Intramolecular Diels-Alder Reactions: The Angularly Methylated *trans*-Perhydroindan Ring System

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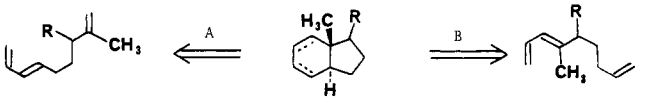
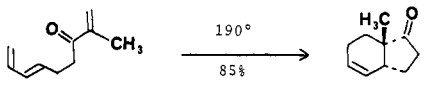
Abstract: The intramolecular Diels-Alder reactions of terminally activated trienes **18-20** lead preferentially to products possessing angularly methylated *trans*-perhydroindan ring systems. The product distribution in these cases is not governed by classical secondary orbital interactions. A high degree of internal asymmetric induction is realized in the cyclizations of (*Z*,*E*)-trienes **19** and **20**, but not in the cyclization of (*E*,*E*)-**18**, which may be a consequence of the preferred conformation of the allylic stereocenter relative to the dienophile double bond. The cyclization of unactivated triene **4** is stereorandom, affording an equal mixture of trans- and cis-fused products. In contrast, the cyclization of unsaturated aldehyde **8** shows reversed selectivity, affording predominantly cis-fused cycloadducts. The latter results are rationalized in terms of a concerted but nonsynchronous transition-state model.

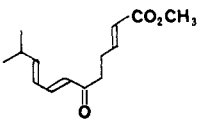
Intramolecular Diels-Alder reactions of substituted methyl deca-2,7(*E*),9(*E*)-trienoates afford predominantly products possessing *trans*-perhydroindan nuclei.[1] The product selectivity in these cases is independent of dienophile stereochemistry.[1b-e] These results prompted us to explore a new strategic approach to the angularly methylated *trans*-perhydroindan ring system, which is an important structural element of steroids and vitamin D derivatives.[2,3] In principle, two different intramolecular Diels-Alder reaction sequences could be used to prepare the desired ring system. In cyclization pathway A, the incipient angular methyl



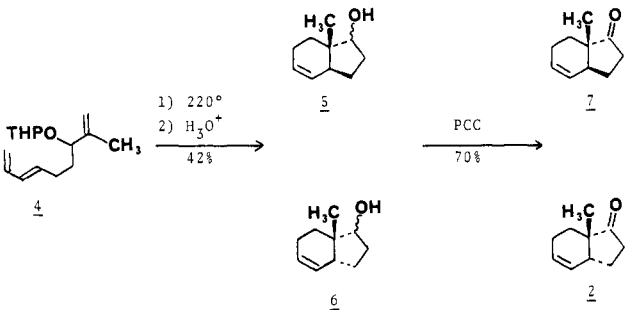
group would be introduced as part of the dienophile, whereas in B the angular methyl group would originate as a butadiene substituent. We describe herein the results of our study of cyclization pathway A.

From the outset, it was not obvious whether or not a dienophile activating group would be required. It was apparent, however, that sp^2-hybridized carbon atoms could not be tolerated at the allylic positions of the chain separating the diene and dienophile. Bajorek and Sutherland had previously shown that cis-fused **2** was the near exclusive product of cyclization of **1**,[3e] and we had been unable to effect intramolecular cyclization of **3**.[4]



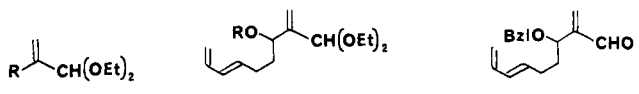


An unactivated substrate, **4**, was prepared by the reaction of



(*E*)-hepta-4,6-dienal[5] with isopropenylmagnesium bromide in tetrahydrofuran (THF) followed by tetrahydropyranylation (69% overall yield). Cyclization of **4** followed by acid hydrolysis afforded a nearly equal mixture of four inseparable cyclization products in 42% combined yield. Oxidation of this mixture with pyridinium chlorochromate (PCC)[6] in CH_2Cl_2 afforded a 50:50 mixture of trans-fused **7** and cis-fused **2** in 70% yield. The lack of stereoselectivity in this Diels-Alder reaction implied that an activating group would be required to achieve maximum selectivity for the trans-fused product.

Aldehyde **8** was considered to be a suitable substrate for cyclization to angularly oxygenated perhydroindene derivatives. Treatment of (*E*)-hepta-4,6-dienal with lithium reagent **9**[7] in THF



9 R = Li
10 R = Cu

11 R = H
12 R = Bzl

8

(1) (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Roush, W. R. *Ibid.* **1979**, *44*, 4008. (c) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390. (d) Roush, W. R.; Ko, A. I.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4264. (e) Roush, W. R.; Gillis, H. R. *Ibid.* **1980**, *45*, 4283.

(2) The classical strategies for the synthesis of this ring system have been summarized, and numerous examples of each are found in the literature of steroid total synthesis. Reviews: (a) Velluz, L.; Valls, J.; Nominé, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 181. (b) Taub, D. In "Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973, Vol. 2. (c) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974. (d) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. See also: (e) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. (f) Landsbury, P. T. *Ibid* **1972**, *5*, 311. (g) Stork, G.; Stotter, P. L. *J. Am. Chem. Soc.* **1969**, *91*, 7780. (h) Brown, H. C.; Negishi, E.-I. *Chem. Commun.* **1968**, 594. (i) Grubbs, R. H.; Miyashita, A. *Ibid.* **1977**, 864. (j) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378. (k) Grieco, P. A.; Takigawa, T.; Moore, D. R. *Ibid* **1979**, *101*, 4380. (l) Stork, G.; Logusch, E. W. *Tetrahedron Lett.* **1979**, 3361. (m) Kametani, T.; Matsumoto, H.; Honda, T.; Fukumoto, K. *Tetrahedron Lett.* **1980**, *21*, 4847.

(3) Angular methyl groups have been introduced by intramolecular Diels-Alder reactions in the *trans*-octalin and *cis*-perhydroindan ring systems: (a) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289. (b) Wilson, S. R.; Mao, D. T. *J. Org. Chem.* **1979**, *44*, 3093. (c) Naf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1979**, *62*, 114. (d) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 5085. (e) Bajorek, J. J. S.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1559. (f) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 1612. (g) See also ref 2m.

(4) Roush, W. R., unpublished results.

(5) Reed, S. F., Jr. *J. Org. Chem.* **1965**, *30*, 1663.

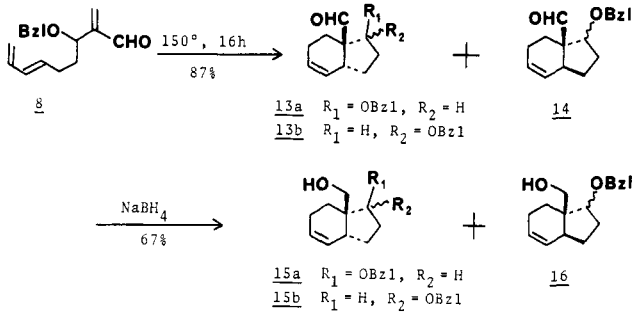
(6) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(7) Depezay, J.-C.; Ficini, J. *Tetrahedron Lett.* **1969**, 4797. Depezay, J.-C.; Le Merrer, Y. *Ibid.* **1974**, 2751, 2755.

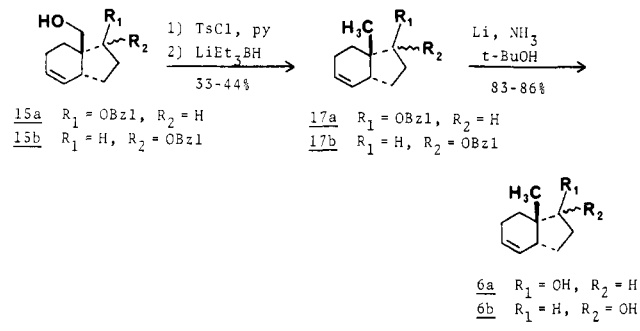
0002-7863/81/1503-6696$01.25/0

at −78 °C afforded alcohol **11** in 36–41% yield. Alternatively, condensation of this aldehyde with the organocopper reagent **10**[8] afforded **11** in somewhat higher yield, 51%. Treatment of **11** with benzyl bromide and NaH in refluxing 1,2-dimethoxyethane (DME) afforded **12**, hydrolysis of which afforded **8** in up to 92% yield.

Cyclization of **8** at 150 °C, in the presence of 2,6-di(*tert*-butyl)-4-methylphenol (BHT) added as a polymerization inhibitor, afforded a mixture of three cycloadducts and uncyclized **8** in 87% combined yield. The ratio of products was determined by integration of the carboxaldehyde resonances in the ^{1}H NMR spectrum: **13a** (38%), **13b** (34%), **14** (22%), and uncyclized **8** (6%). These isomers could not be separated at this stage. Rather, $NaBH_4$ reduction of this mixture afforded a separable mixture of alcohols **15a**, **15b**, and **16** (67% combined yield). PCC oxidation of the individual alcohols afforded pure samples of Diels–Alder adducts **13a**, **13b**, and **14**, respectively.



The ring fusion stereochemistry of aldehydes **13a** and **13b** was determined as follows. Alcohols **15a** and **15b** were tosylated (47–59%, 66–76% based on consumed **15a**, **15b**), and the resulting tosylates were reduced with lithium triethylborohydride[9] in refluxing THF to afford benzyl ethers **17a** and **17b** in 70–75% yield. Debenzylation of these isomers afforded the two epimers of alcohol **6** (83–86% yield), PCC oxidation of which, as before, afforded ketone **2** in greater than 80% yield. Thus, **13a** and **13b** possess cis ring fusions. Hence, the ratio of cis:trans-fused products from the cyclization of **8** is 77:23.[10]

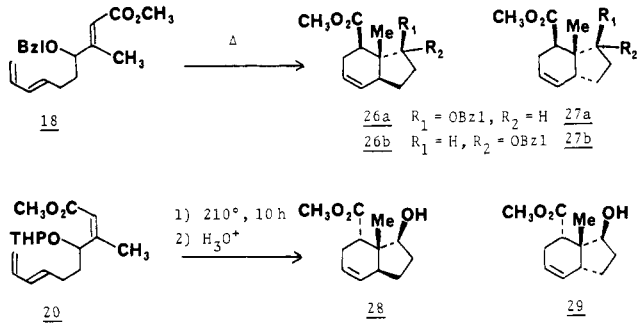


An attempt to alter the selectivity of this cyclization by catalysis[11] with menthyloxyaluminum dichloride[12] led only to polymerization of **8**.

We thus turned to consideration of the effect of activating groups placed at the terminus of the dienophile. Accordingly, triene esters **18**, **19**, and **20** were chosen for study. Syntheses of these compounds are outlined in Scheme I.

