Synthetic Approaches to the Axane Family of Sesquiterpenoids. Total Synthesis of *dl*-Axamide-4, *dl*-Axisonitrile-4, and *dl*-Axisothiocyanate-4

Balan Chenera, Che-Ping Chuang, David J. Hart,* and Chin-Shan Lai

Department of Chemistry, The Ohio State University, 120 W. 18th Ave., Columbus, Ohio 43210

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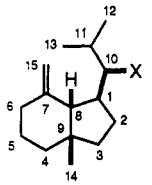
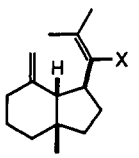
Two methods for the preparation of perhydroindan 7 are described. One involves an intramolecular free radical cyclization in a key step and proceeds in 13 steps and 9% yield from anisole (9). The other involves an intramolecular conjugate addition mediated by pyrrolidine (28 → 7) and proceeds in five steps and 30% overall yield from vinylogous ester 29. Two unsuccessful attempts to convert 7 into axane sesquiterpenoids 1–6 are described. The synthesis of axanes 4–6 was achieved using a potassium *tert*-butoxide catalyzed cyclization of a dienoic keto ester as a key step (47 + 48 → 49). Conversion of α,β-unsaturated ester 49 to vinyl isocyanate 57 was accomplished using a Curtius rearrangement and reduction of 57 with lithium triethylborohydride completed the synthesis of axamide-4 (4). The preparation of axisonitrile-4 (5) and axisothiocyanate-4 (6) from 4 is also described.

Introduction

The axanes are a small family of sesquiterpenoids originally isolated from the marine sponge *Axinella cannabina*.[1-7] Several of these compounds (1–6) have a carbon skeleton that is not common among sesquiterpenes and incorporate a series of nitrogen-containing functional groups rarely found in natural products.[1-4] It has also



1 X = NHCHO
2 X = N=C
3 X = N=C=S

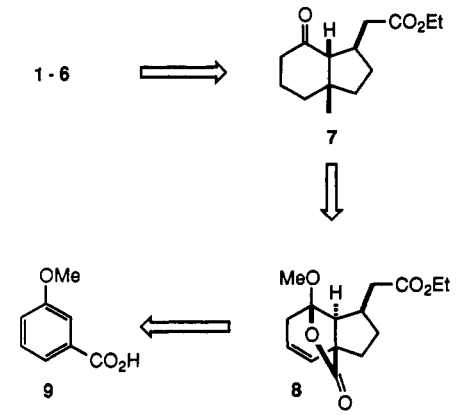


4 X = NHCHO
5 X = N=C
6 X = N=C=S

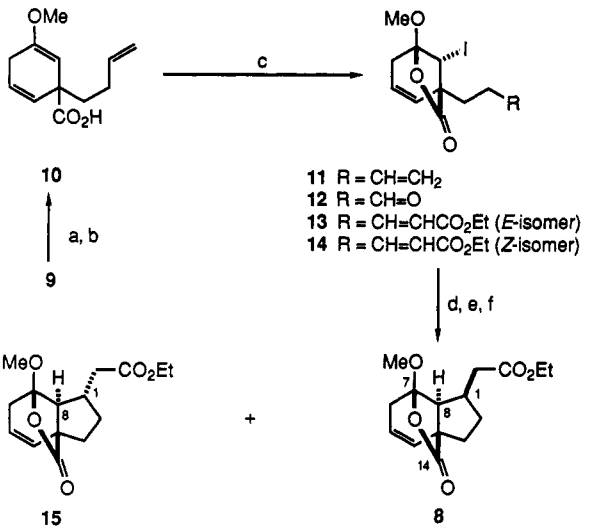
been reported that axisonitrile-1 (2) is an ichthiotoxin that may play a role in the predator–prey relationship between the nudibranch *Phyllidia Pulitzer* and *Axinella cannabina*.[6] Thus, axanes 1–6 are interesting targets for total synthesis. Piers has reported syntheses of racemic axamide-1 (1), axisonitrile-1 (2) and axisothiocyanate-1 (3) using new annulation methodology for construction of the perhydroindan nucleus.[8,9] This article presents an account of two approaches to the axanes, culminating in total syntheses of axamide-4 (4), axisonitrile-4 (5), and axisothiocyanate-4 (6).[10]

A Free Radical Cyclization Approach. Several years ago we reported a reductive alkylation–halolactonization–free radical cyclization route to functionalized perhydroindans.[11,12] Application of this strategy to the axanes 1–6 is outlined antithetically in Scheme I. It was anticipated that keto ester 7 would be an excellent precursor to all of the axane sesquiterpenes. Although a number of routes to 7 can be imagined, it was felt that the aforementioned

Scheme I



Scheme II[a]



[a] (a) Li, NH_3; (b) $H_2C{=}CHCH_2CH_2Br$; (c) $NaHCO_3$, I_2, H_2O–Et_2O; (d) $NaIO_4$, OsO_4, *t*-BuOH, H_2O; (e) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; (f) *n*-Bu_3SnH, AIBN, PhH, Δ.

perhydroindan methodology might provide access to 7 from *m*-anisic acid (9) by way of lactone 8.

The preparation of perhydroindan 8 was accomplished in five steps from *m*-anisic acid as outlined in Scheme II. Reduction of *m*-anisic acid with lithium in ammonia followed by alkylation of the resulting dianion with 4-bromo-1-butene gave crude acid 10, which was treated with sodium bicarbonate and iodine in aqueous ether to afford iodo lactone 11 (66%).[12] Johnson–Lemieux cleavage of the terminal olefin gave aldehyde 12 and a subsequent Wittig reaction gave a mixture of olefins 13 and 14 (57% from

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(3) Adinolfi, M.; De Napoli, L.; Di Blasio, B.; Iengo, A.; Pedone, C.; Santacroce, C. *Tetrahedron Lett.* **1977**, 2815.
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(5) Iengo, A.; Santacroce, C.; Sodano, G. *Experentia* **1979**, *35*, 10.
(6) Cimino, G.; De Rosa, S.; De Stefano, S.; Sodano, G. *Comp. Biochem. Physiol.* **1982**, *73B*, 471.
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(9) Piers, E.; Yeung, B. W. A.; Rettig, S. J. *Tetrahedron* **1987**, *43*, 5521.
(10) For a preliminary account of a portion of this work, see: Hart, D. J.; Lai, C. S. *Synlett* **1989**, 49.
(11) Chuang, C. P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782.
(12) Chuang, C. P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210.

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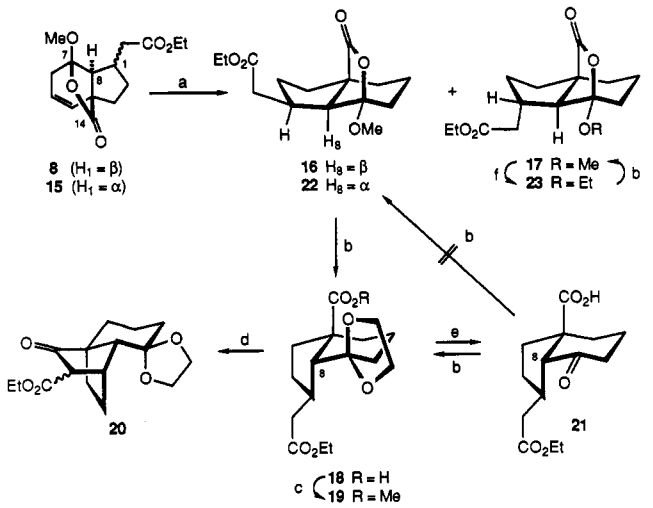
Scheme III[a]



[a] (a) H_2, MeOH, Pd on C; (b) $HOCH_2CH_2OH$, $(MeO)_3CH$, TsOH; (c) CH_2N_2; (d) $LiN(SiMe_3)_2$, PhH, Δ; (e) HCOOH, H_2O; (f) $HOCH_2CH_2OH$, $(EtO)_3CH$, TsOH.

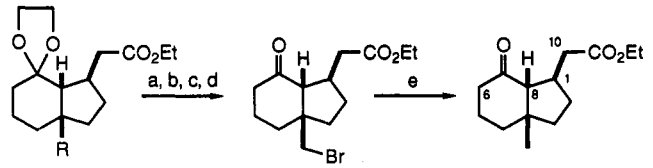
11).[13,14] The *E*:*Z* ratio was 5:1 by integration of the H_β signals which appeared as a doublet of triplets a δ 6.98 (J = 15, 7 Hz) and δ 6.25 (J = 11, 7 Hz) in **13** and **14**, respectively. Pure **13** could be obtained by chromatography (43% from **11**). Treatment of **13** with tri-*n*-butyltin hydride and AIBN in benzene under reflux gave approximately a 10:1 mixture of perhydroindans **8** and **15**, respectively, in 70% yield, while cyclization of a 5:1 mixture of **13** and **14** gave a 4.5:1 mixture of **8** and **15**.[15,16] Once again, the ratio of **8** and **15** was determined by integration of appropriate peaks in the olefinic and methoxy regions of a 500-MHz ^{1}H-NMR spectrum of the mixture. The stereochemical assignments were initially based on analogy with earlier studies and were eventually confirmed using chemical and crystallographic methods (vide infra).[11,12]

From an operational standpoint, the five-step sequence required some precaution. For example, acid **10** underwent protolactonization on standing. Iodo lactones **11**–**14** were also sensitive and decomposed with liberation of iodine on standing. This decomposition could be retarded by adding small amounts of pyridine to **11**–**14** and, on several occasions, gram quantities of each compound were stored for several days before continuing the reaction sequence.

The stereochemical course of the cyclization (**13** + **14** → **8** + **15**) is also notable. The selectivity at C(7) is most likely the result of the preference for a *cis*-oxabicyclo[3.3.0]octane substructure in **8** and **15**. The stereochemical result at C(1) is a function of olefin geometry in the cyclization precursor, an observation consistent with earlier reports from these laboratories.[17] For example, when pure **13**, obtained by chromatography over silica gel, was subjected to cyclization conditions, **8** and **15** were obtained in a 9:1 ratio and 70% yield.

The tasks that had to be accomplished to convert **8** into projected intermediate **7** (Scheme I) were (1) epimerization at C(8), (2) adjustment of oxidation state at C(14), and (3)

Scheme IV[a]



[a] (a) $(COCl)_2$; (b) $NaBH_4$; (c) Ph_3P, CBr_4; (d) HCOOH, H_2O; (e) *n*-Bu_3SnH, AIBN, Δ.

introduction of the C(15) methylidene group. In addition, it was necessary to verify the stereochemical assignment at C(1) in **8** and devise a method for separating **8** from **15**. Several of these objectives were accomplished as outlined in Scheme III. Catalytic hydrogenation of a 5:1 mixture of **8** and **15** gave the same ratio of esters **16** and **17**, respectively, in 83% yield. Treatment of this mixture with ethylene glycol, trimethyl orthoformate, and a catalytic amount of *p*-toluenesulfonic acid gave carboxylic acid **18** in 74% yield and 13% of unchanged **17**, which were easily separated.[18] The carboxylic acid was assigned structure **18** on the basis of the following studies. Treatment of **18** with diazomethane gave ester **19** (87%), which was converted to a β-keto ester, assigned structure **20** (83%), upon subjection to Dieckman condensation conditions. This result established the relative stereochemistry of the acetic acid side chain and angular carboxy group but did not rule out the C(8) epimer of **18**. Evidence for the C(8) assignment was obtained as follows. Hydrolysis of acetal **18** gave a keto acid, assigned structure **21** (90%). This compound was not converted to lactone **16** upon treatment with methanol, trimethyl orthoformate, and *p*-toluenesulfonic acid, although including ethylene glycol in the reaction mixture did return **18** (84%). We imagine that had **21** been epimeric at C(8), **16** would have been produced. In fact, it is reasonable that **21** did not give lactone **22** since such a structure contains a strained, trans-fused oxabicyclo[3.3.0]octane substructure as previously mentioned. Finally, the minor perhydroindan **17** is not really inert to the ketalization reaction (**16** + **17** → **18** + **17**). In fact, it undergoes an identity reaction. This was detected by substituting triethyl orthoformate for trimethyl orthoformate in the ketalization brew. Under these conditions, **17** gave **23** in 76% yield. As expected, **23** was converted to **17** (82%) under the original ketalization conditions.

To summarize, *trans*-perhydroindan **16** is converted to *cis*-perhydroindan **18** via lactone cleavage, epimerization at C(8), and subsequent ketal formation. The epimerization at C(8) is most likely driven by thermodynamics as C(8) isomers of **18** and **21** would experience a pseudo-1,3-diaxial interaction between the acetic acid side chain and angular carboxy group.

With the stereochemical problem solved, reduction of the angular carboxy group was accomplished as shown in Scheme IV. Acid **18** was converted to alcohol **25** (83%) via acid chloride **24**.[19] Treatment of **25** with triphenylphosphine and carbon tetrabromide followed by hydrolysis of ketal **26** using aqueous formic acid gave bromo ketone **27** (80%).[20] Reduction of **27** with tri-*n*-butyltin hydride afforded **7** in 90% yield.[15] It is notable that the C(6) and

(13) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(14) Isler, O.; Gutmann, H.; Montavon, M.; Ruegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957**, *40*, 1242.
(15) For a review of tri-*n*-butyltin hydride chemistry, see: Neumann, W. P. *Synthesis* **1987**, 665.
(16) For recent reviews of radical cyclization chemistry, see: Curran, D. P. *Synthesis* **1988**, 417, 489.
(17) Hart, D. J.; Huang, H. C.; Kishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507.
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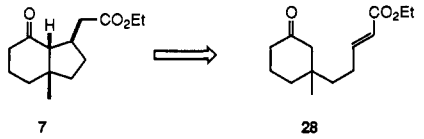
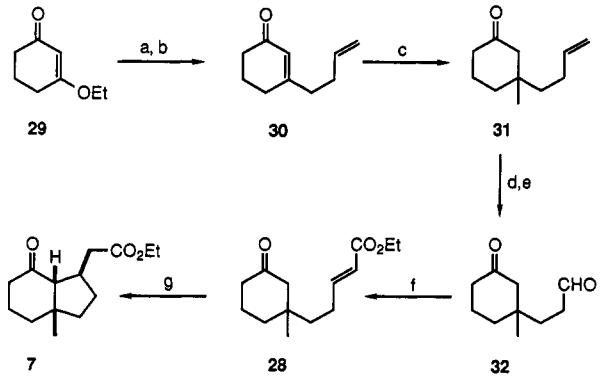
(19) Bablert, J. H.; Invergo, B. J. *Tetrahedron Lett.* **1981**, 11.
(20) Poulter, C. D.; Muscio, O. J.; Goodfellow, R. J. *J. Org. Chem.* **1975**, *40*, 159.

