A Stereoselective Total Synthesis of (±)-Alliacol A and Congeners of *Marasmius Alliaceus*

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Synthesis of alliacolide(**1**), alliacol A (**2**), and 12-noralliacolide (**4**), members of the alliacane family of sesquiterpene lactones, was accomplished through both *syn*- and *anti*-modes of intramolecular S_N' displacement. Two routes to 12-noralliacolide (**4**) are presented, which contrast brevity and efficiency in stereoselection (i.e. **14** → **16/17** *versus* **37a/b** → **38**). Since both routes culminate in C-ring annulation, introduction of the correct stereochemical arrangement relied heavily on the structural features of the hydrindane (AB) precursor(s). Choice of the proper AB system **24** facilitated production of tetrahydrofuran **38**. With the full skeleton in place, **38** was efficiently epoxidized and oxidized to **4**. 12-Noralliacolide (**4**) served as an appropriate relay substrate for conversion to alliacol A (**2**) and several other alliacanes.

Background and Problem

In 1977, Hanson and Thaller[1] isolated a novel sesquiterpene, alliacolide (**1**), from cultures of the basidiomycete *Marasmius alliaceus*.[2] Full spectroscopic analysis, as well as X-ray crystallography, revealed a compact arrangement of an epoxide and a unique tertiary β-hydroxy γ-lactone. Biogenetically, these fungal sesquiterpenoids likely arise from farnesyl pyrophosphate. Hanson and co-workers used enrichment patterns, generated upon addition of labeled acetates and mevalonates to the culture broth, to show that the biosynthesis resulted in an abnormal arrangement of isoprene units.[3] On the basis of this evidence and the need for a link to farnesyl pyrophosphate, they proposed that this pattern originated through ring contraction; conducted through formation and opening of an appropriately situated cyclopropane.[4] The precursor to this rearrangement suggests a direct link to cadinane biosynthesis.

An exhaustive study of the crude extracts provided several other metabolites (Figure 1), including the biologically-active constituents alliacol A (**2**) and B (**3**).[1b-d] These substrates demonstrated effective inhibition of DNA synthesis in ascitic Ehrlich carcinoma at concentrations of 10 and 20 μg/mL, respectively.[5] This activity likely results from nucleophilic addition (i.e., cysteine, often present in enzymes) to the electrophilic α,β-unsaturated lactone.[6] This hypothesis was supported by the fact that preincubative treatment of both **2** and **3** with cysteine drastically reduced their cytotoxic activity.[5]

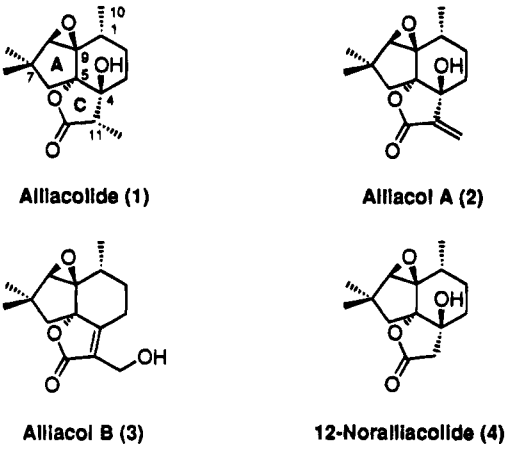

Figure 1. Several sesquiterpene metabolites isolated from cultures of *Marasmius Alliaceus*.

Furthermore, the potency of these metabolites is enhanced due to the presence of polar groups (i.e. OH, present in **2** and **3**) proximal to the Michael acceptor, as described by Kupchan.[6c] The biological activity, as well as the unique structure and biosynthesis, attracted our attention to the synthesis of alliacol A (**2**).

In 1985, Raphael communicated an approach to alliacol B (**3**) implementing acidification of an appropriate ε-hy-

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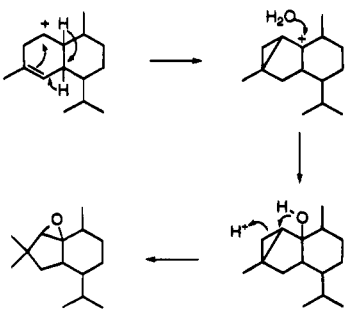
(1) (a) Farrell, I. W.; Halsall, T. G.; Thaller, V.; Bradshaw, A. P. W.; Hanson, J. R.; Sadler, I. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1790. (b) King, T. J.; Farrell, I. W.; Halsall, T. G.; Thaller, V. *J. Chem. Soc., Chem. Commun.* **1977**, 727. (c) Avent, A. G.; Hanson, J. R.; Hitchcock, P. B.; Yeoh, B. L. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2749.

(2) *Marasmius Alliaceus* is a tall, thin mushroom native to European beechwood forest. Its name originates from its strong garlicky odor.

(3) (a) Bradshaw, A. P. W.; Hanson, J. R.; Sadler, I. H. *J. Chem. Soc., Chem. Commun.* **1981**, 631. (b) Bradshaw, A. P. W.; Hanson, J. R.; Sadler, I. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2787. (c) Hanson, J. R. *Pure Appl. Chem.* **1981**, *53*, 1155. (d) Bradshaw, A. P. W.; Hanson, J. R.; Sadler, I. H. *J. Chem. Soc., Chem. Commun.* **1982**, 292. (e) Avent, A. G.; Hanson, J. R.; Yeoh, B. L. *J. Chem. Res. (S)* **1986**, 422.

(4) The late stages of Hanson's biosynthesis develops the hydrindane ring-system by way of a ring-contraction. Formally, they proposed that this proceeded through formation and acid-catalyzed opening of an appropriately situated cyclopropane. Upon opening, the subsequent cation could be intercepted by an adjacent hydroxyl group, providing the C(8)–C(9) epoxide.



(5) Anke, T.; Watson, W. H.; Giannetti, B. M.; Steglich, W. *J. Antibiot.* **1981**, *34*, 1271.