Condensation of (*E*)-hepta-4,6-dienal with α-ethoxyvinyllithium[13] in THF at −78 °C followed by alcohol protection and enol ether hydrolysis afforded **21** in 67–75% overall yield. Wadsworth–Emmons–Horner reaction of **21** with the lithium anion of trimethylphosphonoacetate in THF afforded an easily separated 81:19 mixture of **18** and **19** in 72–79% combined yield. The dienophile stereochemistry of **18** and **19** was assigned by comparison of the chemical shifts of the vinyl CH_3 groups.[14]

A far superior route to (*Z*)-triene **20** involved treatment of (*E*)-hepta-4,6-dienal with HC≡CMgBr in THF at 0 °C followed by alcohol protection to give **22** in 73% yield. Carbomethoxylation of **22** afforded the thermally unstable ester **23** which readily undergoes an intramolecular Diels–Alder reaction to **24**. Crude **23**, without purification, was treated with $(CH_3)_2CuLi$ in diethyl ether (−78 °C, 5 min)[15] to afford **20**, a mixture of THP diastereomers, in 85–90% overall yield. The stereochemistry assigned to **20** was confirmed by separation of the THP diastereomers and hydrolysis of each to the same butenolide, **25**.

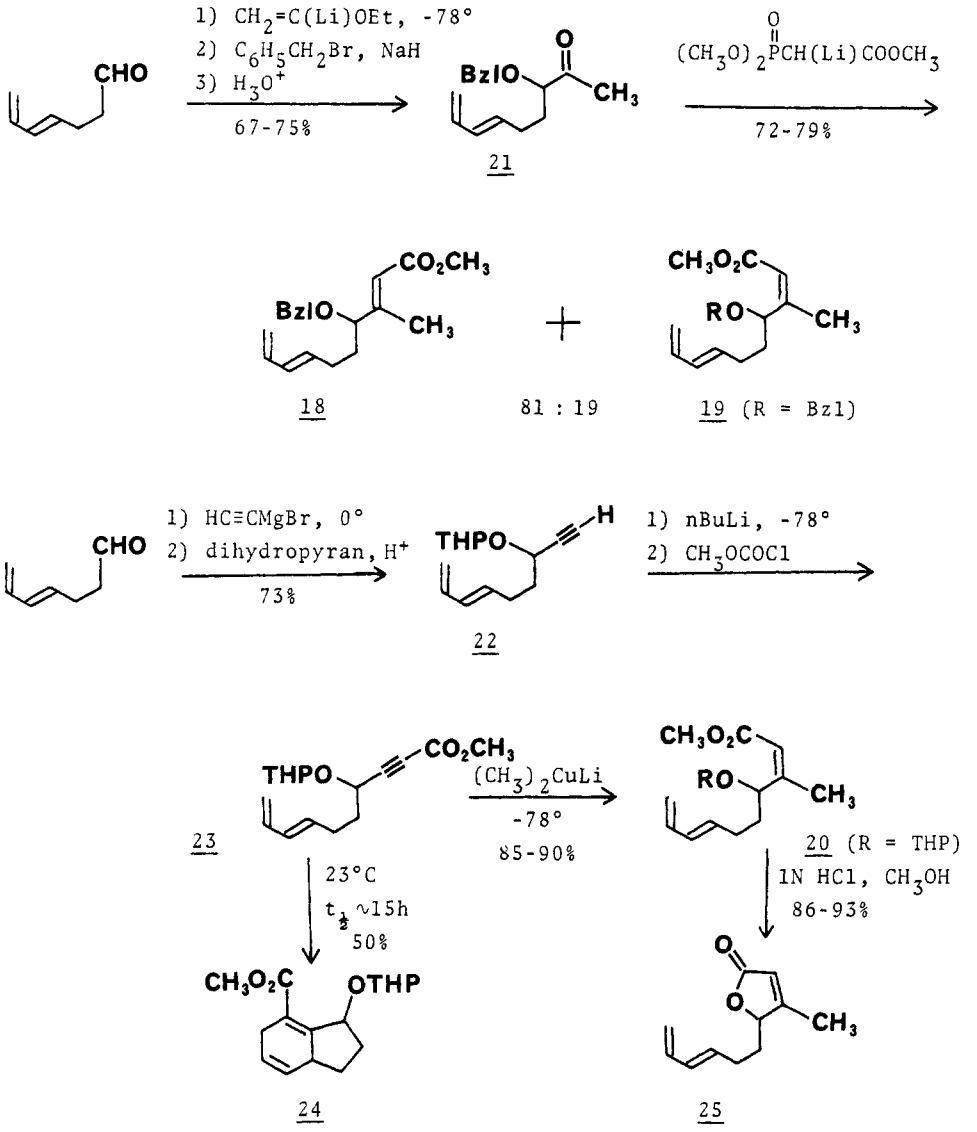


Cyclization of **18** (toluene, bis(trimethylsilyl)acetamide, 250 °C, 6 h, 75%; 240 °C, 11 h, 67%; 220 °C, 37 h, 53%) afforded a mixture of four cycloadducts, the ratios of which were determined by integration of the angular methyl signals in the ^{1}H NMR spectrum of the mixture: **26a** (40%), **26b** (30%), **27a** (17%), and **27b** (13%). The ratio of these isomers did not vary as a function of reaction temperature. Chromatography of these mixtures afforded homogeneous samples of **26b** and **27b** and a 3:1 mixture of **26a**:**27a**. A pure sample of **26a** was obtained by saponification of the latter mixture followed by fractional crystallization of the corresponding acids and then CH_2N_2 esterification. The stereochemistry assigned to these compounds was confirmed by the chemical evidence summarized in Scheme II. It is clear from these results that trans-fused cycloadducts predominate in the cyclization of **18** but only with moderate selectivity (~70:30). Attempts to catalyze the cyclization of **18** with $AlCl_3$ or $EtAlCl_2$ were unsuccessful.[11]

In contrast, cyclization of **20** afforded mainly a mixture of two, rather than four, products. Hydrolysis of this mixture followed by chromatography afforded hydroxy esters **28** and **29** in 76–80% yield.[16] The ratio of **28**:**29** was determined to be 80:20 by gas chromatography.[17] The minor product **29** was shown to possess a cis ring fusion by PCC oxidation to **30** followed by $NaBH_4$ reduction to lactone **31** (Scheme II). PCC oxidation of **28** afforded ketone **32**, $NaBH_4$ reduction of which afforded unchanged **28**. This series of transformations allows assignment of stereochemistry to C-1 of **28**, since $NaBH_4$ is expected to approach **32** from the face opposite to the angular methyl group.[18]

(8) Grieco, P. A., Wang, C. J.; Majetich, G. *J. Org. Chem.* **1976**, *41*, 726.
(9) Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 171.
(10) Professor D. S. Taber, Vanderbilt University, has informed us of his analogous results with a triene related to **8**.
(11) For references to previous studies of Lewis acid-catalyzed intramolecule Diels–Alder reactions, see Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1980**, *45*, 4267.
(12) Hashimoto, S.-I., Korneshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437; Hayakawa, Y.; Fueno, T.; Furukawa, J. *J. Polym. Sci.* **1967**, *5*, 2099.
(13) α-Ethoxyvinyllithium was prepared using the procedure described for α-methoxyvinyllithium: Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
(14) Jackman, L. M.; Wiley, R. H. *J. Chem. Soc.* **1960**, 2886.
(15) (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (b) Siddall, J. B.; Biskup, M.; Fried, J. H. *Ibid.* **1969**, *91*, 1853. (c) Klein, J.; Turkel, R. M. *Ibid.* **1969**, *91*, 6186. (d) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *Ibid.* **1972**, *94*, 4395.
(16) In one case, the Diels–Alder reaction of **20** also afforded small quantities (~5% total) of alcohols **33a** and **33b**, which we believe derive from the *E* isomer of **20**, a probable isomeric impurity produced during the cuprate reaction of **23**.
(17) The Diels–Alder reaction of **19** (210 °C, 11 h) afforded the benzyl ethers corresponding to **28** and **29** in the ratio 82:18 (83% yield).
(18) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold Publishing Corp.: New York, 1959. See also, ref 2a–c.

Scheme I



The stereochemical assignments for **26a**, **26b**, and **27a** were confirmed by correlation with **28** and **29** (Scheme II). Debenzylation of **26b** afforded **33b** in 84% yield, while analogous deprotection of the 3:1 mixture of **26a** and **27a** afforded **33a** (41%) and **34** (14%), respectively. Alcohol **33a** prepared in this manner was identical in all respects with a sample prepared by epimerization of **28** (ratio **33a**:**28** = 80:20, 62% yield). Similarly, **34** and **29** were correlated by epimerization (ratio **34**:**29** = 55:45, 83% yield). Oxidation of either **33a** or **33b** with PCC afforded ketone **35** in 83–88% yield. Reduction of **35** with $NaBH_4$ afforded an 87:13 mixture of **33a**:**33b** (86% yield), thus confirming the assignment of stereochemistry to C-1 of these isomers. Finally, PCC oxidation of **34** afforded **36** in 87% yield. Therefore, **26a**, **26b**, and **28** must possess trans ring fusions.

In retrospect, it is possible to assign stereochemistry to these Diels–Alder adducts on the basis of spectroscopic data. For example, the ^1H resonance for the angular methyl groups can be used to assign ring fusion stereochemistry; in all cases, the angular methyl groups of the trans-fused compounds appear at higher field than does the angular methyl resonance for the corresponding cis-fused isomers.[19] When observable, the C=C stretching frequency for trans-fused compounds appeared in the range 1635–1645 cm^{-1}, whereas for the cis-fused isomers this stretching frequency occurred in the range 1650–1660 cm^{-1}.[1e] The lower frequency observed for the trans-fused isomers undoubtedly reflects the inherent strain of this ring system.[2a,20] In addition, the resonance for H_7, the proton α to the carbomethoxyl group, provides much useful stereochemical information. For trans-fused compounds such as **26a** and **33a**, the signal for C-7H appears as a doublet of doublets, J = 10–11 and 6–6.4 Hz. These data require that the carbomethoxyl group occupy an equatorial position in these compounds. For **28**, C-7H appears as a doublet of doublets, J = 5.9, 2.1 Hz, which requires that the carbomethoxyl group occupy an axial position. On the other hand, the magnitude of the coupling constants for the C-7H resonances of **27a** (dd, J = 6.0, 2.8 Hz), **36** (t, J = 5.5 Hz), **29** (dd, J = 6.5, 4.5 Hz), and **30** (t, J = 5.9 Hz) implies conformational mobility in these compounds, particularly for **29**, **30**, and **36**, which is possible only if the ring fusions are cis.