Scheme V



Scheme VI[a]



[a] (a) $H_2C{=}CHCH_2CH_2MgBr$; (b) H_3O^+; (c) Me_2CuLi; (d) O_3, MeOH; (e) Me_2S; (f) $Ph_3P{=}CHCO_2Et$; (g) pyrrolidine, HOAc (cat.), THF.

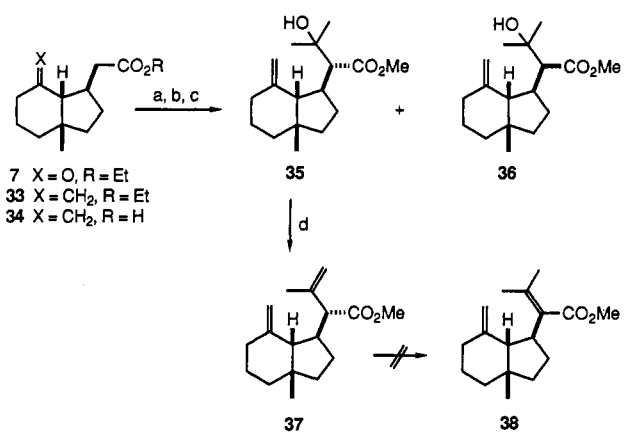
C(8) hydrogens of **7** could be exchanged (CF_3CO_2D) without C(8) isomerization, confirming the suggestion that the cis ring juncture is favored on the basis of thermodynamics.

To summarize, projected key intermediate **7** was prepared from *m*-anisic acid in 13 steps and 9% overall yield. Although attempts to convert **7** to the axane sesquiterpenes were pursued (vide infra), it was eventually found that the free radical cyclization route provided insufficient quantities of material. Thus, an alternative route to **7** was sought.

An Intramolecular Conjugate Addition Approach. An alternate approach to keto ester **7** is outlined in Scheme V. It was imagined that **7** might be obtained from an intramolecular conjugate addition (**28** → **7**). Based on a similar approach to perhydroindans reported by Heathcock, it was hoped that the cyclization would follow the required regiochemical and stereochemical course.[21]

The preparation and cyclization of unsaturated keto ester **28** are outlined in Scheme VI. Treatment of vinylogous ester **29** with 3-butenylmagnesium bromide followed by acidic hydrolysis of the addition product gave α,β-unsaturated ketone **30** in 73% yield.[22] Treatment of **30** with lithium dimethylcuprate gave ketone **31** in 90% yield.[23] Ketone **31** was also prepared in 78% yield using a copper-catalyzed conjugate addition reaction of 3-butenylmagnesium bromide to commercially available 3-methylcyclohex-2-en-1-one. Due to the expense of the cyclohexenone, however, the route shown in Scheme VI was preferred. Conversion of enone **31** to unsaturated ester **28** was accomplished using a two-step reaction sequence. Ozonolysis of **31** followed by a reductive workup using dimethyl sulfide gave aldehyde **32** in 88% yield. A Wittig reaction between **32** and (carbethoxymethylidene)triphenylphosphorane in benzene at room temperature gave **28** in 81% yield as a separable 5:1 mixture of *E* and *Z* isomers, respectively. Encouraged by the perhydroindan synthesis reported by Heathcock, keto ester **28** was treated

Scheme VII[a]



[a] (a) $Ph_3P{=}CH_2$; (b) NaOH, H_2O; (c) LDA; $Me_2C{=}O$, CH_2N_2; (e) $[C_6H_5C(CF_3)_2O]_2S(C_6H_5)_2$ (Martin's sulfurane).

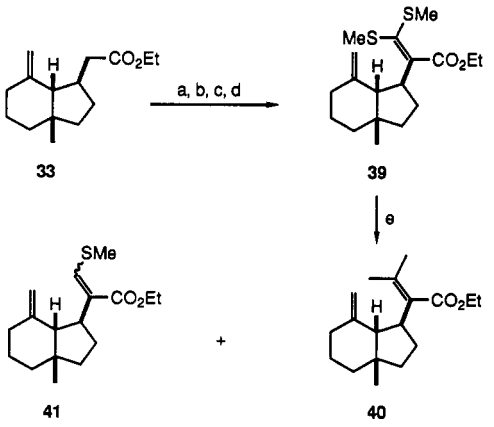
with potassium *tert*-butoxide in *tert*-butyl alcohol with the hope of obtaining **7**. Unfortunately, a total of four products were detected by capillary GC analysis of the crude reaction mixture. GC-MS analysis showed that the four compounds were isomeric (parent ion at *m/e* 238), but coinjection studies indicated that the desired product **7** only constituted 7% of the mixture, assuming equal GC response factors. The use of other bases (NaOEt/EtOH and NaH/THF) did not improve the yield of **7**. Amine-mediated cyclizations provided better results. Thus, treatment of **28** with pyrrolidine, piperidine, or diethylamine in the presence of a catalytic amount of acetic acid gave isomer mixtures in which **7** was the major product.[24] The best results were obtained when 1 equiv of pyrrolidine was used in tetrahydrofuran at 60 °C. Under these conditions, keto ester **7** was isolated in 65% yield with 93% purity by GC.

In summary, the intramolecular conjugate addition route to **7** described in Scheme VI was accomplished in five steps and 30% overall yield from enone **29**. This sequence provided **7** in quantities that allowed us to pursue its use (vide infra) as an intermediate in the preparation of axanes **1–6**.

Attempted Conversion of Ester 7 to Axanes 1–6. Several procedures for converting **7** to axanes **1–6** were explored. Only two of these studies will be presented here. One study involved introduction of the C(10) isopropyl group using aldol chemistry (Scheme VII). Treatment of keto ester **7** with methylidenetriphenylphosphorane gave olefin **33** in 80% yield. Attempts to condense the enolate of **33** with acetone were unsuccessful. Therefore reactions of the dianion of the derived acid **34** were examined. Hydrolysis of **33** using 5% aqueous sodium hydroxide gave **34** (84%). Treatment of the dianion derived from **34** with acetone, followed by esterification of the resulting hydroxy acids with diazomethane, gave β-hydroxy esters **35** (50%) and **36** (32%).[25] The structure of **36** was established by X-ray crystallography.[26] Although this sequence provided material with the carbon skeleton of the axanes intact, it was eventually abandoned for two reasons: (1) the major product from the aldol condensation (**35**) did not have the

(21) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165.
(22) Gannon, W. F.; House, H. O. In *Organic Syntheses*; Baumgarten, H. C., Ed.; Wiley: New York, 1973; Vol 5; p 539.
(23) Posner, G. H. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1972; Vol 19, pp 1–113.
(24) For amine-mediated intramolecular conjugate additions to α,β-unsaturated esters, see: Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1984**, 715. Hirai, Y.; Terada, T.; Yamazaki, T. *J. Am. Chem. Soc.* **1988**, *110*, 958.
(25) Moersch, G. W.; Burkett, A. R. *J. Org. Chem.* **1971**, *36*, 1150.
(26) We thank Dr. Judith C. Gallucci for performing the X-ray crystallographic analysis of **36** at the Ohio State University Crystallographic Facility. Details are given in the supplementary material.

Scheme VIII[a]



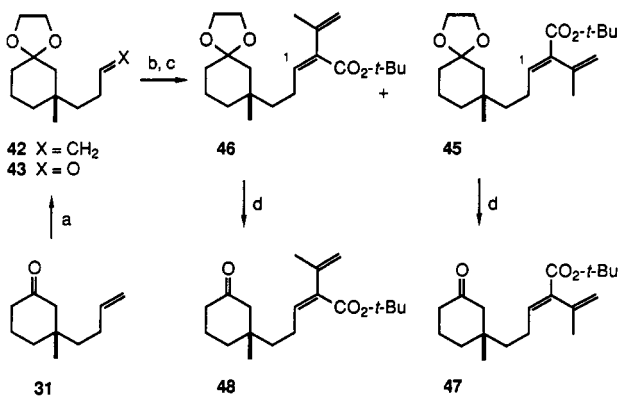
[a] (a) LDA; (b) CS_2; (c) LDA; (d) MeI; (e) Me_2CuLi, Et_2O, 25 → 50 °C, 12 h.

C(10) stereochemistry needed to prepare axanes **1–3** and (2) although dehydration of **35** to **37** was achieved in quantitative yield using Martin's sulfurane, conversion of **37** to α,β-unsaturated acid **38** (a projected precursor of axanes **4–6**) could not be accomplished.[27]

Another study involved introduction of the C(10) isopropylidene group using a ketene dithioacetal intermediate (Scheme VIII). Sequential treatment of **33** with lithium diisopropylamide, carbon disulfide, another equivalent of lithium diisopropylamide, and iodomethane gave ketene dithioacetal **39** in 80% yield.[28] It was hoped that the methylthio groups in **39** could be replaced with methyl groups using organocopper reagents.[29] Unfortunately, complex product mixtures were obtained when using Me_2CuLi, $Me_2Cu(CN)Li_2$, and $Me_2Cu(SCN)Li_2$. Separation of products was difficult and structure assignments were based principally on ^1H NMR spectra collected on partially purified compounds as well as GC-MS data. On one occasion, reasonably pure samples of the desired compound **40** (9%) and reduction product **41** (12%) were isolated from a reaction between **39** and lithium dimethylcuprate.[30] The yield of **40**, however, was unacceptable for use in the preparation of axanes **4–6** and this route was also abandoned. It was eventually decided to incorporate the C(10) isopropyl group at an earlier stage of the synthesis. This strategy ultimately led to the synthesis of axanes **4–6** as outlined in the following section.

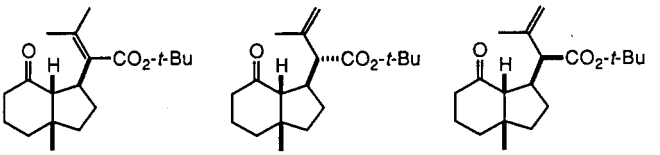
Total Synthesis of Axanes 4–6. It was next decided to investigate the cyclization of dienoic esters **47** and **48**. These substrates were prepared as outlined in Scheme IX. Ketone **31** was converted to acetal **42** (83%) and ozonolysis of the olefin afforded aldehyde **43** in 90% yield. Peterson olefination of **43** using the lithium enolate of α-trimethylsilyl ester **44** gave a 2:1 mixture of isomeric esters **45** and **46**, respectively, in 63% yield.[31,32] The isomeric esters were separated and independently hydrolyzed to give **47** (92%) and **48** (95%). Alternatively, the mixture

Scheme IX[a]



[a] (a) $HOCH_2CH_2OH$, TsOH, PhH; (b) O_3; Me_2S; (c) Li enolate of *tert*-butyl 3-methyl-2-(trimethylsilyl)-3-butenoate (**44**), THF, −78 °C; (d) 5% HCl, room temperature, 3 h.

Table I. Cyclizations of 47 and 48 to Perhydroindans 49, 50, and 51



entry	cyclization substrate	conditions[a]	% yield[b] 49	50	51
1	**47**	A	15	60	–
2	**48**	A	–	–	–
3	**47**	B	52	15	8
4	**48**	B	54	14	4
5	**47**:**48** (2:1)	B	45	30	5

[a] Conditions A: pyrrolidine (1 equiv), acetic acid (catalytic), THF, 60 °C. Conditions B: potassium *tert*-butoxide (0.2 equiv), *tert*-butyl alcohol, 60 °C. [b] All yields represent isolated material.

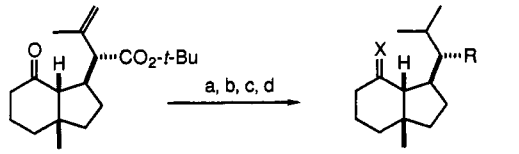
of **45** and **46** could be hydrolyzed to give a mixture of **47** and **48** (96%) and the separation could be conducted at this point. The structures of isomeric olefins **45** and **46** were based on their ^1H NMR spectra. The C(1) protons of the *E* (**45**) and *Z* (**46**) isomers appeared as triplets at δ 6.64 and 5.65, respectively. The lower chemical shift of this proton in the *E* isomer indicates that the ester carbonyl group is conjugated with the 1,3-diene. Due to steric hindrance, the *Z* isomer apparently adopts a conformation in which the diene and ester carbonyl π-frameworks do not overlap, leading to an upfield shift of C(1) vinyl proton. Nuclear Overhauser enhancement experiments also supported the structure assignments.[33] For instance, irradiation of the vinylic methyl group (δ 1.85) in **45** showed no enhancement of the vinyl proton at δ 6.64. On the other hand, irradiation of the vinylic methyl group (δ 1.88) in **46** showed an 11% enhancement of the vinyl proton at δ 5.56.

