3** in 57% yield.



Scheme I[a]



[a] a, CH_3MgBr; b, $H_2C_2O_4 \cdot 2H_2O$, $C_6H_5CH_3$, Δ; c, $LiAlH_4$, Et_2O; d, $C_2H_5OCH{=}CH_2$, $Hg(OAc)_2$; e, $(C_6H_5)_3P{=}CH_2$, Me_2SO.

When the rearrangement was performed in a sealed tube (375 °C, 4 min) the aldehyde **3** was formed as the major product: IR (CCl_4) 2710, 1726, 1638 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 9.65 (t, 1 H, J = 2 Hz), 5.84–5.63 (2 H, m), 5.04–4.88 (4 H, m), 2.79–2.68 (1 H, m), 2.44–2.36 (2 H, m), 1.53–1.33 (2 H, m), 1.03 (3 H, s), 1.02 (3 H, s). The aldehyde **4** (14%) was also formed in the reaction along with an unidentified (6%) aldehyde. Aldehyde **4** was independently shown to arise from **3** (325 °C, 2 h) via Conia rearrangement.[6]

The vinyl ether **8**, prepared as outlined in Scheme I, was rearranged to a diastereomeric mixture (55:45) of aldehydes **9**: 87%; IR (CCl_4) 2725, 1719, 1638 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 9.69 ($\approx$ 0.5 H, t, J = 3.3 Hz, 270 MHz), 9.66 ($\approx$ 0.5 H, d,d, J = 2.4, 2.5 Hz, 270 MHz), 6.00–5.51 (1 H, m) 5.16–4.74 (4 H, m), 1.22 and 0.98 (3 H, 2s). The vinyl ether **10** containing 5% **8** was subjected to Claisen rearrangement at 185 °C to produce a nearly identical mixture of diastereomers.[7] A 50:50 ratio of isomers of the congeneric esters of **9** was obtained[8] when the precursory alcohol of **10** was subjected to the orthoacetate Claisen rearrangement conditions[9] (140 °C). These data reveal a $\Delta\Delta F^{\ddagger}$ which is temperature insensitive over the temperature range studied.[10]

Vinyl ether **11** (Scheme I) gave rise to a single aldehyde **12** (91%; IR (CCl_4) 2721, 1720, 1640 cm^{-1}; NMR ($CDCl_3$, 90 Mz) δ 9.73 (1 H, t, J = 3 Hz), 6.02–5.54 (1 H, m), 5.15–4.73 (4 H, m), 2.44 (2 H, d, J = 3 Hz)) when heated for a short period of time. Prolonged heating gave rise to secondary products.

The equilibrium between 1,2-divinylcyclohexanes and 1,5-cyclodecadienes is one which generally lies to the side of the former and manifests itself in natural products chemistry in the elemane–germacrane equilibrium.[11] The Cope–Claisen rearrangement serves as a means of preparing functionalized

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