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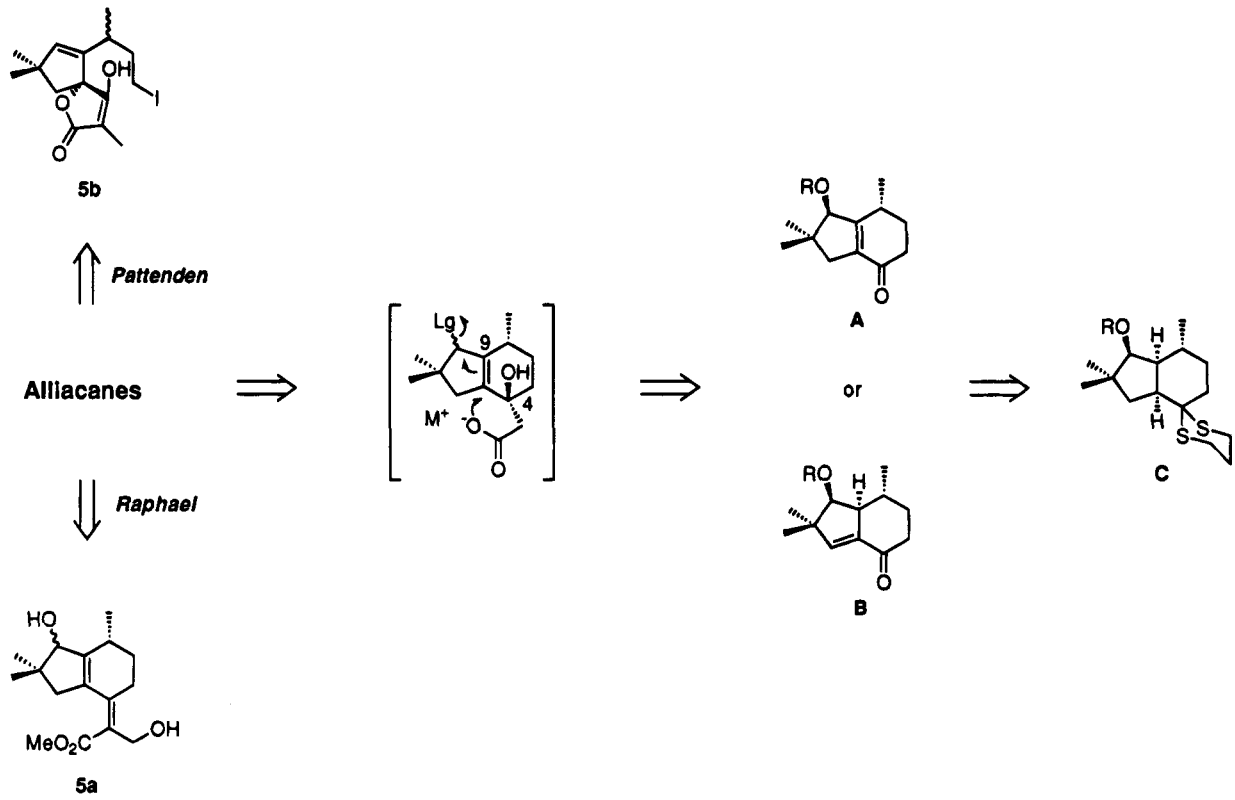
Scheme 1



droxy-unsaturated dienoic ester **5a** (Scheme 1).[7] The lack of a stereochemical bias upon cyclization resulted in the production of both C(5)-diastereomers. Additional complications, such as the inability to introduce the C(8)–C(9)-epoxide *via* peracid epoxidation, prevented their conversion of **5a** to alliacol B (**3**). Soon thereafter, Pattenden completed the synthesis of alliacolide (**1**) through a novel 6-*exo*-trig radical cyclization onto an enol ether (i.e., on **5b**).[8] Although practical, an undesirable epimerization at C(1) during their construction of **5b** forced cyclization on a mixture of diastereomeric iodides. This resulted in the production an unfavorable mixture (1:2) of alliacolide (**1**) and its C(1)-diastereomer (epi-**1**). In our first route,[9] as discussed herein, annulation of the lactonic C-ring provided a 1:1 ratio of alliacol A (**2**) and C(1)-*epi*-alliacol A (epi-**2**).[9] Thus, a strategy for totally eliminating epimeric alliacane intermediates/products remained to be developed.

Synthetic Strategy[10]

Our primary target was 12-noralliacolide (**4**), a minor constituent in the culture broth. We envisioned that **4** could be converted to **2** (and then **1**) through methylenation of the dianion generated from the β-hydroxy γ-lactone.[11] The vulnerability of β-hydroxy carbonyl compounds to acid-catalyzed dehydration and base-induced retro-Claisen made it desirable to postpone C-ring construction to the latest possible stage.

The strategic position of the tertiary hydroxyl group allowed simplification of **4** to its corresponding C(8)–C(9)-alkene (i.e., peracid epoxidation), which in turn could be viewed as arising from an intramolecular S_N' displacement by a carboxylic side chain (Scheme 1). This side chain could be introduced through condensation of a carboxylic enolate with a suitable hydrindenone (**A** or **B**). Proper choice of the hydrindenone template could be used to influence diastereoselection. The first of the two templates (**A**) contained an allylic electrophilic site so as to permit a one-pot lactonization. The latter (**B**) required additional steps to develop the allylic departing group. Both of these templates could be derived from the same intermediate **C**, which in turn arose from manipulating the adduct between dithiane **6** and 2-cyclopenten-1-one.

Construction of the A–B Ring System

Using methodology developed by Heathcock,[12] monolithiated dithiane **6** underwent conjugate addition to 2-cyclopenten-1-one in an HMPA/THF medium (Scheme 2). Treatment of the adduct **7** with dilute acid smoothly induced aldol condensation generating hydrindenone **8**. The C(1)-methyl group was attached by conjugate addition of lithium dimethylcuprate. Although the addition occurred exclusively from the α-face, protonation of the intermediate enolate produced an 87:12 mixture of chromatographically separable *cis*-**9** and *trans*-**9**. The unwanted *trans*-**9** could be converted to an identical

(6) (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Spring, O.; Kupka, J.; Maier, B; Hager, A. *Z. Naturforsch.* **1982**, *C37*, 1087. (c) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147.

(7) Raphael, R. A.; Telfer, S. J. *Tetrahedron Lett.* **1985**, *26*, 489.

(8) (a) Ladlow, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1107. (b) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413.