Cyclizations of substrates **47** and **48** was next attempted using a variety of conditions to give the products shown in Table I. Thus, cyclization of *E*-olefin **47** using pyrrolidine in the presence of acetic acid (entry 1) gave **49** (15%) and **50** (60%). Exposure of *Z*-olefin **48** to identical conditions gave no reaction (entry 2). On the other hand, both **47** and **48** cyclized to give a mixture of **49**, **50**, and **51** upon treatment with 0.2 equiv of potassium *tert*-but-

(27) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.
(28) Dieter, R. K. *J. Org. Chem.* **1981**, *46*, 5031. Ali, S. M.; Tanimoto, S. *J. Chem. Soc., Chem. Commun.* **1989**, 684.
(29) For a relevant review, see: Dieter, R. K. *Tetrahedron* **1986**, 3029.
(30) For reductions related to the preparation of **41**, see: Hojo, M.; Tanimoto, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1284.
(31) 1,1-Dimethylethyl 3-methyl-2-(trimethylsilyl)-3-propenoate (**44**) was prepared in 48% yield by the Ni(0)-catalyzed coupling of the lithium enolate of 1,1-dimethylethyl α-(trimethylsilyl)acetate (Hurdlik, P. F.; Peterson, D.; Chou, D. *Synth. Commun.* **1975**, *5*, 359) with 2-bromopropene (Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833) as described in the Experimental Section.
(32) Albaugh-Robertson, P.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288.
(33) For a discussion, see: Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: New York, 1987; pp 113–118.

oxide in *tert*-butyl alcohol at 60 °C (entries 3–5).

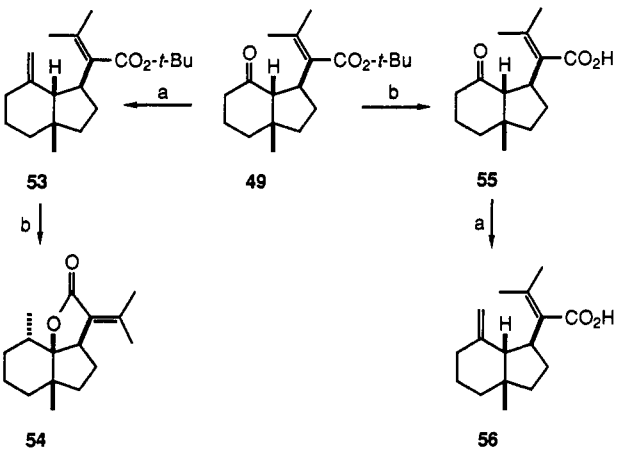
The structures of **49–51** were assigned on the basis of spectral data and chemical correlations. For example, the ^{1}H NMR spectrum of **49** showed two vinylic methyl groups as singlets at δ 1.73 and 1.60, the C(8) angular proton as a doublet at δ 2.55, and the C(1) proton as a ddd at δ 3.41. Other data, such as the ^{13}C NMR, IR, and mass spectra, also supported the structure assignment. Finally, the use of **49** in the synthesis of axanes **4–6** confirmed this structure assignment (vide infra). The gross structure of **50** was consistent with spectral data and the stereochemical assignment at C(10) was confirmed by converting **50** to **52**, an intermediate in the Piers synthesis of 10-*epi*-axamide-1.[9] Thus hydrogenation of **50** and Wittig olefination of the resulting saturated ester gave **52b** (84%). Reduction of **52b** with lithium aluminum hydride follow by oxidation of the resulting alcohol (**52c**) gave a sample of **52d** (48%) whose ^{1}H NMR spectrum was identical to a spectrum provided by Professor Piers.[34] Finally, the structural relationship between **49**, **50**, and **51** was demonstrated when **49** was converted to a mixture of **50** (13%) and **51** (16%) along with recovered **49** (60%) upon treatment with 4.0 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol for 40 h at room temperature.



(a) H_2, Pd/C (b) $Ph_3P{=}CH_2$ (c) $LiAlH_4$ (d) Jones

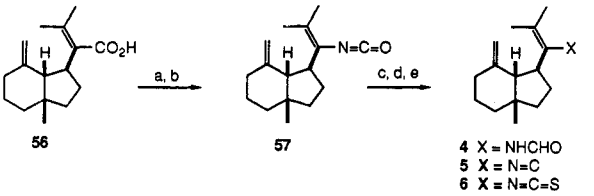
Some aspects of these cyclizations are notable. For example, there was a dramatic difference in the behavior of **47** and **48** upon treatment with pyrrolidine. It is possible that the *Z*-olefin **48** does not cyclize because of (a) the aforementioned lack of overlap between the ester carbonyl group and diene moiety and/or (b) the inability of the enamine of **48**, a presumed intermediate in the cyclization, to cyclize to a species that enjoys electrostatic stabilization of an intermediate zwitterion. It is also interesting that in all of the cyclizations, the ratio of **50**:**51** is on the side of **50**. This partitioning is quite pronounced in the pyrrolidine-mediated cyclization of **47** (entry 1). The epimerization experiment (**49** → **50** + **51**) indicates that this partitioning is not thermodynamically controlled. One rationalization of this selectivity is that cyclization leads to an intermediate imminium enolate that is protonated at C(10) from a conformation that enjoys electrostatic stabilization.[35] Steric factors in this conformation suggest that kinetic protonation should afford the observed product (**50**). Conformational arguments invoked to rationalize acyclic diastereoselection in enolate alkylations

Scheme X[a]



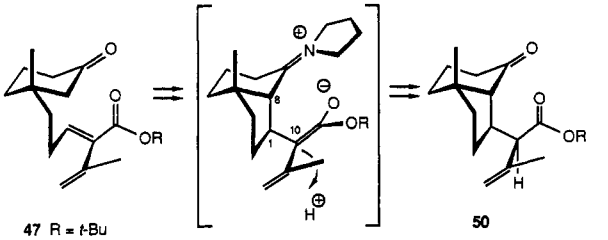
[a] (a) $Ph_3P{=}CH_2$; (b) CF_3CO_2H.

Scheme XI[b]



[b] NaH; (b) $(PhO)_2P(O)N_3$; (c) $LiEt_3BH$, THF, −78 °C; (d) TsCl, pyridine; (e) S_8, 120 °C, 20 h.

may also play a role in the observed stereoselectivity.[36] Whatever the origin of stereoselectivity, the relationship of the result to the general problem of terpenoid side-chain diastereocontrol is notable.



The aforementioned sequence gave rapid access to gram quantities of α,β-unsaturated ester **49**. This material was suitable for conversion into axanes **4–6** as outlined in Schemes X and XI. Wittig methylenation of **49** gave dienoate **53** in 78% yield. Treatment of **53** with trifluoroacetic acid, however, failed to give the expected acid **56**. Instead, a γ-lactone, assigned structure **54** on the basis of spectral data, was obtained. It was suspected that protonation of the exocyclic methylene generated a tertiary carbocation. Proton migration followed by capture of the resulting tertiary carbocation by the ester (or acid) produced the observed lactone. The *tert*-butyl group was removed prior to the methylenation to avoid this problem. Thus, treatment of **49** with trifluoroacetic acid gave keto acid **55** (95%) and olefination of **55** gave **56** in 78% yield.

At this point of the synthesis, an efficient route to carboxylic acid **56** had been developed (10 steps and 9.3% overall yield from 1,3-cyclohexanedione). The remaining task was conversion of the carboxy group into the nitrogen-containing functional groups present in axanes **4–6**.

(34) We thank Professor Piers for providing us with 400-MHz ^{1}H NMR spectra of **52d** and C(10)-*epi*-**52d**.

(35) A stereoselective intramolecular amine-mediated conjugate addition to an α-acetamidoacrylate has been reported: Kozikowski, A. P.; Greco, M. N.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 6874. Interpretation of this result is difficult due in part to the undefined nature of olefin geometry in the α-acetamidoacrylate. For discussions of stereochemical aspects of enamine conjugate additions relevant to the model proposed here, see: Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Ed.; Wiley: New York, 1991; Vol. 20, pp 87–170. Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, pp 125–259.

(36) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. See also: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.

It was projected that this could be accomplished if the carboxy group could be degraded to an isocyanate using a Curtius rearrangement or some related process.

Treatment of acid **56** with thionyl chloride and pyridine in dichloromethane did not give the expected acyl chloride. It was suspected that migration of the exocyclic double bond was a problem as ^{1}H NMR analysis indicated disappearance of the vinyl protons. After several trials, isocyanate **57** was prepared in 77% yield by treating **56** with 1 equiv of sodium hydride followed by stirring the resulting sodium carboxylate with diphenyl phosphorazidate at room temperature (Scheme XI).[37] Treatment of **57** with an equivalent of lithium triethylborohydride in tetrahydrofuran at −78 °C gave racemic axamide-4 (**4**) in 90% yield.[38] It is notable that in solution axamide-4 (**4**) exists as a 3:1 mixture of geometrical isomers. This is apparent from the ^{1}H NMR spectrum which shows signals due to the N–H as broad singlets at δ 6.77 (major isomer) and 6.32 (minor isomer). The angular methyl and vinylic protons from both geometrical isomers can also be observed. In addition to the ^{1}H NMR spectrum, the ^{13}C NMR, IR, and mass spectra were all in accord with the assigned structure and published data. Treatment of **4** with *p*-toluenesulfonyl chloride and pyridine gave racemic axisonitrile-4 (**5**) as a white solid (mp 61–63 °C) in 90% yield.[39] Finally, heating **5** with sulfur at 120 °C for 20 h gave axisothiocyanate-4 (**6**) in 70% yield.[40] The spectral data for **5** and **6** were consistent with the assigned structures, and, where available, agreed with data published for the natural products. Although it is typical to make a physical comparison between synthetic and natural materials when conducting a study of the type presented in this synthesis, it was not possibleto do so in this case as attempts to obtain authentic material met failure. Indirectly, however, a comparison was made. Recall that **50** (and thus **49**) was correlated with an intermediate in the Piers synthesis of axisonitrile-1 (**1**). Since Piers was able to compare synthetic **1** with a sample of natural axisonitrile-1 (**1**) and axanes **4–6** have been correllated with axanes **1–3**, our material was indirectly correlated with natural materials.[4,8,9]

In conclusion, the first synthesis of axanes **4–6** has been accomplished. The synthesis of axamide-4 (**4**) requires only 11 steps from 3-ethoxycyclohex-2-en-1-one (**29**) and proceeds in 9% overall yield. The synthesis required the development of an effective route to vinyl formamides and uncovered an intramolecular conjugate addition of relevance to the general problem of terpenoid side-chain synthesis. Studies designed to explore the generality of the later observation are being pursued.

Experimental Section

All melting points and boiling points are uncorrected. ^{13}C NMR multiplicities were determined from off-resonance decoupled, DEPT, or INEPT spectra. Mass spectra were obtained at an ionization energy of 70 eV. Compounds for which exact masses are reported exhibited no significant peaks at *m/e* greater than that of the parent. Reactions were conducted under a blanket of Ar or N_2 and solvents were dried when deemed necessary.

Ethyl (3′*R,3′a*R**,7′a*R**)-Tetrahydro-7′a-(hydroxymethyl)spiro[1,3-dioxolane-2,4′(3′a*H*)-indan]-3′-acetate (25).** To a solution of 1.22 g (3.91 mmol) of **18** in 30 mL of benzene cooled in an ice–water bath was added 2.18 g (1.72 mmol) of oxalyl chloride dropwise over a 10-min period. The mixture was stirred at rt for 2.5 h while Ar was bubbled through the solution. The solvent was removed in vacuo, and the resulting crude **24** was dissolved in 30 mL of THF and 3 mL of *N,N*-dimethylformamide. The mixture was cooled in a dry ice–acetone bath and a solution of 400 mg (10.5 mmol) of sodium borohydride in 10 mL of *N,N*-dimethylformamide was added over a 10-min period. The mixture was stirred at −78 °C for 10 min and then the reaction temperature was allowed to increase slowly to rt over a 30-min period. The solution was diluted with 300 mL of ether, washed with three 200-mL portions of 1 N HCl and three 150-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with EtOAc–hexane, 1:1) to give 972 mg (83%) of **25**: IR (CH_2Cl_2) 3650, 3450, 1725 cm^{-1}; ^{1}H NMR (CCl_4, 90 MHz) δ 1.25 (t, *J* = 6 Hz, 3 H, CH_3), 1.25–2.7 (m with s (OH) at δ 2.5, 15 H), 3.43 (s, 2 H, OCH_2), 3.9 (br s, 4 H, OCH_2), 4.08 (q, *J* = 6 Hz, 2 H, OCH_2); ^{13}C NMR ($CDCl_3$, 125 HMz) 14.2 (q), 20.3 (t), 28.4 (t), 28.5 (t), 29.9 (t), 35.4 (t), 37.6 (d), 41.4 (t), 48.8 (s), 53.5 (d), 59.9 (t), 64.0 (t), 64.2 (t), 69.6 (t), 111.3 (s), 173.3 (s); MS, *m/e* (rel intensity) 298 (6), 113 (10), 99 (100), 86 (16), 55 (12); exact mass calcd for $C_{16}H_{26}O_5$ 298.1780, found 298.1757.

Ethyl (1*R,3a*R**,7a*R**)-3a-(Bromomethyl)hexahydro-7-oxo-1-indanacetate (27).** To a solution of 860 mg (2.89 mmol) of **25** and 3.0 g (9.03 mmol) of carbon tetrabromide in 40 mL of CH_2Cl_2 was added 2.2 g (8.4 mmol) of triphenylphosphine in small portions over a 15-min period. The reaction mixture was stirred at rt for 27 h. Solvent was removed in vacuo and the residue was chromatographed over 30 g of silica gel (eluted with EtOAc–hexane, 1:4) to give a mixture of ketal **26** and ketone **27**.

The mixture of **26** and **27** was dissolved in 15 mL of 80% aqueous formic acid. The mixture was stirred at 0 °C for 2 h, diluted with 300 mL of ether, washed with three 150-mL portions of water, two 150-mL portions of saturated aqueous $NaHCO_3$, and two 150-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with EtOAc–hexane, 1:5) to give 734 mg (80%) of **27**: IR (CH_2Cl_2) 1730, 1700, cm^{-1}; ^{1}H NMR (CCl_4, 90 MHz) δ 1.23 (t, *J* = 6 Hz, 3 H, CO_2CCH_3), 1.6–2.9 (m, 14 H), 3.30 and 3.47 (AB, *J* = 9 Hz, 2 H, CH_2Br), 4.03 (q, *J* = 6 Hz, 2 H, OCH_2); MS, *m/e* (rel intensity) 271 (9), 223 (45), 177 (100), 149 (17), 135 (52), 91 (13); exact mass calcd for $C_{14}H_{21}O_3Br$ 316.0674, found 316.0659.