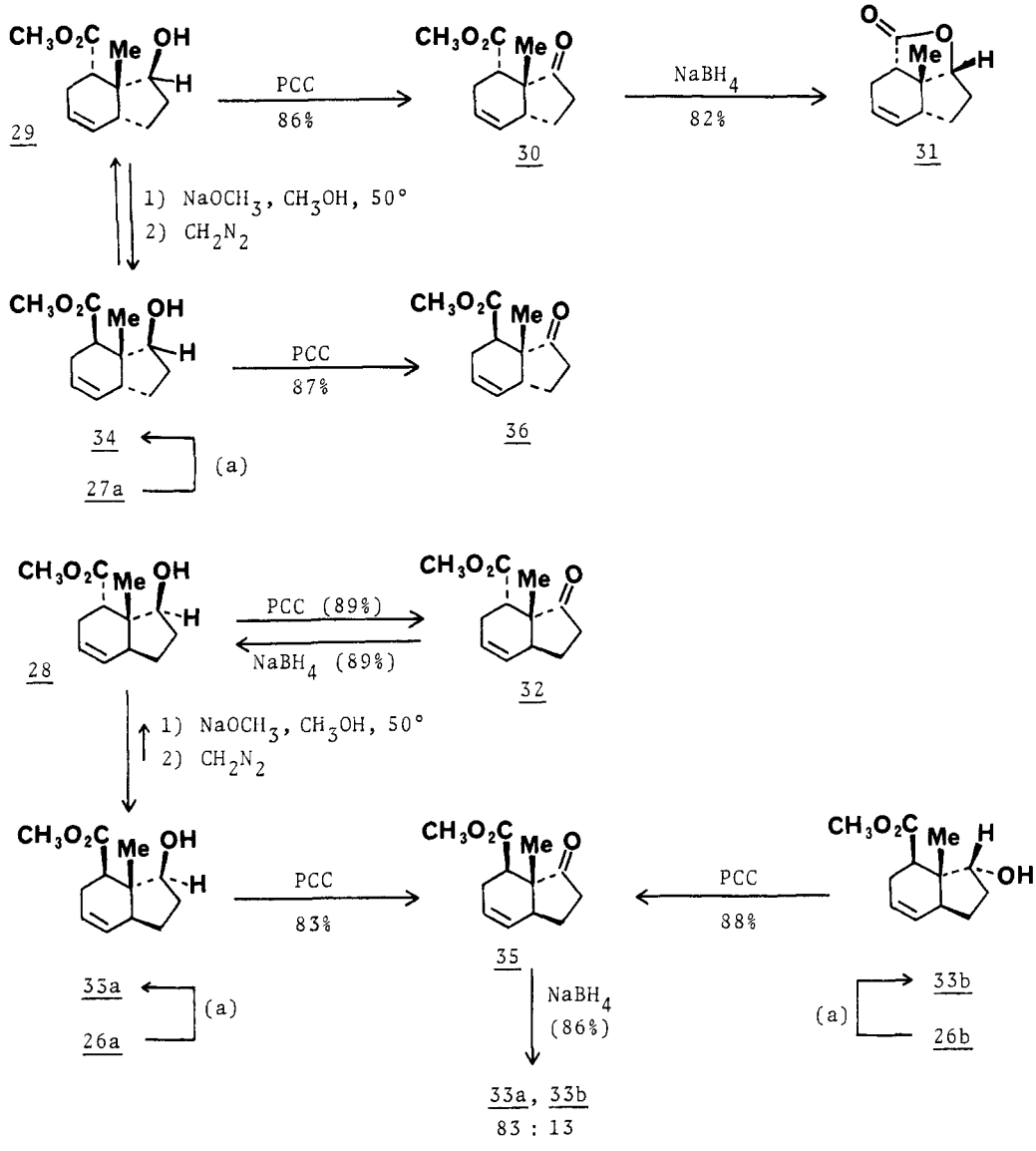
This study demonstrates that the dienophile activating group plays a crucial role in determining the stereochemical outcome of intramolecular Diels–Alder reactions. The stereoselectivity in these cases, however, is not a consequence of classical secondary orbital stabilization of endo transition states.[21] Our previous

(19) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1972; pp 241–245, and references therein.

(20) An analogous trend has been observed in the IR spectra of cis- and trans-fused bicyclo[4.3.0]non-3-enes: Turecek, F.; Vystrcil, A. *Collect. Czech. Chem. Commun.* **1976**, *41*, 1581. We thank Dr. Turecek for bringing this work to our attention.

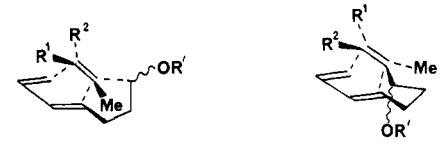
(21) Hoffman, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4388.

Scheme II



(a) (i) NaOH, CH_3OH, 95°; (ii) Li, NH_3, t-BuOH, -33°; (iii) CH_2N_2

studies of methyl deca-2,8,10-trienoates[1b-e] and methyl undeca-2,8,10-trienoates[22] established that product distributions from thermal cyclizations of carbomethoxyl activated trienes, which in most cases require temperatures of at least 150 °C for a practical rate of cyclization, are independent of dienophile stereochemistry. It is well known that the endo rule is well obeyed by open-chain dienes and dienophiles only at low reaction temperatures.[23] The preferential formation of trans-fused products from the decatrienoates, then, was rationalized by molecular model analyses which indicated that the transition states leading to the cis-fused products were destablized by strain and subtle nonbonded interactions relative to the trans-fused transition states.[1b,d] Differences in transition-state strain were apparent only if one moved the dienophile away from the butadiene, along the reaction coordinate, until the geometry of the boat conformation of the product cyclohexene was reached.[1d] The present results with unsaturated esters **18** (preferential endo cyclization), **19**,[17] and **20** (preferential exo cyclization) appear to be fully consistent with this model. In terms of the transition states involved, the major products from **18**–**20** arose in each case from transition state A.



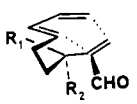
A B

endo-18	$R_1 = COOCH_3$, $R_2 = H$	*exo*-18
exo-19,20	$R_1 = H$, $R_2 = COOCH_3$	*endo*-19,20
endo-4	$R_1 = R_2 = H$	*exo*-4

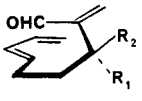
This model cannot be entirely correct, however. If strain and steric interactions alone are responsible for the preferential formation of trans-fused cycloadducts from the decatrienoates, then one would predict that the cyclization of **4** should also show a preference for the trans-fused product, for the cis-fused transition state (B) of **4** is no less strained than the exo transition state (B) of **18**, nor is the trans-fused transition state (A) of **4** any more strained or sterically encumbered than the exo transition state (A) of **19** or **20**. Clearly, other factors must also be involved since the cyclization of **4** afforded a 1:1 mixture of trans- and cis-fused products.

(22) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.
(23) Reviews of the Diels–Alder reaction: (a) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (b) Sauer, J. *Ibid.* **1967**, *6*, 16. (c) Onishenko, A. S. "Diene Synthesis" (Engl. Trans.); Israel Program for Scientific Translations: Jerusalem, 1964. (d) Wollweber, H. "Diels–Alder Reaction", Georg Thieme Verlag: Stuttgart, 1972, and references therein.

This model is further weakened by the results of cyclization of **8**, which afforded a 77:23 mixture of cis:trans-fused products. In this case, the major products derived from transition state C



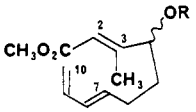
C



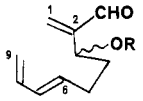
D

in which the carboxaldehyde group occupies an exo position relative to the diene. Based on the rationale mentioned above, it would be expected that cis-fused transition state C should be somewhat higher in energy than trans-fused transition state D.

It has been suggested that Diels–Alder reactions involving unsymmetrical components occur by concerted but nonsynchronous mechanisms in which bond formation between the olefinic termini having the largest coefficients precedes bond formation at the other center.[24] In the cases of **18–20**, as well as for all of the other decatrienoates studied in our laboratory, the coefficient of the LUMO at C-3 should be greater than the coefficient at



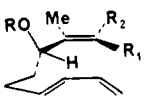
18

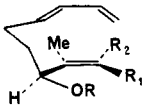


8

C-2.[24b] The HOMO coefficients of the two terminal diene carbons should be comparable.[25a] Hence, bonding between carbons 3 and 7 should precede bonding between carbons 2 and 10.[24b,25b] Under these circumstances, steric or nonbonded interactions involving the atoms on the chain separating the diene and dienophile develop at an early stage of the reaction and become a dominant factor on the course of the reaction. Analysis of molecular models indicates that these interactions are most severe in the cis-fused transition state as was originally suggested.[1b,d,24a] In the case of **8**, however, the LUMO coefficient at C-1 should be larger than the coefficient at C-2, and bonding between carbons 1 and 9 therefore should precede bonding between carbons 2 and 6. Examination of molecular models of **8** reveals that close approach of carbons 1 and 9 is best accommodated by a skewed cis-fused transition state in which non-bonded interactions between the diene and dienophile are minimized. This, presumably, becomes the dominant factor in the cyclization of **8**.[26] For **4**, on the other hand, the coefficients of the dienophilic carbons should fall between the limits defined by the coefficients of **8** and **18–20**, and hence the cyclization of **4** would be expected to be less selective than these other trienes.

Another interesting aspect of these reactions is the high degree of internal asymmetric induction realized in the cyclizations of **19**[17] and **20**. This presumably reflects the preference for the allylic systems of these compounds to adopt eclipsed conformation E, in which steric interactions between the allylic substituents and the carboalkoxyl group are minimized.[27] Exo cyclization via





E $R_1 = COOCH_3$, $R_2 = H$ F

G $R_1 = H$, $R_2 = COOCH_3$ H

conformation E leads to **28**, whereas endo cyclization via E leads to **29**. Products of cyclization via conformation F were not observed in the cyclizations of **19** or **20**. Analogous steric interactions are less pronounced in the allylic conformations G and H of **18**, and cyclization occurs readily from either conformation. The ratio of products deriving from conformations G and H for **18** is 57:43. It is noteworthy that the magnitude of asymmetric induction realized in the cyclizations of **18** vs. **20** is consistent with the relative degrees of asymmetric induction realized in the peracid oxidations and cyclopropanations of *E* vs. *Z* allylic alcohols.[28]

This study demonstrates that the angularly methylated *trans*-perhydroindan ring system can be constructed by intramolecular Diels–Alder reactions, but that maximum selectivity is achieved only if the dienophile possesses a terminal activating substituent. The use of carbon-based dienophile activating groups may pose problems in applications of these reactions to steroid or vitamin D syntheses, since these natural products do not possess carbon substituents at C-12 of the steroid or seco-steroid ring systems. We are currently studying methods for increasing the selectivity of these cyclizations and will report on these studies in due course.