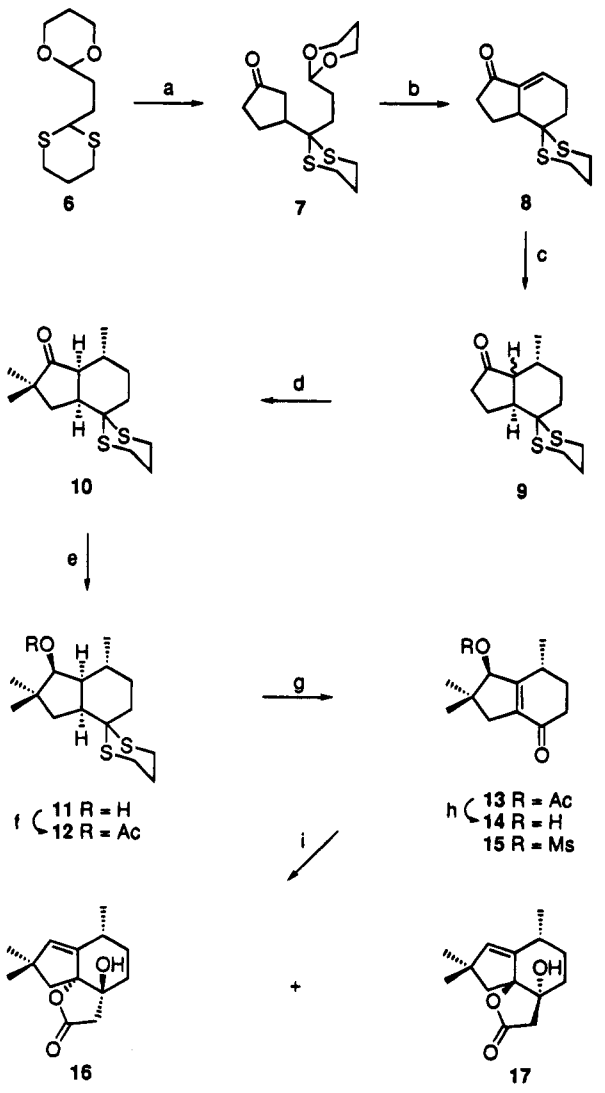
(9) Lansbury, P. T.; Zhi, B. *Tetrahedron Lett.* **1988**, *29*, 5735.

(10) For additional approaches and detailed investigations see: (a) La Clair, J. J., Ph. D. Thesis, The State University of New York at Buffalo, Buffalo, NY, 1993. (b) Zhi, B., Ph. D. Thesis, The State University of New York at Buffalo, Buffalo, NY, 1988.

(11) (a) Chamberlin, A. R.; Dezube, M. *Tetrahedron Lett.* **1982**, *23*, 3055. (b) Shieh, H.-M.; Prestwich, G. D. *J. Org. Chem.* **1981**, *46*, 4319.

(12) For the synthesis and use of 2-(1,3-dioxan-2-yl)-1-(1,3-dithia-2-yl)ethane see: Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190.

Scheme 2[a]



[a] (a) (i) *n*-BuLi, HMPA, THF; (ii) 2-cyclopenten-1-one, −78 °C, 18 h; 82%. (b) 10% HCl, THF, Δ; 97%. (c) (i) $LiCuMe_2$, THF, 0 °C; (ii) isomerize *trans*-**10** to *cis*-**10** via: *p*-TsOH, Ph, Δ; 96%. (d) (i) LDA, THF; (ii) MeI, −78 °C, 2 h; (iii) −20 °C, 18 h; (iv) LDA, HMPA, THF, −78 °C; (v) MeI, −78 °C to rt; 96%. (e) L-Selectride, THF, 0 °C to rt, 99%. (f) Ac_2O, cat. DMAP, pyridine, 95%. (g) CAN (4 equiv), 25% aq MeCN, 5 min, 25−45%. (h) K_2CO_3, 10% aq MeOH, rt, 18 h, 97%. (i) (i) MsCl (1.5 equiv), Et_3N (3.0 equiv), THF, 0 °C; (ii) DILA (5 equiv), HMPA (5 equiv), THF, 0 °C to rt, 12 h; 47% of a 1:1 mixture.

mixture (87:12 ratio of cis:trans) when warmed with a catalytic amount of *p*-toluenesulfonic acid in benzene solution. A few cycles increased the yield of the cis-isomer to 96%.

The *gem*-methyl groups were introduced in one step through repetitive deprotonation (LDA) and alkylation (MeI) of *cis*-**9**.[13] Careful control of temperature and amounts of amide base prevented generation of unwanted regioisomers. Ketone **10** was reduced with L-Selectride to provide the β-alcohol **11**, whose relative configuration was confirmed by X-ray crystallographic examination of the derived acetate **12**. This rapid entry provided the hydrindane framework along with selectively-protected functionalities for introduction of the lactone in an overall yield of 70%.

Investigation of Tandem γ-Lactone Annulation

In order to set the stage for implementation of a tandem cyclization, dethioketalization of **11** (moving toward template **A**) became an immediate goal. Initial screening of an array of standard hydrolytic methods[14] did not produce a significant amount of ketone **18**. Initial failure of electrophilic activation turned our attention to oxidative processes. In order to accomplish this, the secondary hydroxyl group was protected as its acetate **12** (Ac_2O, cat. DMAP, pyridine). Subsequent oxidation with ceric ammonium nitrate (CAN) in wet acetonitrile produced a variable yield (40−45%) of conjugated ketone **13** ($\nu_{C=O}$ 1660 cm^{-1}).[15] Presumably, the remainder of the material from **12** derived from functionalization on the other side of the incipient carbonyl. The unexpected formation of an α,β-unsaturated ketone was unprecedented and not extendible to other less hindered substrates (e.g., β-decalones). Nevertheless, this fortuitous discovery did circumvent the need for multistep incorporation of unsaturation and directly provided a precursor to template **A**.

Acetate **13** was readily hydrolyzed under standard conditions (K_2CO_3, wet MeOH), producing allylic alcohol **14**. Mesylation of **14** using sulfene conditions[16] provided an interesting bis-electrophile **15**. The enhanced reactivity of the carbonyl group (as compared to the allylic mesylate) made it reasonable to expect that an ester enolate(s) would undergo initial Claisen condensation. The original strategy was devised to utilize both nucleophilic sites of dilithium acetate (DILA) in the above predicted sequence.[17,18] The addition of a preformed solution of DILA in HMPA/THF to a freshly-prepared solution of **15** provided an inseparable 1:1 mixture of both diastereomeric γ-lactones **16** and **17** (in a combined yield of 47%). Although S_N' reactions are reported to be more favorable when the nucleophilic and electrophilic partners are *syn*-orientated,[19] Corey and others have reported examples with *anti*-reactivity.[20] In the present situation, both *syn*- and *anti*-modes of displacement were observed. This arose from a lack of stereochemical control during the enolate-addition to **15**. *The fact that **15** gave both **16** and **17** was nevertheless informative, in that the leaving group orientation would not be crucial to the displacement once the carboxylate side chain was correctly in place.* Although, the mixture (**16** + **17**) could be

(13) *cis*-**9** was efficiently resolved by C. R. Johnson's *N,S*-dimethylphenylsulfoximine method: (a) Johnson, C. R. *Aldrichim. Acta* **1985**, *18*, 3. (b) Johnson, C. R.; Zeller, J. R. *Tetrahedron* **1984**, *40*, 1225. However, for the purposes of our studies, the remainder of the synthesis was conducted on racemic material.