Ethyl (1*R,3a*S**,7a*R**)-Hexahydro-3a-methyl-7-oxo-1-indanacetate (7). Preparation From 27.** A solution of 1.52 g (2.19 mmol) of **27**, 2.75 g (4.9 mmol) of tri-*n*-butyltin hydride, and 15 mg of AIBN In 70 mL of benzene was heated under reflux for 1.5 h. The solvent was removed in vacuo and the residue was chromatographed over 15 g of silica gel (eluted with EtOAc–hexane, 1:6) to give 1.03 g (90%) of **7**.

Preparation from 28. To a solution of 1.99 g (8.36 mmol) of unsaturated ester **28** in 7 mL of dry THF were added 0.54 g (7.55 mmol) of pyrrolidine and 1.4 mg (0.02 mmol) of glacial acetic acid in one portion. The resulting solution was heated under gentle reflux at 100–110 °C (bath temperature) under Ar for 4 h. The mixture was diluted with 60 mL of ether and occasionally shaken with 20 mL of 2% aqueous HCl over a 15–20-min period. The aqueous layer was extracted with three 15-mL portions of ether. The combined extracts were washed with 10 mL of water, 20 mL of saturated aqueous $NaHCO_3$, and two 20-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was distilled using a Kugelrohr apparatus (oven temperature of 100–105 °C) at 0.11 mmHg to give 1.30 g (65%) of bicyclic ester **7** as a light yellow liquid: IR (CH_2Cl_2) 1730, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 3 H, CH_3), 1.16 (t, *J* = 7 Hz, 3 H, CH_3), 1.14–1.89 (m, 8 H), 2.05–2.50 (m, 5 H, CH_2COEt, CHC=O, and CH_2C=O), 2.61–2.71 (m, 1 H, CH), 4.02 (q, *J* = 7 Hz, 2 H, OCH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.09 (q), 22.35 (t), 26.36 (q), 30.32 (t), 33.83 (t), 37.63 (t), 39.63 (t), 39.81 (d), 39.95 (t), 47.23 (s), 60.24 (t), 66.90 (d), 172.36 (s), 214.16 (s); exact mass calcd for $C_{15}H_{24}O_2$ 236.1777, found 236.1779.

3-(3-Butenyl)-2-cyclohexen-1-one (30). To a stirred mixture of 13.8 g (0.58 mmol) of magnesium turnings in 50 mL of dry THF was added a few crystals of iodine, followed by 5.0 g (37.0 mmol) of 4-bromo-1-butene in one portion. After the onset of Grignard formation, a solution of 73.4 g (0.54 mmol) of 4-bromo-1-butene in 150 mL of dry THF was added at a rate such that the mixture

(37) Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1974**, *22*, 849.
(38) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1973**, *95*, 1669. To our knowledge this represents a new method for the preparation of vinylformamides.
(39) Jertler, W. R.; Corey, E. J. *J. Org. Chem.* **1958**, *23*, 1221.
(40) Boyer, J. H.; Ramakrishnan, V. T. *J. Org. Chem.* **1972**, *37*, 1360.

maintained a gentle reflux. After the addition was complete, the reaction mixture was brought to reflux for 1 h. The resulting solution was cooled to 0 °C and was added dropwise to a solution of 67.2 g (0.48 mmol) of enol ether of **29** in 50 mL of dry THF over a 1-h period. The resulting mixture was stirred at rt for another 1 h and then warmed to 50 °C for 30 min. To the solution was added 150 mL of 6 N HCl dropwise at 0 °C over a 30-min period. The resulting mixture was stirred vigorously at 0 °C for 3 h and at rt for 1 h. The organic phase was separated and the aqueous layer was extracted with three 100-mL portions of ether. The organic layers were combined, washed with one 50-mL portion of water, two 50-mL portions of saturated aqueous $NaHCO_3$, and three 50-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual light brown liquid was distilled to give 53.0 g (73%) of enone **30** as a clear liquid: bp 105–106 °C at 4.6 mmHg; IR (neat) 1665, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.87 (m, 2 H, CH_2), 2.2 (m, 8 H, CH_2 manifold), 4.9–5.0 (m, 2 H, $=CH_2$), 5.65–5.8 (m, with br s at δ 5.8, 2 H, =CH and =CHC=O); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 22.3 (t), 29.3 (t), 30.6 (t), 36.7 (t), 36.9 (t), 115.1 (t), 125.5 (d), 136.6 (d), 164.9 (s), 199.0 (s); exact mass calcd for $C_{10}H_{14}O$ 150.1047, found 150.1044.

3-(3-Butenyl)-3-methylcyclohexanone (31). To a suspension of 35.7 g (0.17 mmol) of CuBr in 50 mL dry THF at −20 °C was slowly added 266 mL (0.35 mmol) of 1.3 M ethereal methyllithium. The resulting clear solution was allowed to stir at 0 °C for 15 min and then cooled to −30 °C. To the clear reaction mixture was added dropwise 20.0 g (0.13 mmol) of enone **30** in 50 mL of dry THF over a 40-min period. The resulting bright yellow mixture was allowed to stir at −30 °C for 4 h and at 0 °C for 0.5 h. To this mixture at 0 °C was slowly added 30 mL of saturated aqueous ammonium chloride. The mixture was diluted with 400 mL of ether and washed with two 300-mL portions of saturated aqueous ammonium chloride. The combined blue aqueous phases were extracted with three 200-mL portions of ether. The organic layers were combined, washed with 200 mL of water, 100 mL of 2% aqueous HCl, and three 200-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual liquid was distilled to yield 19.8 g (89%) of ketone **30** as a clear liquid: bp 68–70 °C at 1 mmHg; IR (neat) 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz), δ 0.92 (s, 3 H, CH_3), 1.30–2.28 (m, 12 H), 4.89–5.02 (m, 2 H, $=CH_2$), 5.69–5.85 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 22.0 (t), 24.8 (q), 27.8 (t), 35.8 (t), 38.5 (s), 40.8 (t), 40.9 (t), 53.6 (t), 114.3 (t), 138.7 (d), 211.9 (s); exact mass calcd for $C_{11}H_{18}O$ 166.1370, found 166.1369.

3-(1-Methyl-2-oxocyclohexyl)propionaldehyde (32). Through a stirred solution of 9.00 g (54.2 mmol) of ketone **31** in 50 mL of methanol was passed a stream of ozone (Welsbach ozone generator) at the flow rate of 1 mmol min^{-1} at −78 °C. When the reaction mixture maintained a blue color for 1 min, the stream of ozone was replaced by nitrogen and the solution was purged for 1 h. To the resulting reaction mixture was added 50 mL of dimethyl sulfide. The mixture was stirred at −78 °C for 3 h, allowed to warm slowly to rt, and stirred at rt for 4 h. Solvents and low-boiling materials were removed in vacuo using a mechanical pump and the crude aldehyde **32** thus obtained was quickly used in the next reaction without further purification.

On a smaller scale, 330 mg (1.99 mmol) of ketone **31** was oxidized as above to yield a crude liquid which was chromatographed over 15 g of silica gel (eluted with EtOAc–hexane, 1.9) to give 296 mg (88%) of aldehyde **32** as a clear liquid: IR (neat) 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.75 (s, 3 H, CH_3), 1.41–1.49 (m, 4 H, CH_2), 1.65–1.76 (m, 2 H, CH_2), 1.91–2.00 (m, 2 H, CH_2), 2.07 (m, 2 H, CH_2), 2.23–2.30 (m, 2 H, CH_2), 9.60 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 21.6 (t), 24.1 (q), 32.8 (t), 35.3 (t), 37.6 (s), 38.0 (t), 40.4 (t), 52.8 (t), 201.4 (d), 210.7 (s); exact mass calcd for $C_{10}H_{16}O_2$ 168.1192, found 168.1188.

Ethyl (*E*)-5-(1-Methyl-3-oxocyclohexyl)-2-pentenoate (28). To a solution of crude aldehyde **32** (obtained from ozonolysis of 54.2 mmol of **31**) in 70 mL dry benzene under dry Ar was added 23.4 g (67 mmol) of $Ph_3P{=}CHCO_2Et$ in one portion. The resulting solution was stirred at rt for 8 h and at 50 °C for 2 h and the mixture was concentrated in vacuo. The resulting slurry was diluted with 200 mL of ether and the solid residue was removed by filtration. The filter cake was rinsed with 150 mL ether and the combined ether solutions were concentrated in vacuo to give a brown liquid which was distilled through a Vigreaux column to yield 10.44 g (81%) of unsaturated ester **28** as an 83:17 mixture of *E* and *Z* geometrical isomers, respectively: bp 136–140 °C/0.8–1.0 mmHg. A portion of the mixture was subjected to MPLC to afford pure samples of each isomer. **(*E*)-28**: GC t_R = 8.02 min; IR (neat) 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.83 (s, 3 H, CH_3), 1.15 (t, J = 7 Hz, 3 H, CH_3), 1.24–2.97 (m, 12 H, CH_2), 4.05 (q, J = 7 Hz, 2 H, OCH_2), 5.70 (d, J = 15.8 Hz, 1 H, =CHC=O), 6.82 (dt, J = 15.8, 6.8 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.1 (q), 21.9 (t), 24.6 (q), 26.2 (t), 35.7 (t), 38.4 (s), 39.7 (t), 40.8 (t), 53.3 (t), 60.0 (t), 121.4 (d), 148.6 (d), 166.4 (s), 211.3 (s); MS, *m/e* (rel intensity) 223 (7), 192 (14), 177 (6), 164 (8), 149 (10), 127 (15), 111 (100); exact mass calcd for $C_{14}H_{22}O_3$ 238.1580, found 238.1579. **(*Z*)-28**: GC t_R = 7.20 min; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.94 (s, 3 H, CH_3), 1.27 (t, J = 7 Hz, 3 H, CH_3), 1.34–2.70 (m, 12 H, CH_2), 4.17 (q, J = 7 Hz, 2 H, OCH_2), 5.75 (d, J = 11.5 Hz, 1 H, =CHC=O), 6.18 (dt, J = 11.5, 7.0 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.3 (q), 22.0 (t), 23.4 (t), 24.8 (q), 35.5 (t), 38.6 (s), 40.6 (t), 41.0 (t), 53.7 (t), 59.8 (t), 119.8 (d), 149.9 (d), 166.1 (s), 211.9 (s).

Ethyl (1*R,3a*S**,7a*R**)-Hexahydro-3a-methyl-7-methylene-1-indanacetate (33).** A mixture of 5 g (14.0 mmol) of methyltriphenylphosphonium bromide and 1.29 g (10.7 mmol) of potassium *tert*-butoxide in 70 mL of *tert*-butyl alcohol was stirred at rt for 1.5 h followed by the addition of a solution of 255 mg (1.07 mmol) of **7** in 10 mL of *tert*-butyl alcohol dropwise over a 5-min period. The reaction mixture was stirred at rt for 30 min, diluted with 120 mL of ether, washed with three 100-mL portions of 1 N aqueous HCl and three 100-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with EtOAc–hexane, 1:10) to give 213 mg (84%) of **33**: IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 0.97 (s, 3 H, CH_3), 1.2–2.7 (m with t (J = 6 Hz) at δ 1.25, 17 H), 4.0 (q, J = 6 Hz, 2 H, OCH_2), 4.5–4.8 (m, 2 H, =CH); MS, *m/e* (rel intensity) 236 (15), 221 (81), 191 (20), 175 (21), 148 (100), 107 (33), 93 (54); exact mass calcd for $C_{15}H_{24}O_2$ 236.1777, found 236.1779.

(1*R,3a*S**,7a*R**)-Hexahydro-3a-methyl-7-methylene-1-indanacetic Acid (34).** A solution of 205 mg (0.86 mmol) of ester **33** in 3 mL of 5% aqueous sodium hydroxide and 3 mL of methanol was heated under reflux for 2 h. The mixture was diluted with 100 mL of CH_2Cl_2 and acidified with 1 N aqueous HCl. The CH_2Cl_2 layer was washed with three 75-mL portions of brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with hexane–EtOAc, 2:1) to give 151 mg (84%) of acid **34**: mp 91–92 °C; IR (CH_2Cl_2) 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (s, 3 H, CH_3), 1.2–1.7 (m, 8 H), 2.1 (m, 4 H), 2.5 (m, 2 H), 4.6 (br s, 1 H, $=CH_2$), 4.75 (br s, 1 H, $=CH_2$), 11.1 (br s, 1 H, COOH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.7 (t), 25.1 (q), 29.1 (t), 30.5 (t), 33.7 (t), 37.9 (d), 39.5 (t), 39.9 (t), 43.4 (s), 61.5 (d), 110.7 (t), 147.5 (s), 179.9 (s); exact mass calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1468.