Experimental Section

^1H NMR spectra were measured at 60 MHz on Perkin-Elmer R-24B and Varian T-60 instruments, at 90 MHz on a JOEL HFX 90Q instrument, at 250 MHz on a Bruker 250 instrument, and at 270 MHz on a Bruker 270 instrument located at the NMR facility, Francis Bitter National Magnet Laboratory. Chemical shifts are reported in δ units relative to internal Me_4Si. Infrared spectra were measured on a Perkin-Elmer Model 283B infrared spectrophotometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. High resolution mass spectra were provided by the Facility supported by NIH Grant RR0317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high-resolution mass spectrometer equipped with an IBM 1800 computer system to process data recorded on photographic plates. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ. Melting points were recorded on a Fisher-Johns hot-stage melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried (120 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from sodium benzophenone ketyl; CH_2Cl_2 and Me_2SO were distilled from CaH_2; benzene was distilled from $LiAlH_4$; toluene was distilled from sodium metal. Preparative thin layer chromatography (TLC) was performed using 20 × 20 cm plates coated with 0.25-, 0.5-, and 1.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether. Column chromatography was performed using activity I Woelm silica gel. Flash chromatography was performed as described by Still.[29] All chromatography solvents were distilled prior to use.

2-Methyl-3-tetrahydropyranyloxynona-1,6(*E*),8-triene (4). To 221 mg (9.1 mmol) of Mg turnings and two small iodine crystals in 15 mL of THF was added 0.2 mL of 2-bromopropene. After the reaction was initiated, an additional 0.6 mL (total: 0.8 mL, 9.0 mmol) of 2-bromopropene was added. After 40 min, 625 mg (5.7 mmol) of (*E*)-hepta-

(24) (a) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146. (b) Houk, K. N. *Ibid* **1973**, *95*, 4092. (c) McIver, J. W. *Acc. Chem. Res.* **1974**, *7*, 72. (d) **Note Added in Proof**: see also, White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273.

(25) (a) Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, 1313. (b) Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1976; p 121.

(26) (a) An alternative explanation for these results is that the cyclization of **8** may be dominated by the well-known preference of α-alkyl-substituted acrylate derivatives to undergo exo-Diels–Alder reactions (Konovalov, A. I.; Kamasheva, G. I.; Loskutow, M. P. *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 2064. Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297). (b) Control experiments established that the cyclizations of **8** and **18** are kinetically controlled. It is most probable that the cyclizations of **4**, **19**, and **20** are also kinetically controlled.

(27) (a) Kilb, R. W.; Lin, C. C.; Wilson, E. B., Jr. *J. Chem. Phys.* **1957**, *26*, 1695. (b) Herschbach, D. R.; Krisher, L. C. *Ibid* **1958**, *28*, 728. (c) Bothner-By, A. A.; Naar-Colin, C.; Günther, H. *J. Am. Chem. Soc.* **1962**, *84*, 2748. (d) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis", Interscience Publishers: New York, 1965; pp 19–22.

(28) These reactions have recently been reviewed. See Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2, and references cited therein.

(29) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

4,6-dienal[5] in 5.0 mL of THF was added. This mixture was stirred for 75 min, and then 10 mL of saturated aq. NH_4Cl, 30 mL of H_2O, and 20 mL of ether were added. The organic phase was removed, and the aqueous phase was extracted with CH_2Cl_2 (4×). The combined extracts were dried (Na_2SO_4), filtered, and distilled at atmospheric pressure to a residual volume of 5 mL. This was then dried (Na_2SO_4), filtered, and combined with 4 mL of CH_2Cl_2, a small crystal of *p*-TsOH, and 0.72 mL (8.0 mmol) of dihydropyran. This solution was stirred at room temperature for 25 min, after which the mixture was filtered through Florisil and evaporated to give the crude product. This material was purified by flash chromatography (40 mm column, 20:1 hexane–ether) giving 919 mg (69%) of pure **4**: R_f 0.61 (3:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 5.79–6.52 (m, 3 H), 4.84–5.20 (m, 4 H), 4.59 (m, 1 H), 4.13 (m, 2 H), 3.55 (m, 1 H), 1.58–2.21 (m, 13 H); two CH_3 signals occur at δ 1.65 and 1.75 (THP diastereomers); IR (CH_2Cl_2) cm^{-1} 3080, 3020, 2950, 2850, 1650, 1600; mass spectrum *m/e* 236 (parent ion). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.94; H, 10.07.

Cyclization of 4: 7aβ-Methyl-2,3,3aα,6,7,7a-hexahydro-1*H*-indenone (7) and 7aβ-Methyl-2,3,3aβ,6,7,7a-hexahydro-1*H*-indenone (2). A solution of 655 mg (2.8 mmol) of **4** in 8 mL of dry toluene was transferred to a resealable Carius tube. Bis(trimethylsilyl)acetamide (BSA, 0.2 mL) was added and the resulting mixture was degassed with a stream of argon. The sealed tube was heated at 220 °C for 30 h in an oil bath, and then all volatile components were removed in vacuo. The residue was treated with 4 mL of MeOH and 4 mL of 1 N HCl for 40 min at room temperature. The solution was diluted with 15 mL of H_2O and extracted with CH_2Cl_2 (5×). The combined extracts were dried (Na_2SO_4), filtered, and evaporated. The concentrate was chromatographed over 80 g of silica gel using 1:1 hexane–ether eluant to afford 177 mg (42%) of a mixture of four different alcohols (R_f of mixture 0.2, 3:1 hexane–ether). The ^1H NMR spectrum of this mixture showed the presence of four angular methyl groups: δ 0.96 and 0.91 (assigned to alcohols **6**) and 0.73 and 0.63 (assigned to alcohols **5**). GC analysis of the silyl ethers of **5** and **6** (18 ft × $^1/_8$ in. QF-1 column, 130 °C, 10 mL/min) revealed the presence of four bands which did not fully resolve: retention times 7.0, 7.25, 7.75, and 8.0 min, respectively.

To 130 mg (0.85 mmol) of this mixture in 10 mL of CH_2Cl_2 was added 396 mg (1.8 mmol) of PCC.[6] The mixture was stirred for 2 h at room temperature and then diluted with 10 mL of ether. The organic phase was removed and the residue rinsed with CH_2Cl_2 (3×). The combined organic layers were filtered through Florisil and concentrated in vacuo. GC analysis (10 ft × $^1/_8$ in. SE-30 column, 130 °C, 12.8 mL/min) of the crude product revealed that **7** (retention time 5.9 min) and **2** (retention time 7.1 min) were present in a 50:50 ratio. This mixture was separated by chromatography on a 0.5-mm silica gel preparative plate (4:1 hexane–ether, two developments; mixed fractions were rechromatographed) to give 45 mg (35%) of pure **7** and 45 mg (35%) of pure **2**.

7: R_f 0.54 (1:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 5.66 (s, 2 H), 1.04–2.49 (m, 9 H), 0.89 (s, 3 H); IR (neat) cm^{-1} 3020, 2925, 1740; mass spectrum *m/e* 150 (parent ion). The 2,4-dinitrophenylhydrazone derivative of **7** was prepared and had mp 181.5–182.0 °C (CH_3OH); high resolution mass spectrum (calcd for $C_{16}H_{18}N_4O_4$) 330.13609 (found: 330.13426).

2: R_f 0.58 (1:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 5.70 (s, 2 H), 1.21–2.35 (m, 9 H), 1.04 (s, 3 H); IR (neat) cm^{-1} 3020, 2985, 2935, 1740; mass spectrum *m/e* 150 (parent ion). The 2,4-DNP derivative of **2** was prepared and had mp 150–150.5 °C (CH_3OH; lit.[3e] mp 147–148 °C).

1,1-Diethoxy-3-hydroxy-2-methylenenona-6(*E*),8-diene (11). To a solution of 1.20 g (5.7 mmol) of 1,1-diethoxy-2-bromo-2-propene in 6 mL of ether at −78 °C was added 2.30 mL (5.6 mmol) of 2.45 M *n*-BuLi in hexane. After 30 min at −78 °C, the mixture was warmed to −65 °C and stirred for 30 min. The mixture was then recooled to −78 °C and transferred to a well-stirred, precooled (−78 °C) suspension of 1.09 g (5.7 mmol) of cuprous iodide (CuI) in 6 mL of ether. After 30 min at −78 °C, the mixture was slowly warmed (30 min) to −50 °C and then recooled to −78 °C.[8] To this mixture was then added 275 mg (2.5 mmol) of (*E*)-hepta-4,6-dienal[5] in 4 mL of ether. The resulting mixture was stirred at −78 °C (30 min) and −65 °C (60 min) and then slowly warmed (30 min) to −30 °C. The reaction was then quenched with 25 mL of saturated aqueous NH_4Cl. The resulting suspension was filtered through Celite, and the ether layer was removed. The aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed over 80 g of silica gel with 4:1 (500 mL) and 1:1 (500 mL) of hexane–ether as eluant to give 304 mg (51%) of pure **11**: R_f 0.22 (3:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 5.95–6.42 (m, 3 H), 5.27 (br s, 2 H), 5.09 (m, 2 H), 4.90 (s, 1 H), 3.76 (br q, J = 2.2, 4.9 Hz, 1 H), 3.30–3.70 (m, 4 H), 2.74 (d, J = 4.9 Hz, 1 H), 1.30–1.85 (m, 4 H), 1.21 (t, J = 5.3 Hz, 6 H); IR (CH_2Cl_2) cm^{-1} 3600, 3520, 3090, 3040, 2970, 2930, 2880, 1720, 1650, 1605; mass spectrum *m/e* 194 (parent ion minus ethanol; no parent ion observed).

3-Benzyloxy-2-methylenenona-6(*E*),8-dienal (8). A solution of 508 mg (2.12 mmol) of **11** in 7 mL of dry DME was added to 153 mg (3.2 mmol) of a 50% dispersion of NaH in oil (prewashed with dry ether to remove oil). This mixture was stirred for 5 min, and then 0.30 mL (2.5 mmol) of benzyl bromide was added. This mixture was heated at 85 °C for 4 h, and then was allowed to stand at room temperature for 8 h. The solution was diluted with 40 mL of brine and extracted with CH_2Cl_2 (4 × 25 mL portions). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo, giving crude **12**. Without purification, the crude **12** was dissolved in a mixture of 5 mL of 1 N HCl and 15 mL of acetone. This mixture was stirred at room temperature for 4.5 h and then diluted with 40 mL of H_2O. The solution was extracted with CH_2Cl_2 (4 × 20 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Aldehyde **8** was purified by chromatography on 60 g of silica gel (20:1 hexane–ether), giving 496 mg (92%) of pure **8**: R_f 0.39 (3:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 9.63 (s, 1 H), 7.32 (s, 5 H), 6.55 (s, 1 H), 4.90–6.54 (m, 6 H), 4.23–4.55 (m, 3 H), 2.16 (m, 2 H), 1.70 (m, 2 H); IR (CH_2Cl_2) cm^{-1} 3040, 2930, 2885, 1690, 1655, 1605; mass spectrum *m/e* 256 (parent ion). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.24; H, 8.04.