(14) (a) Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. (b) Block, E. *Organic Chemistry Series of Monographs: Reactions of Organosulfur Compounds, Vol. 37*; Academic Press: New York, 1978. For additional examples of hydrolytically-stable dithianes see: (c) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287. (d) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

(15) Lansbury, P. T.; Zhi, B.-Z. *Tetrahedron Lett.* **1988**, *29*, 179.

(16) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195, is most often credited with this discovery; the first application of sulfene was actually conducted by Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1962**, *84*, 313.

(17) (a) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521. (b) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509.

(18) The expectation was that the carbon site ($pK_a \approx 24$) would undergo irreversible addition while the carboxylate ($pK_a \approx 5$) would undergo rapid reversion. In actuality the initially-produced carboxylate serves to enhance the nucleophilicity of the dianion, see: (a) Creger, P. L. *J. Am. Chem. Soc.* **1967**, *89*, 2500. (b) Gronert, S.; Streitwieser, A. *J. Am. Chem. Soc.* **1988**, *110*, 4418.

(19) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.

(20) (a) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201. (b) Bordwell, F. G.; Clemens, A. H.; Cheng, J.-P. *J. Am. Chem. Soc.* **1987**, *109*, 1773.

converted to **2** (at which time the undesired diastereomer was chromatographically removed) and subsequently **1**, there still remained the problem of stereocontrol.

Stereoselectivity Arose through a Two-Staged Lactonization[21]

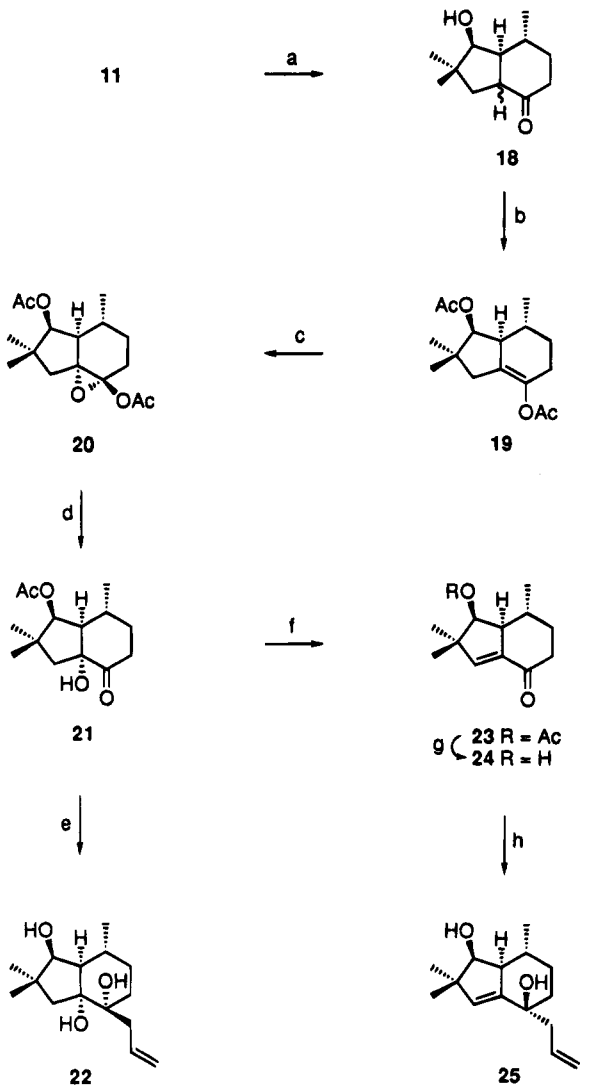
Compared to the flat template **A** (i.e. **15**), the isomeric hydrindenone **B** (see Scheme 1) is less planar and seemed to offer better prospects for α-face addition of an ester enolate (to C(4)). Shifting attention to templates such as **B** required a reexamination of the protocols for dithiane hydrolysis. The use of a highly reactive methylating agent, trimethyloxonium tetrafluoroborate, provided a 5:1 mixture of γ-hydroxy ketones **18** (stereochemistry undetermined) in 85% yield.[22] This ketonic mixture **18** was converted to a single enol acetate **19** under acid catalysis (Scheme 3).[23] The bent shape of **19** permitted exclusive attack of m-CPBA to the α-face of the double bond, which boded well for later carbonyl additions. Mild base hydrolysis of epoxy acetate **20** provided α-hydroxy ketone **21**.

Our original intention was to use the hydroxyl group in **21** to direct an ester enolate into the α-face of the carbonyl, either in an inter-[24] or intramolecular sense.[25] Unfortunately, nucleophilic additions (including a wide variety of allyl organometallics and enolates) to **21** produced exclusively the undesired C(4)-stereoisomer. For instance, addition of allylmagnesium chloride to **21** provided triol **22**, as determined by X-ray crystallography. Additionally, this crystal structure corroborated the stereochemical outcome of the C(5)-oxidation sequence (i.e. **19** → **21**). Since protection or inversion of the tertiary alcohol in **21** was not feasible,[26] dehydration provided a rational alternative. The presence of only one hydrogen *anti*-parallel to the C(5)-hydroxyl group dictated regiospecific elimination to **23**.

In contrast to the α-hydroxy ketone **21**, allylmagnesium chloride attacked the C(4)-carbonyl of **23** exclusively in the opposite direction, providing diol **25**.[27] Stork and others have shown that carbon-based nucleophiles attack the carbonyl of α,β-unsaturated ketones with unusually high degrees of axial-selectivity; often with increased selection over their saturated counterpart.[28] More recently, Korreda found that exocyclic cycloalkenones (i.e. **23** or **24**) undergo even more pronounced axial attack.[28b,c]

With the establishment of a method to incorporate the desired stereochemical arrangement. Our attention turned to the more concise introduction of an ester

Scheme 3[a]



[a] (a) (i) $Me_3O^+BF_4^-$, CH_2Cl_2, 1.2 h; (ii) $NaHCO_3$, H_2O; 87%. (b) Ac_2O, cat. $HClO_4$, CCl_4, Ph, 96%. (c) m-CPBA, $NaHCO_3$, CH_2Cl_2 −60 °C to rt. (d) 0.05 M aq KOH, MeOH, CH_2CH_2, 95% (two steps). (e) CH_2=$CHCH_2MgCl$ (5 equiv), THF, −78 °C, 85%. (f) *p*-TsOH, MsCl (1.25 equiv), Ph, 96%. (g) K_2CO_3, 10% aq MeOH, 99%. (h) CH_2=$CHCH_2MgCl$ (5 equiv), THF, −78 °C, 95%.