Methyl (α*R,1*S**,3a*S**,7a*R**)-Hexahydro-α-(1-hydroxy-1-methylethyl)-3a-methyl-7-methylene-1-indanacetate (35) and Methyl (α*R**,1*R**,3a*R**,7a*S**)-Hexahydro-α-(1-hydroxy-1-methylethyl)-3a-methyl-7-methylene-1-indanacetate (36).** To a solution of 0.3 mL (2.1 mmol) of diisopropylamine in 2 mL of THF cooled in a dry ice–acetone bath was added 1.3 mL (1.95 mmol) of 1.5 M *n*-BuLi in hexane dropwise over a period of 2 min. The mixture was stirred for 5 min followed by the dropwise addition of 103 mg (0.5 mmol) of **34** in 2 mL of THF over a period of 2 min. The resulting mixture was stirred at 50 °C for 3 h. The mixture was cooled in an ice bath followed by the addition of 0.15 mL of acetone. The mixture was stirred at ice-bath temperature for 3 h and then poured into 100 mL of 1 N HCl, extracted with 150 mL of ether, dried ($MgSO_4$), and concentrated to give 134 mg of an oil. To the oil in 4 mL of CH_2Cl_2 was added a solution of diazomethane in methylene chloride (generated from 250 mg of *N*-methyl-*N*-nitrosourea and 3 mL of 40% aqueous KOH in 10 mL of CH_2Cl_2) until the solution acquired a permanent yellow color (*CAUTION: Diazomethane is hazardous and should be handled with appropriate care!*) The solution was stirred for 10 min and one drop of glacial acetic acid was added followed by 5 g of $MgSO_4$. The resulting mixture was filtered and concentrated in vacuo. The residue was chromatographed over silica gel (EtOAc–hexane, 1:10) to give 70 mg (50%)

of **35** and 45 mg (32%) of **36**. Compound **35**: IR (CH_2Cl_2) 3500, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (s, 3 H, CH_3), 1.2 (s, 6 H, CH_3), 1.2–2.2 (m, 13 H), 3.0 (s, 1 H, OH), 3.71 (s, 3 H, OCH_3), 4.6 (br s, 1 H, =CH), 4.8 (br s, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.8 (t), 25.2 (q), 25.3 (t), 27.1 (q), 29.4 (q), 30.5 (t), 33.1 (t), 39.9 (d), 40.4 (t), 42.2 (s), 51.0 (q), 55.7 (d), 59.3 (d), 71.5 (s), 111.4 (t), 147.3 (s), 175.3 (s); MS, *m/e* (rel intensity) 262 (17), 222 (30), 207 (20), 149 (75), 133 (50), 109 (100), 59 (38). Compound **36**: mp 77–78.5 °C; IR (CH_2Cl_2) 3500, 1705 cm^{-1}; NMR ($CDCl_3$, 500 MHz) δ 0.93 (s, 3 H, CH_3), 1.1 (br d, J = 10 Hz, 1 H), 1.26 (s, 6 H), 1.3–1.7 (m, 6 H), 1.8 (d, 1 H), 1.95 (br d, J = 10 Hz, 1 H), 2.1 (m, 2 H), 2.3 (d, J = 9 Hz, 1 H, $CHCO_2Me$), 2.52 (s, 1 H, OH), 2.74 (qu, J = 9 Hz, 1 H), 3.54 (s, 3 H, OCH_3), 4.66 (br s, 1 H, =CH), 4.74 (br s, 1 H, =CH); MS, *m/e* (rel intensity) 262 (72), 207 (36), 187 (18), 161 (19), 148 (77), 133 (72), 119 (19), 109 (100), 79 (34), 59 (48).

Methyl (αR*,1S*,3aS*,7aR*)-Hexahydro-α-isopropenyl-3a-methyl-7-methylene-1-indanacetate (37). To a solution of 35 mg (0.125 mmol) of **35** in 1 mL of CH_2Cl_2 was added 125 mg (0.19 mmol) of Martin's sulfurane in one portion.[27] The mixture was stirred at rt for 30 min, absorbed on 10 g of silica gel, and eluted with CH_2Cl_2 to give 35 mg (100%) of **37**: IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.94 (s, 3 H, CH_3), 1.1–2.1 (m with s at δ 1.64 and d (J = 10 Hz) at δ 1.83, 14 H), 2.53 (ddd, J = 15.5, 10, 5.4 Hz, 1 H), 3.02 (d, J = 8.3 Hz, 1 H), 3.6 (s, 3 H, OCH_3), 4.6 (br s, 1 H, =CH), 4.72 (q, J = 1 Hz, 1 H, =CH), 4.8 (q, J = 1 Hz, 1 H, =CH), 4.9 (br s, 1 H, =CH); MS, *m/e* (rel intensity) 262 (2), 247 (44), 215 (15), 202 (25), 187 (100), 149 (85), 133 (50), 93 (54), 79 (42); exact mass calcd for $C_{17}H_{26}O_2$ 262.1933; found 262.1924.

Ethyl (1R*,3aS*,7aR*)-α-[Bis(methylthio)methylene]-hexahydro-3a-methyl-7-methylene-1-indanacetate (39). To a stirred solution of 200 mg (1.98 mmol) of diisopropylamine in 4 mL of dry THF under Ar at −78 °C was added 0.83 mL (1.98 mmol) of 2.4 M of *n*-butyllithium in hexane. The solution was stirred for 20 min at −78 °C and at 0 °C for 5 min and cooled to −78 °C. To the mixture was added 0.354 g (1.98 mmol) of hexamethylphosphoramide in one portion. The resulting solution was stirred at −78 °C for 40 min and then 424 mg (1.80 mmol) of ester **33** in 2 mL of dry THF was added. The mixture was stirred at −78 °C for 3 h and −30 °C for 2 h. To the resulting solution was added 151 mg (1.98 mmol) of carbon disulfide in one portion at −30 °C. The mixture was allowed to warm slowly to 0 °C over a 3.5-h period and then cooled to −78 °C. To the mixture was added a second equivalent (1.98 mmol) of LDA in 4 mL of dry THF (prepared as described above) using a cannula at −78 °C. The reaction mixture was allowed to warm to −40 °C followed by stirring for 2 h. To the resulting mixture was added 1.70 g (12 mmol) of methyl iodide in one portion at −40 °C. The mixture was allowed to warm to rt slowly and stirred at rt for 5 h, and 1 mL of saturated aqueous ammonium chloride was added at 0 °C. The mixture was diluted with 30 mL of ether and washed with 10 mL of 2% aqueous HCl and 20 mL of water. The combined aqueous washes were extracted with two 15-mL portions of ether. The combined ethereal layers were washed with 10 mL of saturated aqueous $NaHCO_3$ and two 15-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with EtOAc–hexane, 1:50) to yield 0.464 g (76%) of ketene dithioacetal **39** as a light yellow liquid: IR (neat), 1720, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.95 (s, 3 H, CH_3), 1.19–1.76 (m with t (J = 7 Hz) at δ 1.33, 9 H, CH_2 and CH_3), 1.9–2.4 (m with two s at δ 2.21 and 2.22, 11 H), 3.84 (ddd, J = 11.0, 10.3, 7.5 Hz, 1 H, $CHC{=}C(SMe)_2$), 4.25 (q, J = 7 Hz, 2 H, OCH_2), 4.63 (br t, 1 H, =CH), 4.72 (br t, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.2 (q), 17.0 (q), 17.8 (q), 23.6 (t), 25.0 (q), 27.2 (t), 30.7 (t), 33.2 (t), 40.5 (t), 43.3 (s), 45.6 (d), 59.3 (d), 60.6 (t), 111.4 (t), 135.3 (s), 146.0 (s), 146.5 (s), 168.0 (s); MS, *m/e* (rel intensity) 325 (100, M − CH_3), 311 (5), 297 (5), 279 (20), 251 (25), 231 (20), 219 (30), 203 (45), 185 (20), 171 (15), 157 (20), 109 (25), 91 (20).

Ethyl (1R*,3aR*,7aS*)-Hexahydro-α-isopropylidene-3a-methyl-7-methylene-1-indanacetate (40). To a suspension of 166 mg (0.87 mmol) of copper(I) bromide–dimethyl sulfide complex in 1 mL of dry THF under Ar at −20 °C was added 1.34 mL (1.74 mmol) of 1.3 M ethereal methyllithium. The resulting clear solution was stirred at −20 °C for 30 min and then cooled to −78 °C. To the resulting cuprate was slowly added via cannula 141 mg (0.41 mmol) of ketene dithioacetal **39** in 4 mL of ether. The mixture was allowed to warm to rt, stirred for 10 h, and brought to gentle reflux for 10 h. The mixture was cooled to rt and 1 mL of saturated aqueous ammonium chloride and 100 mL of ether were added. The solution was filtered and the filtrate was washed with 10 mL of saturated aqueous ammonium chloride and two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed using MPLC (Lobar size C; eluted with hexane–EtOAc, 20:1) to give 10 mg (9%) of esters **40** and 15 mg (12%) of a mixture of esters **41**. Ester **40**: IR (neat) 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.95 (s, 3 H, CH_3), 1.32 (t, J = 7 Hz, 3 H, CH_3), 1.20–2.13 (m with two s at δ 1.7 and δ 1.8, 16 H, $=CCH_3$), 2.28 (d, J = 11 Hz, 1 H, =CCH), 3.27 (ddd, J = 11, 11, 7 Hz, 1 H, $CHC(=)CO_2Et$), 4.21 (q, J = 7 Hz, 2 H, OCH_2), 4.62 (br s, 1 H, $=CH_2$), 4.69 (br s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.34 (q), 20.44 (q), 22.99 (q), 23.85 (t), 25.06 (q), 27.76 (t), 30.74 (t), 33.23 (t), 40.59 (t), 42.25 (d), 43.41 (s), 58.92 (d), 59.77 (t), 110.87 (t), 131.70 (s), 135.73 (s), 147.16 (s), 170.44 (s); exact mass calcd for $C_{18}H_{28}O_2$ 276.2089, found 276.2133. The NMR spectra of **41** were complicated due to the presence of geometrical isomers and impurities. GC-MS analysis indicated the presence of two major components that exhibited parent ions at *m/e* 294 and gave an exact mass in agreement with the molecular formula $C_{17}H_{26}O_2S$.

7-(3-Butenyl)-7-methyl-1,4-dioxaspiro[4.5]decane (42). A solution of 13.3 g (80 mmol) of ketone **31**, 24.8 g (400 mmol) of ethylene glycol, 50 mL of dry benzene, 21.2 g (200 mmol) of trimethyl orthoformate, and 0.12 g (0.8 mmol) of *p*-TsOH was stirred at rt under Ar for 6 h. A solution of 12 mL of saturated aqueous $NaHCO_3$ was added slowly. The mixture was concentrated in vacuo and the residue was diluted with 100 mL of ether. The solution was washed with three 20-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual liquid (20.6 g) was chromatographed over 350 g of silica gel (eluted with EtOAc–hexane, 1:20) to give 13.0 g (78%) of ketal **42** as a clear liquid: IR (neat) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.93 (s, 3 H, CH_3), 1.22–1.64 (m, 10 H), 1.95 (m, 2 H, $=CCH_2$), 3.84 (s, 4 H, OCH_2), 4.84–5.0 (m, 2 H, $=CH_2$), 5.70–5.86 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.7 (t), 25.3 (q), 28.1 (t), 34.4 (s), 35.0 (t), 37.1 (t), 42.0 (t), 44.8 (t), 63.8 (t), 64.0 (t), 109.4 (s), 113.7 (t), 139.7 (d), MS, *m/e* (rel intensity) 195 (10), 167 (52), 155 (60), 153 (30), 113 (35), 100 (33), 99 (100), 86 (65); exact mass calcd for $C_{13}H_{22}O_2$ 210.1579, found 210.1574.

7-Methyl-1,4-dioxaspiro[4.5]decane-7-propionaldehyde (43). Through a stirred solution of 10.5 g (50 mmol) of ketal **42** in 100 mL of methanol at −78 °C was passed a stream of ozone (Welsbach ozone generator) at the flow rate of 1.0 mmol min^{-1}. When the reaction mixture maintained a blue color for 1 min, the stream of ozone was replaced by nitrogen and the solution was purged for 1 h. To the resulting clear reaction mixture was added 40 mL of dimethyl sulfide. The mixture was stirred at −78 °C for 3 h, allowed to warm slowly to rt, and stirred for 4 h. The solvent was removed in vacuo and the residual crude liquid (17.5 g) was chromatographed over 150 g of silica gel (eluted with EtOAc–hexane, 1:10) to give 10.1 g (95%) of ketal aldehyde **43** as a colorless liquid: IR (neat) 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.87 (s, 3 H, CH_3), 1.18–1.70 (m, 10 H), 2.30 (m, 2 H, $CH_2C{=}O$), 3.82 (s, 4 H, OCH_2), 9.69 (dd, J = 4, 2 Hz, 1 H, CHO); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.4 (t), 25.6 (q), 33.4 (t), 33.9 (s), 34.7 (t), 36.9 (t), 38.8 (t), 44.5 (t), 63.9 (t), 109.0 (s), 202.8 (d); MS, *m/e* (rel intensity) 167 (35), 155 (35), 153 (25), 125 (10), 113 (30), 100 (30), 99 (100); exact mass calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1763.

1,1-Dimethylethyl 3-Methyl-2-(trimethylsilyl)-3-butenoate (44). To a stirred solution of 10.6 g (115 mmol) of diisopropylamine in 50 mL of dry THF under Ar at −78 °C was added 68.8 mL (110 mmol) of 1.6 M *n*-BuLi in hexane. The solution was stirred for 30 min at −78 °C and the solvent was removed in vacuo at −78 °C. To the residual white solid was added 70 mL of dry THF at −78 °C followed by a solution of 18.8 g (100 mmol) of *tert*-butyl α-(trimethylsilyl)acetate in 50 mL of dry THF followed by stirring at −78 °C for 40 min.

A second flask was charged with 10.9 g (50.0 mmol) of nickel(II) bromide, and 50 mL of dry THF and 31 mL (50.0 mmol) of 1.6 M *n*-BuLi in hexane were added. The solution was stirred under

Ar at −78 °C for 12 min. To the resulting black mixture was added in 12.1 g (100 mmol) of 2-bromopropene at −78 °C, followed by addition of the ester enolate solution via cannula. The cooling bath was then removed and the mixture was stirred at rt for 8 h. The solution was cooled to −78 °C and 120 mL of 5% of aqueous HCl was slowly added. The mixture was allowed to warm to 0 °C, diluted with 200 mL of ether, and filtered through a short column packed with 30 g of alumina topped with a layer of Florosil (60–100 mesh). The column was rinsed with two 150-mL portions of ether and the filtrate was concentrated. The residual liquid (21.2 g) was chromatographed over 400 g of silica gel (eluted with diethyl ether–hexane, 1:30) to give 11.0 g (48%) of ester **44** as a light yellow liquid: IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.15 (s, 9 H, $SiMe_3$), 1.45 (s, 9 H, CMe_3), 1.83 (br s, 3 H, $=CCH_3$), 2.8 (s, 1 H, CHSi), 4.82 (br s, 1 H, =CH), 4.84 (br s, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ −2.0 (q), 24.4 (q), 28.2 (q), 47.9 (d), 79.8 (s), 111.5 (t), 140.6 (s), 172.0 (s); MS, *m/e* (rel intensity) 172 ($M^+ - C_4H_8$), 156 (30), 113 (20), 82 (100), 73 (90), 57 (90).