Cyclization of 8: 1-Benzyloxy-2,3,3aβ,6,7,7a-hexahydroindene-7aβ-carboxaldehyde (13a and 13b) and 1-Benzyloxy-2,3,3aα,6,7,7a-hexahydroindene-7aβ-carboxaldehyde (14). A solution of 281 mg (1.1 mmol) of triene **8** in 7 mL of CCl_4 was transferred to a resealable Carius tube. 2,6-Di(*tert*-butyl)-4-methylphenol (BHT, 4 mg, 0.02 mmol) was added, and the resulting mixture was degassed with a stream of argon. The sealed tube was heated at 150 °C for 18 h in an oil bath, and then all volatile components were removed in vacuo. The residue was chromatographed on two 1.5-mm silica gel plates (3:1 hexane–ether) to afford 245 mg (0.96 mmol, 87%) of a mixture of cycloadducts. Analysis of this mixture by ^1H NMR spectroscopy indicated that four compounds were present: **13a** (38%), **13b** (34%), **14** (22%), and the (*Z*)-butadiene isomer of **8** (6%). Product ratios were assigned by careful integration of the carboxaldehyde resonances. Pure samples of the individual Diels–Alder adducts were obtained as follows.

To a solution of 219 mg (0.85 mmol) of the above mixture of Diels–Alder adducts in 6.0 mL of absolute EtOH was added 50 mg (1.3 mmol) of $NaBH_4$. This mixture was stirred at room temperature for 1.5 h, and then 15 mL of 1 N HCl was added. The resulting solution was extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed on two 0.5-mm silica gel plates (3:1 hexane–ether, two developments; the R_f's which follow are for one developement in this solvent system) to give 44 mg (20%) of **15a** (R_f 0.22), 43 mg (20%) of **15b** (R_f 0.17), and 59 mg (27%) of **16** (R_f 0.13) contaminated with the alcohol corresponding to uncyclized triene.

15a: NMR ($CDCl_3$, 90 MHz) δ 7.32 (s, 5 H), 5.64 (br s, 2 H), 4.65, 4.38 (AB, J_{AB} = 11.6 Hz, benzylic CH_2), 3.81–3.44 (m, 4 H), 2.99 (t, J = 6.7 Hz, 1 H), 2.20–1.13 (m, 8 H); IR (CH_2Cl_2) cm^{-1} 3525, 3020, 2930, 2870, 1650, 1605; mass spectrum *m/e* 258 (parent ion); high resolution mass spectrum (calcd for $C_{17}H_{22}O_2$) 258.16198 (found: 258.16288).

15b: NMR ($CDCl_3$, 90 MHz) δ 7.32 (s, 5 H), 5.65 (br s, 2 H), 4.64, 4.43 (AB, J_{AB} = 12.0 Hz, benzylic CH_2), 3.90–3.44 (m, 4 H), 2.39–1.13 (m, 9 H); IR (CH_2Cl_2) cm^{-1} 3620, 3530, 3025, 2950, 2880, 1650, 1605; mass spectrum *m/e* 258 (parent ion); high resolution mass spectrum (calcd for $C_{17}H_{22}O_2$) 258.16198 (found: 258.16113).

To 18 mg (0.07 mmol) of **15a** in 2.0 mL of CH_2Cl_2 was added 35 mg (0.16 mmol) of pyridinium chlorochromate (PCC).[6] The mixture was stirred for 2 h at 25 °C and then was filtered through Florisil. The dark residue was washed portionwise with 10 mL of Et_2O, and the washings were filtered through Florisil. The combined organic layers were concentrated in vacuo, giving the crude product which was chromatographed on a 0.25-mm silica gel plate (3:1 hexane–ether, R_f 0.58). In this manner there was obtained 16 mg (0.06 mmol, 86%) of aldehyde **13a**: NMR ($CDCl_3$, 90 MHz) δ 9.68 (s, 1 H), 7.29 (s, 5 H), 5.68 (br s, 2 H), 4.56, 4.35 (AB, J = 12.0 Hz, benzylic CH_2), 3.92 (t, J = 5.1 Hz, 1 H), 3.02 (br t, J = 7.8 Hz, 1 H), 2.2–1.3 (m, 8 H); IR (CH_2Cl_2) cm^{-1} 3025, 2925, 2875, 2725, 1725, 1650, 1605; mass spectrum *m/e* 256 (parent ion); high resolution mass spectrum (calcd for $C_{17}H_{20}O_2$) 256.14633 (found: 256.14726).

Oxidation of 20 mg of **15b** by an analogous procedure afforded 14 mg (66%) of pure aldehyde **13b**: R_f 0.56 (3:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 9.57 (s, 1 H), 7.30 (s, 5 H), 5.68 (m, 2 H), 4.45 (s, 2 H), 4.11 (t, J = 7.8 Hz, 1 H), 2.60 (br t, J = 5.6 Hz, 1 H), 2.2–1.5 (m, 8 H); IR (CH_2Cl_2) cm^{-1} 3025, 2960, 2875, 2705, 1720, 1650, 1605; mass

spectrum m/e 256 (parent ion); high resolution mass spectrum (calcd for $C_{17}H_{20}O_2$) 256.14633 (found: 256.14786).

Oxidation of 24 mg of the mixture of **16** and triene alcohol using the procedure described for **15a** afforded 10 mg (42%) of **14** and 6 mg (22%) of the (*Z*)-butadiene isomer of **8**. These compounds were easily separated by silica gel chromatography (0.25-mm plate, 3:1 hexane-ether; R_f (**14**) 0.56; R_f ((*Z*)-**8**) 0.48).

14: NMR ($CDCl_3$, 90 MHz) δ 9.75 (s, 1 H), 7.30 (s, 5 H), 6.00 (br d, J = 11.7 Hz, 1 H), 5.68 (m, 1 H), 4.59, 4.43 (AB, J = 12.2 Hz, benzylic CH_2), 3.94 (d, J = 4.4 Hz, 1 H), 2.36 (br s, 1 H), 2.16–1.13 (m, 8 H); IR (CH_2Cl_2) cm^{-1} 3025, 2940, 2880, 2740, 1715, 1605; mass spectrum m/e 165 (*p*-tropylium ion; no parent ion observed); high resolution mass spectrum (calcd for $C_{10}H_{13}O_2$) (loss of tropylium ion) 165.09155 (found: 165.08848).

(*Z*)-**8**: NMR ($CDCl_3$, 90 MHz) δ 9.65 (s, 1 H), 7.33 (s, 5 H), 6.56 (s, 1 H), 6.17 (s, 1 H), 5.86–5.52 (m, 2 H), 5.1–4.9 (m, 3 H), 5.08 (m, 3 H), 1.7–0.9 (m, 4 H).

Degradation of 15a to 2. To 44 mg (0.17 mmol) of **15a** in 1.5 mL of pyridine was added 38 mg (0.20 mmol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 60 °C for 6 h and then was diluted with 15 mL of H_2O. The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried, filtered, and concentrated in vacuo. The crude product was chromatographed (1.5-mm silica gel preparative plate, 3:1 hexane–ether) to give 13 mg (30%) of recovered **15a** and 32 mg (47%) of the desired tosylate (R_f 0.39 (3:1 hexane–ether); NMR (CCl_4, 60 MHz) δ 7.75 (d, J = 8 Hz, 2 H), 7.25 (s and d, 7 H), 5.62 (br s, 2 H), 4.42 (m, 2 H), 4.05, 3.85 (AB, J = 9 Hz, 2 H), 3.65 (m, 1 H), 2.40 (s, 3 H), 2.3–1.1 (m, 9 H)).

Without further purification, the above tosylate (32 mg, 0.08 mmol) was treated with 3.0 mL (3.0 mmol) of 1 M lithium triethylborohydride in THF.[9] The mixture was stirred at 85 °C for 22 h. The solution was cooled, diluted with 20 mL of 1 N HCl, and then extracted with CH_2Cl_2 (4 × 15 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed on a 0.5-mm silica gel preparative plate (3:1 hexane–ether, R_f 0.65) to give 15 mg (75%) of **17a**: NMR (CCl_4, 60 MHz) δ 7.25 (s, 5 H), 5.52 (br s, 2 H), 4.48 (m, 2 H), 3.52 (t, J = 4 Hz, 1 H), 2.20–1.20 (m, 9 H), 1.00 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3020, 2960, 2930, 2880, 1645, 1600.

A solution of 15 mg (0.06 mmol) of benzyl ether **17a** in 0.3 mL of *t*-BuOH and 2.5 mL of Et_2O was added to a solution of 8 mg (1.2 mmol) of lithium dissolved in 15 mL of NH_3 at −78 °C. The mixture turned colorless after 5 min, and 1.0 mL of saturated aqueous NH_4Cl was added. Ammonia was distilled from the reaction mixture, and then 20 mL of 1N HCl was added. The solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo giving 7.3 mg (83%) of **6a**, R_f 0.18 (3:1 hexane–ether). Oxidation of 7.0 mg of **6a** with PCC according to the procedure previously described afforded 6.0 mg (80%) of ketone **2**.

6a: NMR ($CDCl_4$, 60 MHz) δ 5.52 (br s, 2 H), 3.70 (m, 1 H), 2.25–1.2 (m, 9 H), 0.90 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3600, 3020, 2960, 2930, 2880, 1650, 1600; mass spectrum m/e 152 (parent ion); high resolution mass spectrum (calcd for $C_{10}H_{16}O$) 152.12011 (found: 152.12256).

Degradation of 15b to 2. The procedures employed for degradation of **15b** to **2** were the same as those described for the degradation of **15a**. Thus, alcohol **15b** (43 mg, 0.17 mmol) was converted into the corresponding tosylate (43 mg, 59% yield: R_f 0.35 (3:1 hexane–ether) (10 mg (24%) of **15b** was recovered); NMR (CCl_4, 60 MHz) δ 7.60 (d, J = 8 Hz, 2 H), 7.10 (s and d, 7 H), 5.52 (s, 2 H), 4.30 (br s, 2 H), 3.75 (m, 2 H), 3.65 (m, 1 H), 2.35 (s, 3 H), 2.0–1.4 (m, 9 H)).