(21) Lansbury, P. T.; La Clair, J. J. *Tetrahedron Lett.* **1993**, *34*, 4431.

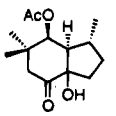
(22) For use of triethyloxonium tetrafluoroborate see: (a) Oishi, T.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1972**, 1085. (b) Stahl, I.; Hetschko, M.; Gosselck, J. *Tetrahedron Lett.* **1971**, 4077.

(23) Fenselau, C. In *Steroid Reactions. An Outline of Organic Chemists*; Djerassi, C., Ed.; Holden-Day, Inc.: San Francisco, 1963, pp 537–592.

(24) For instance, an α-alkoxy ketone could be used to chelatively direct carbonyl-addition, as demonstrated by: (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, 1031. (b) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, 1035. (c) Eliel, E. L.; Frye, S. V.; Hortelano, E. R.; Chen, X.; Bai, X. *Pure Appl. Chem.* **1991**, *63*, 1591. However, all attempts to prepare the substrate were thwarted by α-ketol rearrangement.

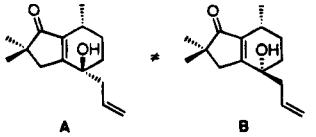
(25) This was envisioned through application of an intramolecular α-acetoxy ketone lactonization, as demonstrated by: (a) Bull, J. R.; Tuinman, A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 212. Although the substrate could be prepared, no lactonization was observed.

(26) Hydroxy ketone **21** readily underwent α-ketol rearrangement to provide an unwanted 6-5 ring system (**A**) under acidic or basic conditions; see: (a) Turner, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 3484. (b) Hardy, D. G.; Rigby, W.; Moody, D. P. *J. Chem. Soc.* **1957**, 2955. (c) Wendler, N. L.; Taub, D.; Walker, R. W. *Tetrahedron* **1960**, *11*, 163. (d) Kirk, D. N.; McHugh, C. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 893.



A

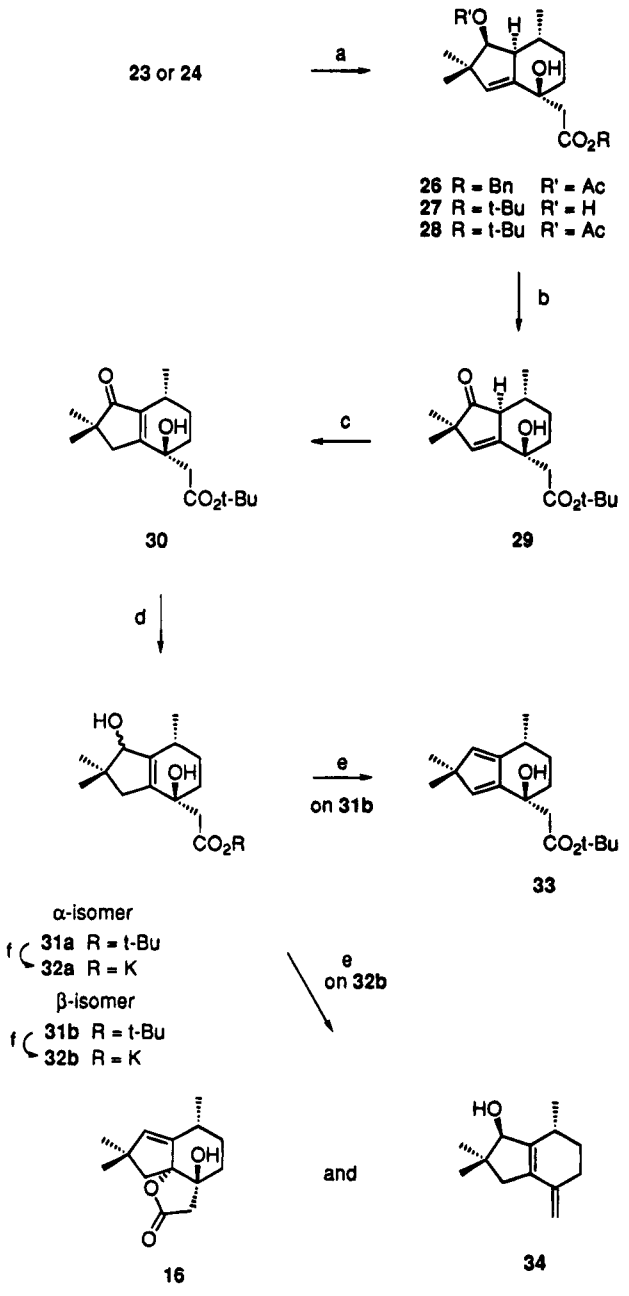
(27) The structure of this carbonyl addition adduct **25** was proven by oxidation (Swern) and double bond isomerization (methanolic KOH) to an enone **A**, which was diastereomeric with the enone **B** generated by oxidation (Swern) and elimination (sodium methoxide in methanol) of triol **22**.



A B

(28) (a) Stork, G.; Stryker, J. M. *Tetrahedron Lett.* **1983**, *24*, 4887. (b) You, Z.; Koreeda, M. *Tetrahedron Lett.* **1993**, *34*, 2745. (c) Koreeda, M.; You, Z. *J. Org. Chem.* **1989**, *54*, 5195. (d) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560. (e) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

Scheme 4[a]



[a] (a) CH_3CO_2R (R = Bn and t-Bu), LDA, (HMPA if R = t-Bu), THF, −78 °C, 1 h, 95%. (b) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C to 0 °C, 87%. (c) NaOMe, MeOH, THF, 0 °C, 30 min, 98%. (d) DIBAL-H, toluene, −78 °C, 98% (~1:1 mixture α:β). (e) MsCl (1.5 equiv), Et_3N (3 equiv), THF, rt, 12 h. (f) K_2CO_3, 10% aq MeOH, ~5 days.