1,1-Dimethylethyl (*Z*)-2-(1-Methylethenyl)-5-(7-methyl-1,4-dioxaspiro[4.5]dec-7-yl)-2-pentenoate (46) and 1,1-Dimethylethyl (*E*)-2-(1-Methylethenyl)-5-(7-methyl-1,4-dioxaspiro[4.5]dec-7-yl)-2-pentenoate (45). To a stirred solution of 2.13 g (21.1 mmol) of diisopropylamine in 30 mL of dry THF under Ar was added 14.1 mL (21.1 mmol) of 1.5 M *n*-BuLi in hexane at −78 °C. The solution was stirred at −78 °C for 20 min and 0 °C for 5 min and cooled to −78 °C. To the mixture was added a solution of 5.0 g (21.9 mmol) of ester **44** in 40 mL of dry THF. The solution was stirred at −78 °C for 1 h and a solution of 3.58 g (16.9 mmol) of ketal aldehyde **43** in 20 mL of dry THF was added using a cannula. The resulting solution was stirred at −78 °C for 2 h and at rt for 8 h. To the mixture were added 20 mL of saturated aqueous ammonium chloride and 300 mL of ether. The organic phase was washed with three 20-mL portions of brine and the combined washes were extracted with two 15-mL portions of ether. The combined etheral layers were dried (Na_2SO_4) and concentrated in vacuo. The residual liquid (8.1 g) was chromatographed over 100 g of silica gel (eluted with EtOAc–hexane, 1:10) to give 3.71 g (63%) of **45** and **46** as a light yellow liquid. This material was a 2:1 mixture of *E* and *Z* isomers, respectively, by integration of selected peaks in the ^1H NMR spectrum of the mixture. Medium pressure liquid chromatography (Lobar size C; eluted with EtOAc–hexane, 1:20) gave 1.24 g of *Z*-isomer **46** and 2.46 g of *E*-isomer **45**. Ester **46**: IR (neat) 1722, 1630, cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.95 (s, 3 H, CH_3), 1.24–1.64 (m with s at δ 1.53, 19 H, aliphatic and *t*-Bu), 1.85 (br s, 3 H, $=CCH_3$), 2.12 (ddd, J = 10, 10, 7 Hz, 2 H, $CH_2C=$), 3.88 (s, 4 H, OCH_2), 4.91 (br s, 1 H, $=CH_2$), 4.96 (br s, 1 H, $=CH_2$), 5.59 (t, J = 7 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.7 (t), 20.1 (q), 24.2 (t), 25.4 (q), 28.2 (q), 34.6 (s), 35.0 (t), 37.1 (t), 41.8 (t), 44.9 (t), 63.9 (t), 64.0 (t), 81.3 (s), 109.3 (s), 113.7 (t), 131.3 (d), 137.7 (s), 139.5 (s), 168.6 (s); MS, *m/e* (rel intensity) 350 (M^+), 294 (10), 251 (15), 195 (10), 155 (100), 111 (20), 99 (70), 86 (25), 57 (30); exact mass calcd for $C_{21}H_{34}O_4$ 350.2460, found 350.2466. Ester **45**: IR (neat) 1709, 1629, 899, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.89 (s, 3 H, CH_3), 1.14–1.58 (m with s at d 1.42, 19 H, aliphatic and *t*-Bu), 1.81 (br s, 3 H, $=CCH_3$), 2.06 (ddd, J = 10, 10, 8 Hz, 2 H, $CH_2C=$), 3.84 (s, 4 H, OCH_2), 4.67 (br s, 1 H, $=CH_2$), 5.03 (br s, 1 H, $=CH_2$), 6.55 (t, J = 7 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.6 (t), 23.0 (q), 23.8 (t), 25.7 (q), 28.0 (q), 34.6 (s), 34.9 (t), 37.0 (t), 41.3 (t), 44.6 (t), 63.9 (t), 63.9 (t), 80.0 (s), 109.2 (s), 115.4 (t), 136.7 (s), 140.4 (s), 142.3 (d), 166.0 (s); MS, *m/e* (rel intensity) 350 (M^+), 294 (10), 251 (15), 155 (100), 111 (20), 89 (55), 86 (20), 57 (30); exact mass calcd for $C_{21}H_{34}O_4$ 350.2460, found 350.2455.

1,1-Dimethylethyl (*Z*)-2-Isopropenyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (48) and 1,1-Dimethylethyl (*E*)-2-Isopropenyl-5-(1-methyl-3-oxocyclohexyl)-2-pentenoate (47). To a stirred solution of 0.82 g (2.34 mmol) of isomeric unsaturated esters **45** and **46** (**45**:**46** = 2:1) in 4 mL of ether and *tert*-butyl alcohol (1:1) at rt was added 5.9 mL (5.9 mmol) of 1 N aqueous HCl and the mixture was stirred at rt for 12 h. The mixture was diluted with 30 mL of ether and washed with 5 mL of water and two 5-mL portions of saturated aqueous $NaHCO_3$. The combined etheral layers were washed with two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual liquid (1.1 g) was chromatographed over 20 g of silica gel (eluted with EtOAc–hexane, 1:10) to give 0.69 g (96%) of a 1.6:1 mixture of unsaturated keto esters **47** and **48**, respectively, by integration of selected peaks in the ^1H NMR spectrum of the mixture. A 0.5-g sample of the mixture was chromatographed using MPLC (Lobar size B; eluted with EtOAc–hexane, 1:15) to give 0.32 g of pure *E*-isomer **47** and 0.18 g of pure *Z*-isomer **48**. Ester **47**: IR (neat) 1710, 1630, 900, 854 cm^{-1}; ^1H NMR (CDCl 250 MHz) δ 0.89 (s, 3 H, CH_3), 1.2–2.3 (m with s's at δ 1.44 (*t*-Bu) and δ 1.82 ($=CCH_3$), 24 H), 4.68 (br s, 1 H, $=CH_2$), 5.06 (br s, 1 H, $=CH_2$), 6.56 (t, J = 7 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 21.9 (t), 23.0 (q), 23.5 (t), 24.6 (q), 28.0 (q), 35.6 (t), 38.6 (s), 40.8 (t), 53.4 (t), 80.3 (s), 102.7 (s), 115.6 (t), 137.3 (s), 140.3 (s), 141.0 (d), 165.8 (s), 211.8 (s); MS, *m/e* (rel intensity) 250 ($M^+ - C_4H_8$), 232 (5), 217 (5), 140 (5), 121 (10), 111 (100), 95 (5), 81 (5), 57 (40). Ester **48**: IR 1716, 888, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.92 (s, 3 H, CH_3), 1.35–2.33 (m with s's at δ 1.52 (*t*-Bu) and δ 2.12 ($=CCH_3$), 24 H), 4.91 (s, 1 H, $=CH_2$), 4.97 (s, 1 H, $=CH_2$), 5.58 (t, J = 7 Hz, 1 H, =CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.0 (q), 22.0 (t), 24.0 (t), 24.7 (q), 28.1 (q), 35.6 (t), 38.5 (s), 40.89 (t), 41.0 (t), 53.6 (t), 81.5 (s), 114.1 (t), 130.1 (d), 138.3 (s), 139.3 (s), 168.4 (s), 211.6 (s): MS, *m/e* (rel intensity) 250 ($M^+ - C_4H_8$), 232 (12), 217 (5), 140 (10), 121 (30), 110 (100), 93 (10), 79 (10), 69 (20), 57 (50).

1,1-Dimethylethyl (1*R,3a*R**,7a*S**)-Hexahydro-α-isopropylidene-3a-methyl-7-oxo-1-indanacetate (49), 1,1-Dimethylethyl (α*R**,1*S**,3a*S**,7a*R**)-Hexahydro-α-isopropenyl-3a-methyl-7-oxo-1-indanacetate (50), and 1,1-Dimethylethyl (α*S**,1*S**,3a*S**,7a*R**)-Hexahydro-α-isopropenyl-3a-methyl-7-oxo-1-indanacetate (51). Preparation from 47 + 48.** To a stirred solution of 3.0 g (9.8 mmol) of a mixture of unsaturated esters **47** (67%) and **48** (33%) in 20 mL of dry *tert*-butyl alcohol at rt under Ar was added in 0.5 mL (0.5 mmol) of a 1 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The reaction mixture was stirred for 30 min at rt and 0.1 g (1.67 mmol) of 98% acetic acid was added. The mixture was filtered through 70 g of silica gel (eluted with EtOAc–hexane, 1:5) and the filtrate was concentrated in vacuo. The residual liquid (3.42 g) was chromatographed over 75 g of silica gel (eluted with EtOAc–hexane, 1:20) to give 1.38 g (46%) of bicyclic ester **49** and 1.08 g (36%) of mixture of bicyclic esters **50** and **51** which were separated by MPLC (Lobar size B; eluted with EtOAc–hexane, 1:50) to give 0.92 g (30%) of ester **50** and 0.16 g (5%) of ester **51**.

Preparation from 47 Using Pyrrolidine as Base. To a stirred solution of 84 mg (0.27 mmol) of ester **47** in 3 mL of dry THF at 80 °C (oil bath) were added 20 mg (0.28 mmol) of pyrrolidine and 1 mg of glacial acetic acid. The resulting solution was stirred under gentle reflux for 10 h and cooled to rt. The mixture was diluted with 30 mL of ether and washed with 5 mL of 5% aqueous HCl. The ether layer was washed with 5 mL of water, 5 mL of saturated aqueous $NaHCO_3$, and two 5-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with EtOAc–hexane, 1:20) to give 50 mg (60%) of ester **50** and 13 mg (15%) of ester **49**.

Preparation from 47 Using *tert*-Butoxide as Base. To a stirred solution of 88 mg (0.29 mmol) of ester **47** in 1.0 mL of dry *tert*-butyl alcohol and 1.5 mL of dry THF at 60 °C was added 0.23 mL (0.06 mmol) of a 0.25 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The mixture was stirred for 30 min at 60 °C, cooled to rt, and quenched with 5 mg (0.08 mmol) of glacial acetic acid. The mixture was diluted with 30 mL of ethyl ether, washed with 5 mL of saturated aqueous $NaHCO_3$ and two 5-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed using MPLC (Lobar size A; eluted with EtOAc–hexane, 1:40) to give 46 mg (52%) of ester **49**, 13 mg (15%) of ester **50**, and 7 mg (8%) of ester **51**.

Preparation from 48 Using *tert*-Butoxide as Base. To a stirred solution of 74 mg (0.24 mmol) of ester **48** in 1.0 mL of dry *tert*-butyl alcohol and 1.0 mL of dry THF at 60 °C was added 0.2 mL (0.05 mmol) of a 0.25 M solution of potassium *tert*-butoxide in *tert*-butyl alcohol. The mixture was stirred for 3 h at 60 °C, cooled to rt, and quenched with 10 mg (0.17 mmol) of glacial acetic acid. The mixture was diluted with 30 mL of ethyl ether, washed 5 mL of saturated aqueous $NaHCO_3$ solution and two 5-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The

residue (0.2 g) was chromatographed using MPLC (Lobar size A; eluted with EtOAc–hexane, 1:40) to give 48 mg (54%) of ester **49**, 12 mg (14%) of ester **50**, and 3.5 mg (4%) of ester **51**. Ester **49**: IR (neat) 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.04 (s, 3 H, CH_3), 1.35–2.52 (m with three s's at δ 1.48 (*t*-Bu), 1.60 (=CCH_3) and 1.73 (=CCH_3), 25 H), 2.55 (d, J = 10.5 Hz, 1 H), 3.41 (m, 1 H, =CCH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.2 (q), 22.3 (t), 22.7 (q), 25.9 (q), 28.1 (q), 28.9 (t), 33.4 (t), 37.6 (t), 40.8 (t), 43.1 (d), 47.8 (s), 64.5 (d), 80.7 (s), 131.2 (s), 135.1 (s), 169.2 (s), 213.6 (s); MS, *m/e* (rel intensity) 250 ($M^+ - C_4H_8$), 232 (40), 217 (100), 189 (60), 177 (30), 111 (35), 57 (90). Ester **50**: IR (neat) 1726, 1708, 1644, 895, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.99 (s, 3 H, CH_3), 1.32–1.8 (m with two s's at δ 1.36 (*t*-Bu) and 1.62 (=CCH_3), 19 H), 1.90 (d, J = 8 Hz, 1 H, HCC=O), 2.1 (m, 2 H), 2.45 (m, 1 H), 2.72 (d, J = 11 Hz, 1 H, =CCH), 2.95 (m, 1 H, *H*CCHCO$_2$R), 4.76 (br s, 1 H, =CH_2), 4.81 (br s, 1 H, =CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 21.2 (q), 23.0 (t), 26.0 (q), 27.8 (q), 28.9 (t), 33.7 (t), 38.2 (t), 39.3 (t), 41.7 (d), 48.8 (s), 60.6 (d), 64.8 (d), 80.2 (s), 114.4 (t), 142.1 (s), 171.9 (s), 213.4 (s); MS, *m/e* (rel intensity) 306 (M^+), 250 (30), 233 (25), 204 (20), 191 (20), 164 (10), 151 (100), 137 (15), 111 (55), 93 (15), 81 (20), 67 (15), 57 (100); exact mass calcd for $C_{19}H_{30}O_3$ 306.2190, found 306.2195. Ester **51**: IR (neat) 1722, 1644, 843, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.00 (s, 3 H, CH_3), 1.2–2.2 (m with two s's at δ 1.35 (*t*-Bu) and 1.69 (=CCH_3), 22 H), 2.7 (m, 1 H), 2.76 (d, J = 11 Hz, 1 H, =CCH), 2.95 (m, 1 H, *H*CCHCO$_2$R), 4.85 (br s, 2 H, =CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.97 (q), 23.38 (t), 25.75 (q), 27.57 (t), 27.77 (q), 33.94 (t), 37.79 (t), 39.34 (t), 42.41 (d), 48.96 (s), 60.32 (d), 67.61 (d), 80.69 (s), 114.73 (t), 142.29 (s), 171.63 (s), 214.05 (s); MS, *m/e* (rel intensity) 306 (M^+), 250 (10), 233 (15), 217 (10), 206 (15), 191 (20), 163 (10), 151 (30), 135 (15), 111 (25), 93 (10), 81 (10), 57 (100); exact mass calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2216.