This tosylate (43 mg, 0.10 mmol) was reduced with lithium triethylborohydride giving 16 mg (70%) of **17b**: R_f 0.74 (3:1 hexane–ether); NMR (CCl_4, 60 MHz) δ 7.25 (s, 5 H), 5.62 (br s, 2 H), 4.48 (m, 2 H), 3.52 (t, J = 6 Hz, 1 H), 2.20–1.20 (m, 9 H), 1.00 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3020, 2975, 2870, 1645, 1600. Benzyl ether **17b** (16.0 mg, 0.07 mmol) was debenzylated with Li in NH_3 giving 8.5 mg (86%) of alcohol **6b** (R_f 0.18, 3:1 hexane–ether). PCC oxidation of **6b** (8.0 mg), as described previously, afforded 7.0 mg (93%) of ketone **2**.

6b: NMR (CCl_4, 60 MHz) δ 5.55 (br s, 2 H), 3.70 (m, 1 H), 2.25–1.2 (m, 9 H), 0.95 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3600, 3020, 2960, 2930, 2880, 1650, 1600; mass spectrum m/e 152 (parent ion).

3-Benzyloxynona-6(*E*),8-dien-2-one (21). To 21 mL (21.9 mmol) of ethyl vinyl ether in 14 mL of THF at −78 °C was added dropwise (over 15 min) 7.8 mL (15.4 mmol) of 1.97 M *t*-BuLi in pentane. The stirred mixture (yellow precipitate) was slowly warmed to 0 °C (clear) and then recooled to −78 °C.[13] To this mixture was then added dropwise 1.10 g (10.0 mmol) of (*E*)-hepta-4,6-dienal[5] in 8 mL of THF. The resulting solution was stirred at −78 °C for 20 min and then slowly warmed to 0 °C. Saturated aqueous NH_4Cl (15 mL) was added. The THF layer was removed and the aqueous layer was extracted with CH_2Cl_2 (5×). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo.

The crude product from the previous step was dissolved in 10 mL of DME. This solution was treated sequentially with 0.774 g (16 mmol) of NaH (50% oil dispersion) and 1.78 mL (15 mmol) of benzyl bromide. The mixture was refluxed for 4 h, cooled, and then diluted with 20 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (7×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo.

The crude mixture of benzyl ethers from the previous step was treated with 10.0 mL of 3 N HCl and 14.0 mL of acetone at ambient temperature for 5 h, after which 20 mL of H_2O was added. The aqueous layer was extracted with CH_2Cl_2 (6×). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to give crude **21**, flash chromatography (50-mm column, 4:1 hexane–ether eluant) of which afforded 1.742 g (71%) of pure **21**: R_f 0.41 (3:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 7.35 (s, 5 H), 4.93–6.50 (m, 5 H), 4.60, 4.39 (AB, J = 11.6 Hz, 2 H), 3.77 (t, J = 6.6 Hz, 1 H), 2.18 (s, 3 H—superimposed on 2.08–2.32 (m, 2 H)), 1.56–1.87 (m, 2 H); IR (CH_2Cl_2) cm^{-1} 3095, 3015, 3005, 2930, 2870, 1710, 1650, 1605; mass spectrum m/e 201 (P − C_2H_3O; no parent ion observed). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65, H, 8.25. Found: C, 78.69; H, 8.44.

Methyl (*E*,*E*)-4-Benzyloxy-3-methyldeca-2,7,9-trienoate (18) and Methyl (*Z*,*E*)-4-Benzyloxy-3-methyldeca-2,7,9-trienoate (19). To 0.72 mL (5.1 mmol) of diisopropylamine in 7 mL of THF at −78 °C was added 1.7 mL (4.1 mmol) of 2.4 M *n*-BuLi in hexane. The mixture was stirred for 15 min and then allowed to warm for 5 min before 0.66 mL (4.1 mmol) of trimethylphosphonoacetate was added. The solution was warmed to 0 °C and then 496 mg (2.0 mmol) of ketone **21** in 4.0 mL of THF was added. The mixture was then stirred at room temperature for 26 h after which it was diluted with 20 mL of saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (6×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product. This material was chromatographed over 80 g of silica gel using 19:1 hexane–ether as eluant to afford 390 mg (64%) of **18** (R_f 0.45, 3:1 hexane–ether) and 95 mg (16%) of **19** (R_f 0.54, 3:1 hexane–ether).

18: NMR ($CDCl_3$, 90 MHz) δ 7.32 (s, 5 H), 4.90–6.38 (m, 6 H), 4.51, 4.22 (AB, J = 11.6 Hz, 2 H), 3.72 (s, 3 H—superimposed on m, 1 H), 2.13 (d, J = 1.2 Hz, 3 H—superimposed on m, 2 H), 1.74 (m, 2 H); IR (CH_2Cl_2) cm^{-1} 3095, 3015, 3005, 2950, 2885, 1715, 1650, 1605; mass spectrum m/e 268 (P − CH_3OH; no parent ion observed). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.18, H, 8.20.

19: NMR ($CDCl_3$, 90 MHz) δ 7.31 (s, 5 H), 4.90–6.41 (m, 6 H), 4.44, 4.29 (AB, J = 11.3 Hz, 2 H), 3.67 (s, 3 H—superimposed on m, 1 H), 2.24 (m, 2 H), 1.90 (d, J = 1.4 Hz, 3 H), 1.77 (m, 2 H); IR (CH_2Cl_2) cm^{-1} 3060, 3020, 2950, 2860, 1712, 1645, 1604; mass spectrum m/e 300 (parent ion); high resolution mass spectrum (calcd for $C_{19}H_{24}O_3$) 300.17254 (found: 300.16948).

3-Tetrahydropyranyloxynona-6(*E*),8-dien-1-yne (22). To a mixture of 410 mg (17 mmol) of Mg turnings in 20 mL of THF containing two small iodine crystals was added 0.3 mL of bromoethane. After the reaction was initiated, an additional 1.0 mL of bromoethane was added (total 1.3 mL, 17.4 mmol). The mixture was stirred for 1 h and then was added via cannula to 10 mL of acetylene saturated THF at 0 °C. Dry acetylene was bubbled through the reaction mixture for 30 min, and then 1.02 g (9.3 mmol) of (*E*)-hepta-4,6-dienal[5] in 3 mL of THF was added. Acetylene was bubbled through the mixture for another 20 min. The mixture was stirred for 2 h at room temperature and then was cooled to 0 °C. Saturated aqueous NH_4Cl (10 mL) was carefully added. The solution was diluted with 30 mL of H_2O, the THF layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4 and then $MgSO_4$) and filtered. Solvent was removed by careful distillation through a Vigreux column until a residual volume of ~30 mL was obtained. To this solution were added 1 mL (10 mmol) of dihydropyran and a few small crystals of *p*-TsOH. The reaction mixture was stirred at room temperature for 1 h and then filtered through Florisil. All volatile components of the filtrate were removed in vacuo, and the resulting crude product was purified by flash chromatography (40 mm column, 20:1 hexane–ether, R_f 0.42, 0.47 (3:1 hexane–ether)) to give **22** (1.52 g, 74%, a mixture of THP diastereomers). This material was distilled (Kugelrohr, 125–135 °C, 1 mm) to give 1.50 g (73%) of pure **22**: NMR ($CDCl_3$, 90 MHz) δ 6.4–3.5 (m, 9 H), 2.45 (d, J = 2.1 Hz, acetylenic C≡C—H of one diastereomer), 2.40 (d, J = 2.1 Hz, acetylenic C≡C—H of second diastereomer), 1.52 (m, 10 H); IR (CH_2Cl_2) cm^{-1} 3300, 2940, 1650, 1600; mass spectrum m/e 220 (parent ion). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.39; H, 8.95.

Methyl (*Z*,*E*)-3-Methyl-4-tetrahydropyranyloxy-deca-2,7,9-trienoate (20). A solution of 930 mg (4.2 mmol) of **22** in 1.5 mL of THF at −78

°C was treated with 2.64 mL (6.4 mmol) of 2.4 M *n*-BuLi in hexane. The mixture was stirred at −78 °C for 10 min, and then 0.5 mL (6.4 mmol) of methyl chloroformate was added. This solution was stirred for 15 min at −78 °C before being allowed to warm to 0 °C. Saturated aqueous NH_4Cl (15 mL) was added and the THF layer was removed. The aqueous layer was extracted with CH_2Cl_2 (5×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo, giving 1.6 g of crude acetylenic ester **23**.

Crude **23** was immediately dissolved in 2 mL of dry ether. This solution was added to a solution of 5.4 mmol $(CH_3)_2CuLi$ in ether at −78 °C (prepared by addition of 7.9 mL (10.8 mmol) of 1.36 M methyllithium in ether to 1.02 g (5.4 mmol) of CuI in 15 mL of ether at 0 °C; this solution was stirred at 0 °C for 10 min and then was cooled to −78 °C). The reaction mixture was stirred at −78 °C for 5 min, and then 1 mL of CH_3OH was added. The mixture was warmed to 0 °C and then saturated aqueous NH_4Cl (15 mL) was added. This mixture was stirred at room temperature for 30 min, and then the ether phase was separated. The aqueous phase was extracted with CH_2Cl_2 (5×). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude product. This material was purified by chromatography on 80 g of silica gel (9:1 hexane ether as eluant), affording 1.11 g (90%) of pure **20**, a mixture of THP diastereomers which was not routinely separated. A small sample was separated by silica gel chromatography (silica gel, 3:1 hexane–ether, R_f 0.29 and 0.33).

20a: R_f 0.29; NMR ($CDCl_3$, 90 MHz) δ 6.52–5.56 (m, 4 H), 5.17–4.89 (m, 2 H), 4.43 (br s, 1 H), 3.68 (s, 3 H), 3.56 (m, 3 H), 2.18 (m, 2 H), 1.82 (s, 3 H), 1.58 (m, 8 H).

20b: R_f 0.33; NMR ($CDCl_3$, 90 MHz) δ 6.42–5.50 (m, 4 H), 5.40–5.15 (m, 2 H), 5.01 (br s, 1 H), 3.67 (s, 3 H superimposed on m, 3 H), 2.15 (m, 2 H), 1.95 (s, 3 H), 1.65 (m, 8 H).

Data on mixture: IR (CH_2Cl_2) cm^{-1} 2950, 2840, 1710, 1650, 1605; mass spectrum *m/e* 294 (parent ion). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.34; H, 8.90. Found: 69.32; H, 8.75.

Intramolecular Diels–Alder Reaction of 23. Diastereomers **23a** and **23b** were separated by chromatography on silica gel (3:1 hexane–ether). Each isomer was dissolved in 10 mL of dry, degassed CH_2Cl_2. These solutions were allowed to stand at room temperature for 110 h (an independent run was monitored by NMR spectroscopy, which indicated that cyclization was complete after 48 h), and then concentrated in vacuo. The crude products were chromatographed (silica gel, 3:1 hexane–ether) giving **24a** (50%) from **23a** and **24b** (50%) from **23b**. In each case, substantial amounts of aromatization products were also obtained.