enolate. Thus, the addition of benzyl acetate to **23** provided a crystalline adduct **26** whose structure was confirmed by X-ray crystallographic analysis. In order to avoid unwanted acetylation of the C(8)-hydroxyl group (as in **23** → **26**), a more hindered ester enolate (*tert*-butyl acetate) was condensed with **24**, providing **27** (Scheme 4).[29]

At this stage, double-bond isomerization was required in order to prepare the allylic leaving group (Scheme 1). This was accomplished by Swern oxidation of **27** to the deconjugated cyclopentenone **29**, which in turn was isomerized with sodium methoxide to **30**. Reduction with DIBAL-H produced a 1:1 mixture of chromatographically-separable allylic alcohols **31a/b**. Other reducing agents did not improve the ratio of diastereomers, but rather increased reduction at unwanted sites (i.e. carboxylic ester and the conjugate position of the unsaturated ketone). The stereochemical assignment was established by the comparison of nOe's. Irradiation of downfield hydrogen at C(8) enhanced the C(1)-hydrogen in **31a** and the C(10)-methyl group in **31b**. Substrates **31a/b** were both candidates for S_N' annulation.[9] Selective activation of the secondary allylic-hydroxyl group (as required for nucleophilic attack by the carboxylic ester side chain) posed the last hurdle.

Our initial efforts focused on elaboration of the β-isomer **31b** due to its increased polarity and, hence, decreased steric congestion about its C(8)-hydroxyl group. Bartlett's iodocarbonation,[30] inspired the treatment of **31** with sulfene[16] in hope of providing **16** *via tert*-butoxycarbonyl participation. Mesylation of **31b** instead generated diene **33**, the result of 1,4-elimination.[31] The apparent ease of elimination suggested the need for a more nucleophilic side chain, initially as the carboxylate. Furthermore, earlier work in our laboratories demonstrated that carboxylic acid salts do not undergo sulfonation under sulfene conditions, due to the lack of a proton source.[32] Thus, ester **31b** was saponified. Unfortunately, competitive retro-Claisen (providing **14**) forced the use of slow, mild methods (i.e. treatment with potassium carbonate in aqueous methanol over 5 days).[33] Mesylation of carboxylate salt **32b** did provide a modest yield of **16**, without any indication of **17**. However, an additional byproduct, **34**, was formed, apparently as a result of mesylation of the tertiary alcohol followed by decarboxylative elimination.[34] Compound **34** matched in all respects (^{1}H-NMR, ^{13}C-NMR, TLC, and IR) with an authentic sample prepared by methylenation of enone **14**.

In order to maximize the yield of **16**, we needed to remove any possibility of the above decarboxylative-elimination of **32** (to **34**). An apparent alternative was reduction of the *unhydrolyzed* esters **31a/b** to their corresponding primary alcohols (Scheme 5). This side chain (in **35a/b**) was not vulnerable to decarboxylation, and it possessed the required nucleophilic characteristics for cyclization. Accommodation of the allylic displacement sequence required selective activation of the C(8)-secondary hydroxyl group. Our first choice was a chloroacetate, due to its ease in manipulation and enhanced ability to depart during displacement (as compared to acetate or ethers).[35] It was anticipated that the primary

(29) The addition to enone **24** with most ester enolates underwent competitive transacetylation of the C(8)-hydroxyl group, prompting additional efforts to attain an enone of the type **30**.

(30) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013.

(31) The addition of an equivalent stoichiometry of methanesulfonyl chloride and triethylamine allowed isolation of a crude mesylate (of **31b**), which eliminated chromatographic purification. A similar outcome was achieved in the analogous methyl ester series, resulting from addition of methyl acetate to **24**.

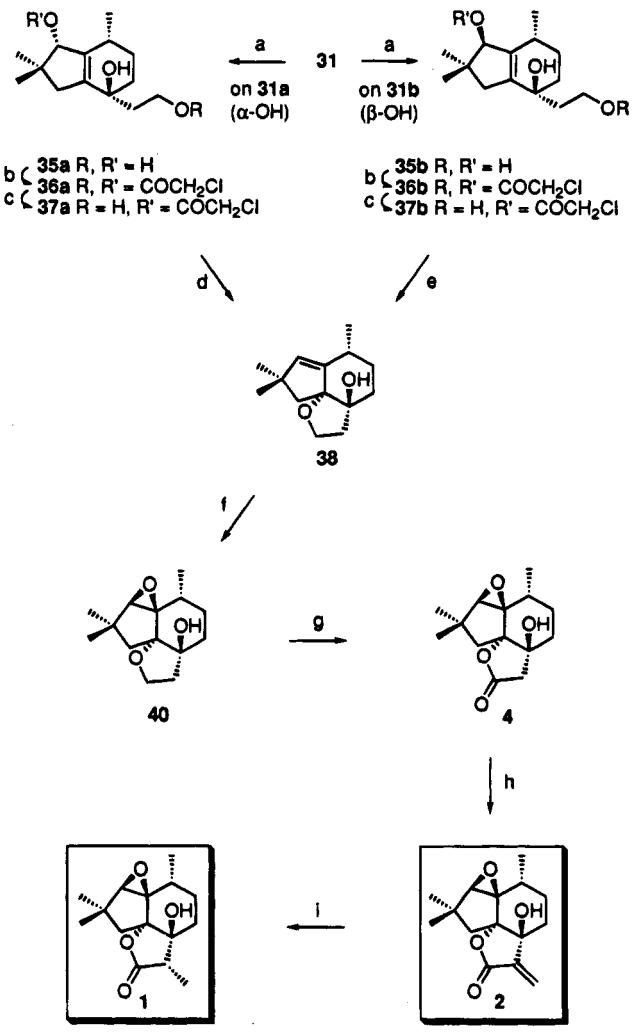
(32) Sulfene reacts reversibly with a carboxylate salt, see: Lansbury, P. T.; Vacca J. P. *Tetrahedron* **1982**, *38*, 2797.

(33) Application of Gassman's anhydrous hydrolysis of *tert*-butyl esters provided largely retro-Claisen product **14**; see: Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

(34) The enhanced ability of the carboxylate to eliminate the C(4)-hydroxyl group can be explained by an intramolecular mesylation through initial formation of a mixed carboxylate−sulfonyl anhydride (via intramolecular protonation of carboxylate's sulfene adduct by the tertiary hydroxyl group). Once mesylated, the β-mesyloxy carboxylate could undergo either β-lactone formation and subsequent decarboxylation or direct eliminative decarboxylation.