1,1-Dimethylethyl (α*R,1*R**,3a*R**,7a*S**)-Hexahydro-α-isopropyl-3a-methyl-7-oxo-1-indanacetate (52a).** A solution of 0.52 g (1.7 mmol) of **51** and 70 mg of 10% palladium on charcoal in 5 mL of EtOAc was hydrogenated at 40 psi in a Parr hydrogenation apparatus at rt for 10 h. The mixture was filtered through a short column of Celite and the filtrate was concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with hexane–EtOAc, 10:1) to give 0.44 g (83%) of ester **52a** as a colorless liquid: IR (neat) 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.82 (d, J = 7 Hz, 3 H, CH_3), 0.92 (d, J = 7 Hz, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.46 (s, 9 H, *t*-Bu), 1.36–2.30 (m, 12 H, CH and CH_2 manifold), 2.5 (m, 1 H, CH), 2.7 (m, 1 H, CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz), δ 18.80 (q), 21.24 (q), 22.88 (t), 25.75 (q), 27.08 (t), 28.04 (d), 28.11 (q), 33.06 (t), 37.88 (t), 40.01 (t), 42.07 (d), 48.44 (s), 57.48 (d), 65.21 (d), 80.15 (s), 173.29 (s), 214.67 (s); exact mass calcd for $C_{19}H_{32}O_3$ 308.2364, found 308.2368.

1,1-Dimethylethyl (α*R,1*R**,3a*R**,7a*S**)-Hexahydro-α-isopropyl-3a-methyl-7-methylene-1-indanacetate (52b).** A mixture of 0.54 g (1.5 mmol) of methyltriphenylphosphonium bromide and 0.16 g (1.4 mmol) of potassium *tert*-butoxide in 3 mL of toluene was stirred at rt under Ar for 3 h, followed by addition of 2 mL of dimethyl sulfoxide. The solution was stirred for 1 h and a solution of 144 mg (0.47 mmol) of ketone **52a** in 1 mL of dimethyl sulfoxide was added via syringe. The resulting mixture was stirred at 60 °C under Ar for 4 h, cooled to rt, and diluted with 2 mL of 5% aqueous HCl. The mixture was stirred at rt for 1 h, diluted with 60 mL of dichlormethane, and washed with three 20-mL portions of water. The combined aqueous washes were extracted with three 10-mL portions of ether. The combined organic phases were washed with 10 mL of saturated aqueous $NaHCO_3$ and two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with hexane–EtOAc, 40:1) to give 140 mg (98%) of ester **52b** as a pale yellow liquid: IR (neat) 1742, 1644, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.88 (d, J = 7 Hz, 6 H, CH_3), 0.93 (s, 3 H, CH_3), 1.47 (s, 9 H, *t*-Bu), 1.15–2.15 (m, 13 H, CH and CH_2 manifold), 2.4 (m, 1 H, C*H*CHCO$_2$R), 4.72 (br s, 1 H, =CH_2), 4.76 (br s, 1 H, =CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.55 (q), 21.07 (q), 23.14 (t), 23.94 (t), 24.88 (q), 28.25 (q), 28.75 (d), 30.49 (t), 32.60 (t), 40.42 (t), 40.83 (d), 43.61 (s), 55.17 (d), 58.53 (d), 79.80 (s), 110.66 (t), 148.03 (s), 174.48 (s); exact mass calcd for $C_{20}H_{34}O_2$ 306.2491, found 306.2531.

(β*R,1*R**,3a*R**,7a*S**)-Hexahydro-β-isopropyl-3a-methyl-7-methylene-1-indanethanol (52c).** To a stirred solution of 115 mg (0.38 mmol) of ester **52b** in 4 mL of ether at rt was added 84 mg (2.2 mmol) of lithium aluminum hydride. The mixture was warmed under reflux for 10 h, cooled to 0 °C, and quenched by dropwise addition of 1 mL of 3 N aqueous HCl. The mixture was diluted with 50 mL of ether and washed with two 10-mL portions of 5% aqueous HCl and two 10-mL portions of water. The combined washes were extracted with three 10-mL portions of ether. The combined ether solutions were washed with 5 mL of saturated aqueous $NaHCO_3$ and two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 10 g of silica gel (eluted with hexane–EtOAc, 20:1) to give 65 mg (74%) of alcohol **52c** as a clear liquid: IR (neat) 3330, 1643, 1030, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.85 (d, J = 7 Hz, 3 H, CH_3), 0.89 (d, J = 7 Hz, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.15–1.97 (m, 12 H), 2.05 (m, 2 H), 2.2 (m, 1 H), 3.67 (m, 2 H, OCH_2), 4.61 (br s, 1 H, =CH_2), 4.75 (br s, 1 H, =CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.54 (q), 21.02 (q), 24.03 (t), 24.55 (t), 25.00 (q), 28.28 (d), 30.49 (t), 32.91 (t), 39.43 (d), 41.04 (t), 42.76 (s), 48.07 (d), 59.70 (d), 61.98 (t), 110.44 (t), 148.53 (s); exact mass calcd for $C_{16}H_{28}O$ 236.2162, found 236.2151.

(α*R,1*R**,3a*R**,7a*S**)-Hexahydro-α-isopropyl-3a-methyl-7-methylene-1-indanacetic acid (52d).** To a stirred solution of 41 mg (0.17 mmol) of alcohol **52c** in 4 mL of acetone at rt was added 0.2 mL (0.48 mmol) of Jones reagent. The solution was stirred at rt for 5 h followed by addition of 0.5 mL of saturated aqueous $NaHCO_3$. The mixture was concentrated in vacuo, diluted with 50 mL of ether, and washed with two 10-mL portions of aqueous HCl–glycine buffer (pH 3) and two 5-mL portions of brine. The combined aqueous washes were extracted with two 10-mL portions of ether. The combined ethereal layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 4 g of silica gel (eluted with hexane–EtOAc, 10:1) to give 29 mg (67%) of acid **52d** as a yellow oil: IR (neat) 1702, 1644, 894 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.92 (d, J = 7 Hz, 3 H, CH_3), 0.94 (d, J = 7 Hz, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.25–2.27 (m, 13 H), 2.45 (m, 1 H), 4.74 (br s, 1 H, =CH_2), 4.79 (br s, 1 H, =CH_2), 10.5 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.62 (q), 20.91 (q), 23.81 (t), 24.00 (t), 24.89 (q), 28.44 (d), 30.62 (t), 32.91 (t), 40.18 (t), 40.38 (d), 43.65 (s), 54.74 (d), 59.01 (d), 111.15 (t), 147.60 (s), 181.07 (s); exact mass calcd for $C_{16}H_{26}O_2$ 250.1929, found 250.1931.

1,1-Dimethylethyl (1*R,3a*S**,7a*R**)-Hexahydro-α-isopropylidene-3a-methyl-7-methylene-1-indanacetate (53).** A flask was charged with 257 mg (0.72 mmol) of methyltriphenylphosphonium bromide, 77 mg (0.68 mmol) of potassium *tert*-butoxide, 2 mL of dry toluene, and 1 mL of dry dimethyl sulfoxide. The mixture was stirred at rt for 8 h. A solution of 56 mg (0.10 mmol) of ester **49** in 1 mL of THF was added via cannula over a period of 30 min at rt. The mixture was stirred for 3 h, 2 mL of 5% aqueous HCl was added, and stirring was continued for 1 h. The mixture was diluted with 40 mL of ether–hexane (1:1), washed with two 5-mL portions of saturated aqueous $NaHCO_3$ and two 5-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue (0.3 g) was chromatographed over 6 g of silica gel (eluted with EtOAc–hexane, 1:40) to give 38 mg (69%) of ester **53** as a pale yellow liquid: IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.97 (s, 3 H, CH_3), 1.2 (m, 1 H), 1.4–1.8 (m with three s's at δ 1.54 (*t*-Bu), 1.63 (=CCH_3) and 1.77 (=CCH_3), 21 H), 2.0 (m, 1 H), 2.15 (m, 2 H), 2.35 (d, J = 10 Hz, 1 H, =CCH), 3.25 (ddd, J = 10, 10, 7 Hz, 1 H, =CCH), 4.65 (br s, 1 H, =CH_2), 4.70 (br s, 1 H, =CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.1 (q), 22.6 (q), 23.8 (t), 25.0 (q), 27.4 (t), 28.11 (q), 30.7 (t), 33.0 (t), 40.7 (t), 42.2 (d), 43.4 (s), 58.8 (d), 80.4 (s), 110.8 (t), 132.8 (s), 133.5 (s), 147.2 (s), 170.0 (s); MS, *m/e* (rel intensity) 248 ($M^+ - C_4H_8$), 233 (100), 215 (30), 193 (45), 148 (40), 133 (40), 109 (60).

(1*R,3a*S**,7*S**,7a*S**)-Hexahydro-7a-hydroxy-α-isopropylidene-3a,7-dimethyl-1-indanacetic Acid, γ-Lactone (54).** To a solution of 121 mg (0.40 mmol) of ester **53** in 1 mL of dichloromethane was added in 1.5 g (13 mmol) of trifluoroacetic acid in one portion. The resulting mixture was stirred for 10 h at rt, diluted with 40 mL of ethyl ether, washed with three 5-mL portions of saturated aqueous $NaHCO_3$ and two 5-mL portions

of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue (0.12 g) was chromatographed over 5 g of silica gel (eluted with EtOAc–hexane, 1:20) to give 86 mg (87%) of lactone **54** as a pale yellow solid: mp 90–93 °C; IR ($CHCl_3$), 1750, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.72 (d, J = 7 Hz, 3 H, CH_3), 1.0 (m, 1 H), 1.08 (s, 3 H, CH_3), 1.3–1.8 (m, 8 H), 1.85 (s, 3 H, $=CCH_3$), 1.88 (m, 1 H), 2.19 (s with underlying m, 4 H, $=CCH_3$), 3.18 (br d, J = 10 Hz, 1 H, =CCH); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 15.9 (q), 19.4 (q), 19.7 (q), 21.1 (t), 24.0 (q), 30.6 (t), 32.3 (t), 35.0 (d), 35.2 (t), 38.0 (t), 42.2 (d), 45.4 (s), 96.1 (s), 128.9 (s), 147.5 (s), 170.7 (s); MS, m/e (rel intensity) 248 (M^+), 233 (40), 215 (15), 187 (15), 177 (35), 149 (50), 135 (15), 123 (20), 209 (100), 95 (30), 81 (30), 67 (25), 55 (40); exact mass calcd for $C_{16}H_{24}O_2$ 248.1802, found 248.1977.

(1*R,3a*R**,7a*S**)-Hexahydro-α-isopropylidene-3a-methyl-7-oxo-1-indanacetic Acid (55).** To a stirred solution of 1.46 g (4.77 mmol) of bicyclic ester **49** in 10 mL of dry methylene chloride was added in 5.47 g (40 mmol) of trifluoroacetic acid in one portion at rt. The reaction mixture was stirred at rt for 4 h and concentrated in vacuo. The residue was diluted with 30 mL of ether and extracted with three 10-mL portions of saturated aqueous $NaHCO_3$ solution. The combined aqueous layers were acidified at 0 °C using concentrated aqueous HCl. The aqueous layer was extracted with four 30-mL portions of ether. The combined ethereal extracts were washed with three 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual solid was recrystallized from hexane–ether (5:1) to give 0.94 g (78%) of acid **55**: mp 133–135 °C; IR ($CHCl_3$) 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.05 (s, 3 H, CH_3), 1.38–2.48 (m with two s's at δ 1.68 and 1.84 ($=CCH_3$), 16 H), 2.54 (d, J = 10.8 Hz, 1 H, CHC=O), 3.43 (m, 1 H, =CCH), 11.23 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 20.9 (q), 21.9 (t), 23.4 (q), 26.3 (q), 29.3 (t), 33.9 (t), 37.5 (t), 40.6 (t), 43.6 (d), 46.5 (s), 64.1 (d), 129.1 (s), 140.3 (s), 173.6 (s), 215.3 (s); MS, m/e (rel intensity) 250 (M^+), 232 (28), 217 (100), 204 (38), 189 (76), 161 (38), 111 (50); exact mass calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1609.

(1*R,3a*R**,7a*S**)-Hexahydro-α-isopropylidene-3a-methyl-7-methylene-1-indanacetic Acid (56).** A flask charged 2.71 g (7.6 mmol) of methyltriphenylphosphonium bromide, 0.84 g (7.5 mmol) of potassium *tert*-butoxide, and 15 mL of dry toluene was stirred at rt under Ar for 3 h. To this yellow mixture was added via cannula a solution of 0.93 g (3.74 mmol) of acid **55** and 90 mg (3.74 mmol) of oil-free sodium hydride in 3 mL of dry THF. The resulting mixture was stirred at rt for 1 h and 15 mL of 5% aqueous HCl was added. The mixture was diluted with 100 mL of ether. The ether layer was washed with two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with EtOAc–hexane, 1:5) to give 0.84 g (91%) of acid **56** as an oily liquid: IR (neat) 1680, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.98 (s, 3 H, CH_3), 1.18–2.15 (m, with two s's at δ 1.73 ($=CCH_3$) and 1.92 ($=CCH_3$), 16 H, CH_2 manifold), 2.40 (d, J = 10.5 Hz, 1 H, =CCH), 3.32 (ddd, J = 10.5, 10.0, 7.0 Hz, 1 H, =CCH), 4.63 (br s, 1 H, $=CH_2$), 4.69 (br s, 1 H, $=CH_2$), 11.81 (br s, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 21.2 (q), 23.4 (q), 23.8 (t), 25.0 (q), 27.8 (t), 30.7 (t), 33.3 (t), 40.5 (t), 42.2 (d), 43.4 (s), 58.8 (d), 110.9 (t), 130.6 (s), 139.5 (s), 147.1 (s), 176.0 (s); MS, m/e (rel intensity) 248 (M^+), 233 (100), 215 (40), 187 (35), 107 (80), 93 (80), 79 (70); exact mass calcd for $C_{16}H_{24}O_2$ 248.1775, found 248.1775.