23a: R_f 0.47; NMR ($CDCl_3$, 90 MHz) δ 6.42–5.70 (m, 3 H), 5.12–4.94 (m, 3 H), 4.57 (t, J = 6.4 Hz, 1 H), 3.78 (s, 3 H), 3.60 (m, 2 H), 2.27 (m, 2 H), 1.65 (m, 8 H); IR (CH_2Cl_2) cm^{-1} 2950, 2870, 2230, 1710, 1650, 1600.

23b: R_f 0.39; NMR ($CDCl_3$, 90 MHz) δ 6.41–5.58 (m, 3 H), 5.12–4.94 (m, 2 H), 4.75 (br s, 1 H), 4.35 (t, J = 6.4 Hz, 1 H), 3.77 (s, 3 H), 3.60 (m, 2 H), 2.23 (m, 2 H), 1.67 (m, 8 H); IR (CH_2Cl_2) cm^{-1} 2950, 2850, 2230, 1710, 1650, 1600.

24a: R_f 0.27; NMR ($CDCl_3$, 90 MHz) δ 5.78 (m, 2 H), 4.80 (m, 2 H), 3.74 (br s, 3 H superimposed on 3.93–2.82 (m, 5 H)), 1.53 (m, 10 H); IR (CH_2Cl_2) cm^{-1} 3025, 2940, 2870, 1715, 1680, 1640; mass spectrum *m/e* 194 (parent − dihydropyran; no parent ion observed); high resolution mass spectrum (calcd for $C_{11}H_{12}O_2$, (loss of 2-hydroxytetrahydropyran) 176.08373 (found: 176.08401).

24b: R_f 0.25; NMR ($CDCl_3$, 90 MHz) δ 5.78 (m, 2 H), 4.80 (m, 2 H), 3.76 (br s, 3 H superimposed on 3.93–2.82 (m, 5 H)), 1.52 (m, 10 H); IR (CH_2Cl_2) cm^{-1} 3025, 2941, 2850, 1715; mass spectrum *m/e* 278 (parent ion); high resolution mass spectrum (parent ion not observed) (calcd for $C_{11}H_{12}O_2$, loss of 2-hydroxytetrahydropyran) 176.08373 (found: 176.08642).

(*Z*,*E*)-4-Hydroxy-3-methyldeca-2,7,9-trienoic Acid γ-Lactone (25). A solution of 41 mg (0.14 mmol) of **20a** in 1 mL of 1 N HCl, 1 mL of CH_3OH, and 1 mL of acetone was stirred for 5 h at room temperture. The solution was diluted with 10 mL of H_2O and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to give 27 mg of crude product. Chromatography of this material on one-half of a 0.25-mm silica gel plate (1:1 ether–hexane, R_f 0.18) gave 22 mg (86%) of pure **25**. A similar hydrolysis of **20b** afforded **25** in 93% yield.

25: NMR ($CDCl_3$, 90 MHz) δ 6.53–5.30 (m, 4 H), 5.07–4.87 (m, 3 H), 2.22 (m, 2 H), 2.06 (s, 3 H), 1.60 (m, 2 H); IR (CH_2Cl_2) cm^{-1} 3030, 2920, 2850, 1750, 1650, 1605; mass spectrum *m/e* 178 (parent ion); high resolution mass spectrum (calcd for $C_{11}H_{14}O_2$) 178.09938 (found: 178.10138).

Intramolecular Diels–Alder Reaction of 18. Methyl 1β-Benzyloxy-7aβ-methyl-2,3,3aα,6,7,7a-hexahydroindene-7β-carboxylate (26a), Methyl 1α-Benzyloxy-7aβ-methyl-2,3,3aα,6,7,7a-hexahydroindene-7β-carboxylate (26b), Methyl 1β-Benzyloxy-7aβ-methyl-2,3,3aβ,6,7,7a-hexahydroindene-7β-carboxylate (27a), and Methyl 1α-Benzyloxy-7aβ-methyl-2,3,3aβ,6,7,7a-hexahydroindene-7β-carboxylate (27b). A solution of 315 mg (1.05 mmol) of **18** in 4 mL of toluene was transferred to a resealable Carius tube. The mixture was degassed with a stream of argon, and then 0.15 mL of bis(trimethylsilyl)acetamide (BSA) was added. The sealed tube was heated in a 240 °C oil bath for 11 h, and then all volatile components were removed in vacuo. Analysis of the ^1H NMR spectrum of this mixture of cyclization products revealed that four cycloadducts were present: **26a** (40%), **26b** (30%), **27a** (17%; NMR δ 1.07 (s, 3 H)), and **27b** (13%). These ratios were determined by careful integration of the signals for the angular methyl groups. The mixture of products was chromatographed on two 0.5-mm silica gel plates (19:1 hexane–ether, four developments) to give 56 mg (18%) of **26b** (R_f 0.50), 131 mg (42%) of a 3:1 mixture of **26a** and **27a** (R_f 0.37), and 23 mg (7%) of **27b** (R_f 0.25). Saponification (1 mL of 1 N NaOH, 3 mL of CH_3OH, and 2 mL of THF, 95 °C, 17 h) of 18 mg (0.26 mmol) of the mixture of **26a** and **27a** followed by crystallization of the product from hexane afforded the carboxylic acid corresponding to **26a**, mp 112.5–113.0 °C. Treatment of 15 mg (0.05 mmol) of this acid with ethereal CH_2N_2 afforded 15 mg (96%) of pure **26a** (following silica gel chromatography).

26a: NMR ($CDCl_3$, 90 MHz) δ 7.29 (s, 5 H), 5.60 (s, 2 H), 4.59, 4.32 (AB, J_{AB} = 22.1 Hz, 2 H), 3.70 (m, 1 H), 3.49 (s, 3 H), 1.6–2.6 (m, 8 H), 0.90 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3020, 2950, 2880, 1730, 1635, 1605; mass spectrum *m/e* 300 (parent ion); high resolution mass spectrum (calcd for $C_{19}H_{24}O_3$) 300.17254 (found: 300.17240).

26b: NMR ($CDCl_3$, 270 MHz) δ 7.33 (s, 5 H), 5.66 (m, 2 H), 4.53, 4.34 (AB, J = 11.1 Hz, 2 H), 3.88 (d, J = 4.6 Hz, 1 H), 3.67 (s, 3 H), 3.24 (dd, J = 10, 6 Hz, H_7), 1.3–2.7 (m, 7 H), 0.77 (s, 3 H); IR (neat) cm^{-1} 3020, 2950, 2875, 2850, 1730; mass spectrum *m/e* 300 (parent ion); high resolution mass spectrum (calcd for $C_{19}H_{24}O_3$) 300.17254 (found: 300.17476).

27b: NMR ($CDCl_3$, 270 MHz) δ 7.35 (m, 5 H), 5.62 (m, 2 H), 4.60, 4.52 (AB, J = 11.1 Hz, 2 H), 3.62 (m, 1 H), 3.58 (s, 3 H), 2.95 (dd, J = 6.0, 2.8 Hz, H_7), 1.4–2.5 (m, 7 H), 0.95 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3020, 2950, 2930, 2880, 1725, 1605; mass spectrum *m/e* 300 (parent ion); high resolution mass spectrum—parent ion not observed (calcd for $C_{12}H_{17}O_3$ (loss of tropylium ion) 209.11777 (found: 209.11682).

Intramolecular Diels–Alder Reaction of 20. Methyl 1β-Hydroxy-7aβ-methyl-2,3,3aα,6,7,7a-hexahydroindene-7α-carboxylate (28) and Methyl 1β-Hydroxy-7aβ-methyl-2,3,3aβ,6,7,7a-hexahydroindene-7α-carboxylate (29). A solution of 1.01 g (3.77 mmol) of **20** in 12 mL of toluene was transferred to a resealable Carius tube. Bis(trimethylsilyl)acetamide (BSA) (0.5 mL) was added and the resulting mixture was degassed with a stream of argon. The sealed tube was heated at 220 °C for 10 h in an oil bath, and then all volatile components were removed in vacuo. The residue was treated with 4 mL of MeOH and 2 mL of 1 N HCl for 40 min at room temperature. This solution was then diluted with 15 mL of water and was extracted with CH_2Cl_2 (6×). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. Analysis of the product mixture by GC (10 ft × $^1/_8$ in. QF-1, 180 °C, 25.6 mL/min) revealed that **28** (retention time 7.8 min) and **29** (retention time 7.0 min) were present in ratio of 80.4:19.6, respectively (average of five separate cyclization experiments). The crude product was chromatographed on 80 g of silica gel (5:1 hexane–ether as eluant; all mixed fractions were rechromatographed) giving 518 mg (65%) of **28** and 93 mg (12%) of **29**.

28: R_f 0.09 (3:1 hexane–ether); NMR ($CDCl_3$, 250 MHz) δ 5.66 (dd, J = 10.0, 1.3 Hz, 1 H), 5.60 (dd, J = 10.0, 3.0 Hz, 1 H), 382 (t, J = 8.3 Hz, 1 H), 3.70 (s, 3 H), 2.79 (dd, J = 5.9, 2.2 Hz, H_7), 1.5–2.3 (m, 9 H), 0.89 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3595, 3020, 2950, 2880, 1728, 1638; mass spectrum *m/e* 192 (P − H_2O; parent ion not observed). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.80; H, 8.40.

29: R_f 0.21 (3:1 hexane–ether); NMR ($CDCl_3$, 250 MHz) δ 5.50 (m, 1 H), 5.43 (dd, J = 10.0, 1.1 Hz, 1 H), 4.37 (td, J = 7.0, 1.4 Hz, 1 H), 3.73 (s, 3 H), 3.67 (d, J = 1.6 Hz, 1 H), 2.74 (dd, J = 10.9, 5.9 Hz, H_7), 1.3–2.4 (m, 7 H), 0.99 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3490, 3020, 2955, 2880, 1765, 1710, 1650; mass spectrum *m/e* 210 (parent ion). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.42.