(35) The increased acidity of chloroacetic acid versus acetic acid supports an increase in leaving potential.

Scheme 5[a]



[a] (a) $LiAlH_4$, Et_2O, 0 °C to rt, 3.5 h, 92% (α-OH), 97% (β-OH). (b) $(ClCH_2CO)_2$ (2.05 equiv), pyridine, cat. DMAP, −78 °C to rt, 30 min, 97% (α-OH), 98% (β-OH). (c) 0.05 M KOH, THF, 0 °C, 15 min, 97% (α-OH), 88% (β-OH). (d) $MgSO_4$, $(i\text{-}Pr)_2NEt$, toluene, 110 °C, 24 h, 85%. (e) (i) LDA, HMPA, THF, −78 °C; (ii) rt, 42 h; 89%. (f) m-CPBA, $NaHCO_3$, CH_2Cl_2, −78 °C to rt, 3.5 h, 98%. (g) $RuCl_3{\cdot}nH_2O$ (0.35 equiv), $NaIO_4$, MeCN, CCl_4, H_2O (2:2:3), rt, 4 days, 98%. (h) (i) LiTMP, HMPA, THF; (ii) Eschenmoser's Salt, -20 °C to rt, 12 h; (iii) treat extracted basic material with MeI; 88%. (i) H_2 (30 psi), Pd-on-C, MeOH, 2 h, 90%.

side chain hydroxyl group would react preferentially, and the latter would also hydrolyze more rapidly. Bischloroacetylation of either triol **35a/b** was accomplished with chloroacetic anhydride (2 equiv), pyridine, and DMAP (catalytic) in methylene chloride. Titration[36] of dilute aqueous potassium hydroxide (approximately 1 equiv) to **36a/b** selectively hydrolyzed the primary chloroacetate, indirectly generating **37a/b**.

Thermal cyclization of **37a**, the *syn*-S_N' precursor, was accomplished by refluxing in toluene containing anhydrous $MgSO_4$ and diisopropylethylamine. These conditions provided a reproducible 85% yield of **38**[37] along with 13% of triene **39**.[38] More forcing conditions were necessary to cyclize **37b** *via* the *anti*-S_N' pathway.[39] Thus, anionic cyclization of the monolithium alkoxide of **37b** in HMPA/THF provided an 89% yield of **38**. Regardless of the exact mechanistic details, we were pleased that both **37a** and **37b** underwent high yielding annulations to **38**.

Attention was next directed toward regioselective oxidation of the tetrahydrofuran, but only after prior oxidation of the vulnerable double bond. Thus, alkene **38** was stereoselectively epoxidized with buffered m-CPBA to the β-epoxide **40**. The conditions chosen assured that peracid attack would be internally-directed (and activated) by the tertiary hydroxyl group. This set the stage for a ruthenium tetroxide oxidation of the tetrahydrofuran **40** to the lactone **4**. Application of the Sharpless-modified catalytic process,[40a] buffered under the conditions of Greene[40b] provided quantitative formation of (±)-12-noralliacolide (**4**), whose ^1H- and ^{13}C-NMR spectra agreed fully with the published data for the natural product.[1]

The conversion of **4** to (±)-alliacol A (**2**) was accomplished in one step, without the need for protection of the sensitive tertiary hydroxyl group.[41] Subjecting the alkoxy enolate, generated by deprotonation of **4** with lithium tetramethylpiperidide, to a large excess of Eschenmoser's salt directly produced α-methylene lactone **2**. Excess iminium salt apparently quarternizes the initially formed Mannich base and promotes elimination to **2** (Scheme 5). Additional material was obtained by methylation of the basic byproducts. Synthetic alliacol (**2**) exhibited spectral properties (^1H and ^{13}C NMR, IR, and R_f) identical to those reported by Hanson and Thaller.[1]

Conversion of **2** to alliacolide (**1**) was undertaken to further establish structure. Catalytic hydrogenation[5] of alliacol A (**2**) cleanly provided **1**. Synthetic (±)-alliacolide (**1**) was identical in all respects (IR, MS, ^1H-NMR, ^{13}C-NMR, and R_f) to an authentic sample of the natural product kindly provided by Hanson and Thaller.

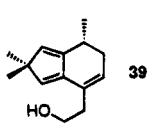
Conclusions

This effort describes the first means to stereoselectively assemble the alliacane family of natural products. The development of this synthesis illustrates that subtle changes in molecular structure can greatly influence the diastereoselectivity of carbonyl addition reactions (e.g. mesyloxy enone **15** lacked facial diastereoselectivity while α-hydroxy ketone **21** and enone **23** demonstrate contrasting selectivity).

(36) The aqueous hydroxide solution was added in a slow dropwise fashion and the reaction was rigorously monitored by TLC analysis to indicate end point.

(37) Production of **38** was indicated by the presence of a vinyl proton (singlet at ~5.5 ppm) in the 400 mHz ^1H-NMR which was in accordance with the known chemical shift for 8,9-deoxyalliacolides. The incorrect isomer appeared in the same range but as a doublet with an allylic coupling of 2.0 Hz.

(38) This triene **39** had spectral (^1H-NMR, ^{13}C-NMR, IR) properties consistent with 6,7-dihydro-4-(hydroxyethyl)-2,2,7-trimethyl-2*H*-indene.



39

(39) The possible operation of the alternative mechanism was supported by the fact that the *syn*-**37a** did not undergo cyclization under the identical anionic conditions; rather hydrolysis to triol **35a** was the major pathway.

(40) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Kanazawa, A. M.; Correa, A.; Denis, J.-N.; Luche, M.-J.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 255.

(41) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.

Interestingly, introduction of the γ-lactone was best achieved through an intramolecular S_N' displacement of an allylic chloroacetate by primary alcohol (**37a/b** to **38**). This displacement occurred regardless of leaving group configuration. The *syn*-displacement (**37a**) occurred with warming. However, generation of a monoalkoxide was needed to drive the *anti*-displacement. Our first approach, *via* dilithium acetate addition to **15**, prepared alliacol A (**2**) in eleven steps with an overall yield of 3%. The two-staged approach, *via* **37**, required 22 manipulations, but provided an overall yield of ~20%[42] of **2**, demonstrating the significant gain obtained through the generation of high degrees of stereocontrol (at all stages)!