1-[(1*R,3a*R**,7a*S**)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl Isocyanate (57).** To a stirred solution of 142 mg (0.57 mmol) of acid **56** in 2.0 mL of dry THF under Ar at rt was added 13.7 mg (0.57 mmol) of oil-free sodium hydride. The mixture was stirred for 10 min at rt and cooled to 0 °C, and a solution of 165 mg (0.60 mmol) of diphenyl phosphorazidate in 10 mL of dry THF was added in one portion at 0 °C. The mixture was stirred at 0 °C for 1 h and at rt for 10 h. The mixture was diluted with 40 mL of ether, washed with two 5-mL portions of 2% aqueous HCl and two 10-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue (263 mg) was chromatographed over 3 g of silica gel (eluted with ether–hexane, 1:20) to give 108 mg (77%) of isocyanate **57** as a colorless liquid: IR (neat) 2240, 900, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.01 (s, 3 H, CH_3), 1.28 (m, 1 H), 1.45–1.8 (m with two s's at 1.62 ($=CCH_3$) and 1.75 ($=CCH_3$), 13 H), 1.85–2.2 (m, 3 H), 3.38 (ddd, J = 10.7, 10.0, 6.5 Hz, 1 H, =CCH), 4.58 (br s, 1 H, $=CH_2$), 4.70 (br s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.1 (q), 20.7 (q), 23.6 (t), 24.9 (q), 26.3 (t), 30.7 (t), 33.1 (t), 40.5 (t), 43.5 (s), 43.5 (d), 58.6 (d), 110.8 (t), 121.9 (s), 124.8 (s), 126.0 (s), 146.4 (s); MS, m/e (rel intensity) 245 (M^+), 230 (60), 189 (30), 174 (30), 123 (100), 109 (50); exact mass calcd for $C_{16}H_{23}NO$ 245.1780, found 245.1771.

***N*-[1-[(1*R**,3a*R**,7a*S**)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl]formamide (4).** To a stirred solution of 0.54 g (2.21 mmol) of isocyanate **57** in 20 mL of dry THF at −78 °C under Ar was added 2.3 mL (2.3 mmol) of 1.0 M of lithium triethylborohydride in THF. The mixture was stirred at −78 °C for 1 h and 3 mL of saturated aqueous $NaHCO_3$ was added. The mixture was warmed to rt, diluted with 40 mL of ether, washed with three 5-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with EtOAc–hexane, 1:5) to yield 0.50 g (91%) of formamide **4**, which slowly solidified. This material was a 3:1 mixture of geometrical isomers by integration of selected peaks in the ^1H NMR spectrum of the mixture. The ^{13}C NMR of this mixture also showed one major isomer and one minor one: mp 95–105 °C; IR ($CHCl_3$) 3380, 1680, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.95 and 0.96 (two s, 3 H, CH_3 of major and minor isomer, respectively), 0.9–2.12 (m with two s's at δ 1.70 and 1.72 ($=CCH_3$), 17 H), 3.33–3.45 (m, 1 H, =CCH), 4.51 (br s, 0.75 H, $=CH_2$), 4.57 (br s, 0.25 H, $=CH_2$), 4.70 (br s, 1 H, $=CH_2$), 6.32 (br s, 0.25 H, NH), 6.77 (br d, J = 11 Hz, 0.75 H, NH), 7.84 (d, J = 11 Hz, 0.75 H, CHO), 8.22 (d, J = 1 Hz, 0.25 H, CHO); ^{13}C NMR ($CDCl_3$, 62.5 MHz, major isomer) δ 19.69 (q), 20.55 (q), 23.88 (t), 24.91 (q), 25.99 (t), 30.74 (t), 33.64 (t), 40.17 (t), 42.65 (d), 43.19 (s), 57.83 (d), 110.58 (t), 128.30 (s), 129.31 (s), 146.89 (s), 166.15 (d); ^{13}C NMR ($CDCl_3$, 62.5 MHz, minor isomer) δ 19.61 (q), 20.95 (q), 23.81 (t), 25.05 (q), 26.17 (t), 30.64 (t), 33.35 (t), 40.53 (t), 43.12 (d), 43.19 (s), 58.21 (d), 110.58 (t), 126.32 (s), 130.12 (s), 147.10 (s), 159.56 (d); MS, m/e (rel intensity) 247 (M^+), 232 (20), 204 (40), 187 (100), 159 (30), 109 (55); exact mass calcd for $C_{16}H_{25}NO$ 247.1936, found 247.1952.

1-[(1*R,3a*R**,7a*S**)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl Isocyanide (5).** To a solution of 344 mg (1.39 mmol) of formamide **4** in 5 mL of dry pyridine was added 535 mg (2.8 mmol) of *p*-toluenesulfonyl chloride at rt. The mixture was stirred at rt for 15 h and cooled to 0 °C, and 3 g of crushed ice was added. The mixture was stirred at 0 °C for 30 min, diluted with 50 mL of petroleum ether–ethyl ether, (1:1), and washed with three 10-mL portions of 3% aqueous HCl and two 10-mL portions of brine. Combined aqueous layers were extracted with three 15-mL portions of petroleum ether. Organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel (eluted with petroleum ether, bp 35–60 °C) to give 0.32 g (100%) of isocyanide **5** as a pale yellow solid: mp 61–63 °C; IR (neat) 2100, 1640, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.00 (s, 3 H, CH_3), 1.25–2.2 (m with two s's at δ 1.67 and 1.89 ($=CCH_3$), 17 H, CH_2 manifold), 3.20 (br ddd, J = 11.0, 10.0, 6.0 Hz, 1 H, =CCH), 4.62 (br s, 1 H, $=CH_2$), 4.69 (br s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.06 (q), 21.61 (q), 23.64 (t), 24.76 (q), 26.32 (t), 30.69 (t), 33.48 (t), 40.28 (t), 41.69 (d), 43.19 (s), 58.21 (d), 111.05 (t), 124.35 (s), 134.28 (s), 145.99 (s), 161.99 (s); MS, m/e (rel intensity) 229 (M^+), 214 (100), 186 (45), 134 (30), 107 (65), 93 (85), 79 (65); exact mass calcd for $C_{16}H_{23}N$ 229.1842, found 229.1841.

1-[(1*R,3a*R**,7a*S**)-Hexahydro-3a-methyl-7-methylene-1-indanyl]-2-methylpropenyl Isothiocyanate (6).** A mixture of 204 mg (0.89 mmol) of isocyanide **5** and 45 mg (1.4 mmol) of sulfur powder was heated at 120 °C under Ar for 10 h. The mixture was cooled to rt, diluted with 30 mL of petroleum ether, stirred for 10 min, washed with two 5-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residue (0.24 g) was chromatographed over 10 g of silica gel (eluted with petroleum ether, bp 35–60 °C) to give 166 mg (71%) of isothiocyanate **6** as a yellow oil: IR (neat) 2080, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.01 (s, 3 H, CH_3), 1.24–2.2 (m with two s's at δ 1.65 and 1.82 ($=CCH_3$), 16 H), 3.32 (ddd, J = 11.0, 10.0, 6.0 Hz, 1 H, =CCH), 4.61 (br s, 1 H, $=CH_2$), 4.70 (br s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 19.2 (q), 21.2 (q), 23.6 (t), 24.9 (q), 26.4 (t), 30.6 (t), 33.0 (t), 40.3 (t), 43.3 (d), 43.4 (s), 58.5 (d), 111.0 (t), 126.2 (s), 130.8 (s), 131.6 (s), 146.0 (s); MS, m/e (rel intensity) 261 (M^+), 246 (15), 228 (15), 203 (100), 139 (40), 109 (30), 93 (30), 79 (30),

69 (40); exact mass calcd for $C_{16}H_{23}NS$ 261.1581, found 261.1578.

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Registry No. 1, 56012-88-5; 2, 53822-96-1; 3, 53822-97-2; (±)-4, 127516-52-3; (±)-5, 127516-53-4; (±)-6, 127516-54-5; (±)-7, 139017-42-8; (±)-8, 139068-72-7; 9, 586-38-9; (±)-11, 114860-79-6; (±)-13, 139068-67-0; (±)-14, 139068-68-1; (±)-15, 139068-69-2; (±)-16, 139017-43-9; (±)-17, 139068-70-5; (±)-18, 139017-44-0; (±)-19, 139017-45-1; (±)-20 (isomer 1), 139017-46-2; (±)-20 (isomer 2), 139068-71-6; (±)-21, 139017-47-3; (±)-23, 139017-48-4; (±)-25, 139017-49-5; (±)-26, 139017-50-8; (±)-27, 139017-51-9; (±)-(*E*)-28, 139017-52-0; (±)-(*Z*)-28, 139017-65-5; 29, 5323-87-5; 30, 22627-45-8; (±)-31, 121363-31-3; (±)-32, 139017-53-1; (±)-33, 139017-54-2; (±)-34, 139017-55-3; (±)-35, 139017-56-4; (±)-36, 139017-57-5; (±)-37, 139017-58-6; (±)-39, 139017-59-7; (±)-40, 139017-60-0; (±)-(*E*)-41, 139017-61-1; (±)-(*Z*)-41, 139017-62-2; (±)-42, 127488-38-4; (±)-43, 127488-39-5; (±)-44, 127488-40-8; (±)-45, 127488-41-9; (±)-46, 127488-50-0; (±)-47, 127488-36-2; (±)-48, 127488-49-7; (±)-49, 127488-37-3; (±)-50, 127488-42-0; (±)-51, 127488-43-1; (±)-52a, 139040-97-4; (±)-52b, 139017-63-3; (±)-52c, 139017-64-4; (±)-52d, 106536-89-4; (±)-53, 127488-44-2; (±)-54, 127488-45-3; (±)-55, 127488-46-4; (±)-56, 127488-47-5; (±)-57, 127488-48-6; $(CH_3)_3SiCH_2CO_2Bu$-*t*, 41108-81-0.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for selected compounds, crystallographic data for compound 36, and experimental procedures for reactions presented in Schemes II and III (70 pages). Ordering information is given on any current masthead page.

A New Synthesis of Phthalides by Internal Trapping in Ortho-Lithiated Carbamates Derived from Benzylic Alcohols†

M. Rita Paleo, Carlos Lamas, Luis Castedo,* and Domingo Domínguez

Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago y Sección de Alcaloides del CSIC, 15706 Santiago de Compostela, Spain

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The addition of *t*-BuLi to a low-temperature THF solution of *o*-bromocarbamates **2** leads to *ortho*-lithiated intermediates **3**, in which internal trapping by the electrophile on the side chain then takes place. This novel Parham-type anionic cyclization procedure affords the variously substituted phthalides **5** in high yields and can also be used for the preparation of lactones **8**, which are useful for the synthesis of aristocularine alkaloids.

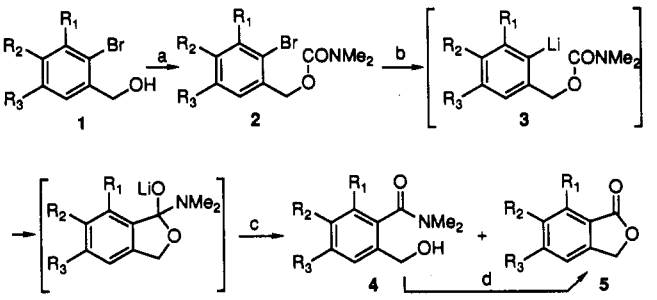
Introduction

Phthalides are versatile starting materials for the synthesis of a variety of structures. Carbanions derived from proton abstraction at the benzylic position have received considerable attention during the last decade as useful 1,4-dipole synthetic equivalents[1] for the preparation of linear and angular polycyclic aromatic systems[2] and some pharmacologically interesting isoquinoline alkaloids.[3] On the other hand, the electrophilic nature of the carbonyl of 3-halogenophthalides has been exploited by us for the assembly of isoindoloisoquinolines and benzo[*b*]-phenanthridines.[4] Phthalides are also appropriate precursors for isobenzofurans, which are highly reactive species, in synthetically useful cycloaddition reactions.[5]

Classical methods for the preparation of phthalides depend on the chloromethylation of benzoic acids, but they usually give low yields and are not suitable for the regioselective preparation of substituted phthalides.[6] More recent syntheses are based on transition-metal-catalyzed carbonylation of ortho-substituted benzyl alcohols,[7] cyanation of *o*-halogenobenzyl alcohols,[8] or metalation–carboxylation of *m*-alkoxybenzyl derivatives. The latter strategy is based on the ortho-directing effect of alkoxy substituents[9] and is thus only suitable for the synthesis of 7-alkoxyphthalides, which are obtained in moderate yields.[10] Other routes based on ortho-lithiated aromatic derivatives of benzamides,[11] oxazolines,[12] or benzaldehydes[13] have also been reported.[14]

In this paper, we describe a new method by which a variety of phthalides can be obtained by lithium–halogen interchange followed by internal trapping from carbamates derived from *o*-bromobenzylic alcohols.

Scheme I[a]



[a] Reagents and conditions: (a) DMF, NaH, *N*,*N*-dimethylcarbamoyl chloride; (b) THF, *t*-BuLi, −95 °C; (c) MeOH, −95 °C to rt; (d) MeOH, rt or TFA, rt.

† Dedicated to Prof. M. P. Cava on the occasion of his 65th birthday.

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