Methyl 7aβ-Methyl-2,3,3aβ,6,7,7a-hexahydroinden-1-one-7α-carboxylate (30). A solution of 57 mg (0.3 mmol) of alcohol **29** in 6 mL of CH_2Cl_2 was treated with 135 mg (0.6 mmol) of PCC. The mixture was stirred for 2 h at room temperature and then diluted with 10 mL of ether. The organic phase was removed and the residue was rinsed with Et_2O (4×). The combined organic extracts were filtered through Florisil and evaporated. Chromatography of the product on a 0.5-mm silica gel plate (1:1 hexane–ether, two developments; R_f 0.36 (one development in this solvent system)) afforded 49 mg (86%) of pure **30**: mp 52.0–52.5 °C (hexane); NMR ($CDCl_3$, 250 MHz) δ 5.73 (m, 2 H), 3.66 (s, 3 H), 2.74 (t, J = 5.9 Hz, H_7), 1.6–2.5 (m, 7 H), 1.21 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3025, 2955, 2895, 1735; mass spectrum *m/e* 208 (parent ion).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C. 68.96; H, 7.77.

1α-Hydroxy-7aβ-methyl-2,3,3aβ,6,7,7a-hexahydroindene-7α-carboxylate γ-Lactone (31). A solution of 25 mg (0.1 mmol) of keto ester **30** in 4 mL of absolute EtOH was treated with 50 mg (1.3 mmol) of $NaBH_4$. This solution was stirred for 5 h at room temperature, and then 8 mL of 1 N HCl and 10 mL of H_2O were added. The solution was extracted with CH_2Cl_2 (4 × 15 mL). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give 22 mg of crude product. This sample was combined with 9 mg of crude product from a parallel experiment. This mixture was chromatographed (0.25-mm silica gel plate, 40:1 CH_2Cl_2-CH_3OH) to afford 23 mg (82%) of **31** (R_f 0.39 (1:1 ether–hexane); 0.84 (10:1 CH_2Cl_2–CH_3OH)), 4 mg (12%) of alcohol **29**, and 2 mg (6%) of recovered **30**.

31: NMR ($CDCl_3$, 90 MHz) δ 5.7 (br s, 2 H), 4.5 (d, J = 3.2 Hz, 1 H), 1.3–2.8 (m, 8 H), 1.14 (s, 3 H); IR (neat) cm^{-1} 3020, 2950, 2865, 1765, 1655; mass spectrum m/e 178 (parent ion); high resolution mass spectrum (calcd for $C_{11}H_{14}O_2$) 178.09938 (found: 178.09671).

Methyl 7aβ-Methyl-2,3,3aα,6,7,7a-hexahydroinden-1-one-7α-carboxylate (32). Alcohol **28** (92 mg, 0.4 mmol) was oxidized with PCC (206 mg, 0.9 mmol) using the procedure described for **30**. In this manner, 81 mg (89%) of pure **32** was obtained.

32: R_f 0.37 (1:1 hexane–ether); NMR ($CDCl_3$, 250 MHz) δ 5.77 (ddd, J = 10.0, 4.3, 2.1 Hz, 1 H), 5.61 (ddd, J = 10.0, 6.7, 2.3 Hz, 1 H), 3.65 (s, 3 H), 3.08 (m, 1 H), 2.94 (dd, J = 7.5, 1.9 Hz, 1 H), 2.25–2.63 (m, 6H), 0.90 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3020, 2950, 1740; mass spectrum m/e 208 (parent ion). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.17; H, 7.90.

$NaBH_4$ Reduction of 32. Ketone **32** (10.0 mg, 0.048 mmol) was reduced with $NaBH_4$ (18 mg) in ethanol (2 mL) using the procedure described for reduction of **30**, giving 9.0 mg (88%) of pure **28** following silica gel chromatography.

Methyl 1α-Hydroxy-7aβ-methyl-2,3,3aα,6,7,7a-hexahydroindene-7β-carboxylate (33b). A solution of 52 mg (0.2 mmol) of **26b** in 2 mL of THF, 3 mL of MeOH, and 1 mL of 1 N NaOH was heated at 95 °C for 17 h. The solution was then cooled and diluted with 10 mL of 1 N HCl. This solution was extracted with CH_2Cl_2 (5×). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give 48 mg (98%) of crude carboxylic acid.

A solution of 22 mg (0.08 mmol) of the above acid in 2.5 mL of THF and 0.5 mL of t-BuOH was added to a solution of 3.5 mg (0.5 mmol) of lithium in liquid ammonia at −78 °C. This mixture was allowed to warm slowly to reflux. The solution was refluxed for 20 min, and then 1 mL of saturated aqueous NH_4Cl was added. Ammonia was distilled from the reaction mixture, and the residue was dissolved in 15 mL of 1 N HCl. This solution was extracted with CH_2Cl_2 (4×). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting product was esterified with ethereal CH_2N_2 and then chromatographed on one-half of a 0.25-mm silica gel plate (1:1 hexane–ether, R_f 0.27). In this manner there was obtained 14 mg (86%) of alcohol **33b**: NMR ($CDCl_3$, 90 MHz) δ 5.65 (m, 2 H), 3.92 (m, 1 H), 3.75 (s, 3 H), 2.98 (m, 2 H), 1.00–2.59 (m, 7 H), 0.58 (s, 3 H); IR (neat) cm^{-1} 3520, 3020, 2950, 2875, 2850, 1735, 1705, 1640; mass spectrum m/e 210 (parent ion); high resolution mass spectrum (calcd for $C_{12}H_{18}O_3$) 210.12559 (found: 210.12555).

Methyl 1β-Hydroxy-7aβ-methyl-2,3,3aα,6,7,7a-hexahydroindene-7β-carboxylate (33a) and Methyl 1β-Hydroxy-7aβ-methyl-2,3,3aβ,6,7,7a-hexahydroindene-7β-carboxylate (34). A mixture of **26a** and **27a** (140 mg, 0.5 mmol, ~3:1, respectively) was saponified using the procedure described for **33b**. The crude product was chromatographed (0.5-mm silica gel plate, 2:1 hexane–ether) to afford 91 mg (69%) of a 3:1 mixture of the corresponding carboxylic acids.

A portion of this mixture of acids (41 mg, 0.14 mmol) was reduced with Li in NH_3 and esterified with CH_2N_2 using the procedure described for **33b**. The two products were separated by silica gel chromatography (0.5-mm silica gel plate, 1:1 hexane–ether) to give 6 mg (20%;, 14% overall) of **34** and 18 mg (59%; 41% overall) of **33a**.

33a: R_f 0.26; NMR ($CDCl_3$, 250 MHz) δ 5.59 (s, 2 H), 3.73–4.02 (m, 2 H), 3.73 (s, 3 H), 2.62 (dd, J = 11.0, 6.5 Hz, H_7), 2.1–2.5 (m, 4 H), 1.4–1.7 (m, 3 H), 0.77 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3600, 3490, 3020, 2970, 2880, 1730, 1710, 1645; mass spectrum m/e 210 (parent ion). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.46; H, 8.48.

34: R_f 0.19; NMR ($CDCl_3$, 90 MHz) δ 5.67 (s, 2 H), 4.05 (m, 1 H), 3.70 (s, 3 H), 1.2–2.4 (m, 9 H), 0.97 (s, 3 H); IR (neat) cm^{-1} 3450, 3020, 2950, 2880, 1735, 1650; mass spectrum m/e 210 (parent ion); high resolution mass spectrum (calcd for $C_{12}H_{18}O_3$) 210.12559 (found: 210.12539).

Epimerization of 28. A solution of $NaOCH_3$ in CH_3OH was prepared by adding 42 mg (1.8 mmol) of Na to 1.0 mL of dry, thoroughly degassed (argon) CH_3OH in a resealable Carius tube. To this solution was added, with continuous N_2 purge, a solution of 73 mg (0.35 mmol) of **28** in 3 mL of dry, degassed methanol. The tube was sealed and heated in a 50 °C oil bath for 48 h. The cooled solution was diluted with 20 mL of 0.5 N HCl and then extracted with CH_2Cl_2 (8×). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was esterified with excess ethereal CH_2N_2, and the resulting mixture of esters was separated by silica gel chromatography (0.5-mm preparative plate, 3:1 hexane–ether, three developments). In this manner there were obtained 8.9 mg (13%) of recovered **28** and 36 mg (49%) of **33a**. Alcohol **33a** prepared by this method was identical in all respects with the compound prepared by debenzylation of **26a**.

Epimerization of 29. Alcohol **29** (72 mg, 0.34 mmol) was epimerized using the procedure described for **28** (1.0 mmol of $NaOCH_3$ was employed; 65 °C, 24 h). The resulting mixture of esters was separated by chromatography (0.5-mm silica gel plate, 1:1 hexane–ether) giving 27 mg (38%) of recovered **29** and 33 mg (45%) of **34**. Alcohol **34** so obtained was identical with the compound prepared by debenzylation of **27a**.

Methyl 7aβ-Methyl-2,3,3aα,6,7,7a-hexahydroinden-1-one-7β-carboxylate (35). A solution of 30 mg (0.14 mmol) of **33a** in 4 mL of CH_2Cl_2 was oxidized with 67.7 mg (0.30 mmol) of PCC using the procedure described for **30**. The crude product was purified by chromatography (0.5-mm silica gel plate, 1:1 ether–hexane, two developments; R_f 0.40, one development in this solvent system) giving 25 mg (83%) of **35**. Similarly, oxidation of 6.5 mg of **33b** afforded 5.7 mg (88%) of **35**: mp 63.0–63.5 °C (hexane); NMR ($CDCl_3$, 250 MHz) δ 5.69 (m, 2 H), 3.75 (s, 3 H), 2.75 (dd, J = 9.9, 7.8 Hz, 1 H), 2.52 (m, 2 H), 2.38 (m, 2 H), 1.96–2.36 (m, 2 H), 1.75 (m, 1 H), 1.11 (s, 3 H); IR (CH_2Cl_2) cm^{-1} 3020, 2950, 2850, 1735; mass spectrum m/e 208 (parent ion). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.22; H, 7.80.

$NaBH_4$ Reduction of 35. Ketone **35** (6 mg) was reduced with $NaBH_4$ (11 mg) in ethanol (2.0 mL) using the procedure described for reduction of **30**, giving 5.0 mg (86%) of a 87:13 mixture of **33a**:**33b** following silica gel chromatography.

Methyl 7aβ-Methyl-2,3,3aβ,6,7,7a-hexahydroinden-1-one-7β-carboxylate (36). Alcohol **34** (16 mg, 0.08 mmol) was oxidized with PCC (35 mg, 0.2 mmol) using the procedure described for **30**, giving 14.0 mg (87%) of **36** following silica gel chromatograhy: R_f 0.40 (1:1 hexane–ether); NMR ($CDCl_3$, 90 MHz) δ 5.68 (s, 2 H), 3.66 (s, 3 H), 2.84 (m, 2 H), 1.58–2.44 (m, 6 H), 1.08 (s, 3 H); IR (neat) cm^{-1} 3020, 2950, 1735, 1650; mass spectrum m/e 208 (parent ion); high resolution mass spectrum (calcd for $C_{12}H_{16}O_3$) 208.10994 (found: 208.10797).

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