Experimental Section

General. All reactions were performed under argon in rigorously dried glassware and stirred with a Teflon-coated stir bars, unless otherwise indicated. Reagents were added to reaction vessels *via* a cannula or dry syringe. Anhydrous solvents were freshly-distilled as follows: tetrahydrofuran (THF) and ether from sodium benzophenone ketyl; benzene and toluene from sodium metal; methanol from magnesium; and acetonitrile and methylene chloride from calcium hydride. Dimethyl sulfoxide and HMPA were dried over 13X molecular sieves and stored in $CaCl_2$-desiccated containers. All alkyllithium reagents (n-BuLi, MeLi, and LDA) were standardized by titration with dry diphenylacetic acid prior to their use. Triethylamine and *N,N*-diisopropylethylamine were freshly-distilled from sodium. Pyridine was purchased anhydrous from Aldrich Chemical Co. Methyl iodide was stored over P_2O_5 and distilled immediately prior to its use. Chromatography was performed either through flash chromatography, radial chromatography on a Chromatotron (Harrison Research), or preparative thin layer chromatography (PTLC) on 100, 250, or 1000 μm thickness GHLF plates (Analtech). Thin layer chromatography (TLC) was routinely used to monitor all reactions. TLC plates were developed by a combination of UV light and/or scorching plates after treatment with a cobalt chloride/sulfuric acid solution. Infrared spectra were measured on a Perkin Elmer 727B prism spectrometer and were standardized to polystyrene (1601 cm^{-1}). Samples were prepared on sodium chloride (NaCl) plates; neat or in a chloroform smear. ^{1}H-NMR spectra and ^{13}C-NMR spectra were collected at 400 MHz on a Varian VXR-400S spectrometer and 75 MHz on a Varian Gemini-300, respectively. COSY45 were measured at 300 MHz on a Varian Gemini-300. Mass spectra were obtained on a VG 70-SE high resolution, magnetic sector instrument using CI, FAB, or desorption chemical ionization (DCI) modes.

1,2,3,3a,5,6-Hexahydro-4,4-(1,3-propanediyldithio)-4*H*-inden-1-one (8). *n*-Butyllithium (2.44 M in hexanes, 43 mL, 105 mmol) was added to a solution of 2-(1,3-dioxan-2-yl)-1-(1,3-dithianyl)ethane (**6**)[12] (23.5 g, 100 mmol) in anhyd THF (125 mL), at −78 °C, over 25 min. The temperature was raised to −20 °C over 2.5 h and maintained at this temperature for 1 h. The mixture was recooled to −78 °C, and HMPA (36.4 mL, 209 mmol) was added dropwise. After 30 min, 2-cyclopenten-1-one (8.80 mL, 105 mmol) was added over the period of 1 h. This mixture was vigorously stirred at −78 °C for 24 h. Upon completion, the temperature was warmed to 0 °C and kept at this temperature for an additional 1 h. The reaction was quenched with an ammonium hydroxide−ammonium chloride (pH = 7.0) buffer (35 mL) and extracted with ether (1000 mL, 2 × 150 mL). The combined organic phases were washed with water (4 × 100 mL) and brine (120 mL), dried ($MgSO_4$), filtered through a 100 g pad of silica gel, and concentrated. Flash chromatography (SiO_2, 40−80% ether/hexanes) yielded 24.3 g (77%, 82% corrected yield based on recovery of **6**) of waxy solid **7**: mp 55−57.5 °C; R_f = 0.25 (charred, 50% ether/hexanes); IR ($CHCl_3$) 1743 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.59 (t, *J* = 4.8 Hz, 1H), 4.11 (dd, *J* = 5.0, 10.6 Hz, 2H), 3.76 (dt, *J* = 2.0, 10.6 Hz, 2H), 2.89 (m, 2H), 2.69 (m, 2H), 2.56 (m, 2H), 2.38 (m, 2H), 2.13 (m, 7H), 1.83 (m, 1H), 1.78 (m, 2H), 1.35 (d, *J* = 13.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 217.9, 101.7, 66.7, 55.9, 43.6, 39.7, 38.6, 30.5, 30.2, 25.3, 25.2, 24.8, 23.2.

Ketone **7** (7.05 g, 22.3 mmol) was refluxed in a mixture of 10% HCl (102 mL) and THF (760 mL) for 3−4 h. Upon TLC evidence for completion, the reaction was cooled to rt, neutralized with saturated sodium bicarbonate (to pH > 7), and extracted with ether (2 × 100 mL). The combined organic phases were washed with water (3 × 75 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 5.02 g (94%, 97% corrected yield based on recovery of **7**) of enone **8**: mp 133−134 °C (needles); R_f = 0.41 (UV-active, 50% ether/hexanes); IR ($CHCl_3$) 3025, 1719, 1659 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.72 (dd, *J* = 3.2, 6.8 Hz, 1H), 3.23 (ddd, *J* = 2.8, 12.1, 14.0 Hz, 1H), 2.86 (m, 3H), 3.70 (m, 2H), 2.45−2.03 (m, 5H), 2.09 (m, 2H), 1.85 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 204.8, 136.2, 132.4, 51.4, 48.4, 37.5, 33.3, 25.7, 25.3, 25.2, 24.3, 21.9.

(3a*S*,7*R*,7a*S*)-7-Methyl-4,4-(1,3-propanediyldithio)-indan-1-one (*cis*-9). A solution of methyllithium (1.24 M in ether, 152 mL, 188 mmol) was added to a copper(I) iodide (18.0g, 94.4 mmol) suspended in anhyd THF (340 mL) at 0 °C. Forty five minutes later, enone **8** (7.53 g, 31.4 mmol) was added in anhyd THF (200 mL). After 3 h at 0 °C, 10% acetic acid (30 mL) was added. The reaction mixture was warmed to rt. An ammonium hydroxide−ammonium chloride (pH = 8.0) buffer (ca. 200 mL) was added until the mixture became homogeneous. The resulting solution was extracted with ether (1100 mL, 2 × 150 mL). The combined organic phases were washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, hexanes to 66% ether/hexanes) yielded 963 mg (12%) of *trans*-**9** and 6.89 g (87%, 96% improved yield from repetitive equilibration of *trans*-**9**) of *cis*-**9**. Recrystallization from cyclohexane yielded highly pure samples of either *cis*-**9** and *trans*-**9**. *cis*-**9**: mp 67−69 °C (prisms); R_f = 0.47 (50% ether/hexanes); IR ($CHCl_3$) 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.83 (t, *J* =5.6 Hz, 4H), 2.80 (m, 1H), 2.68 (dd, *J* = 9.2, 19.2 Hz, 1H), 2.19 (m, 4H), 1.97 (m, 4H), 1.59 (m, 2H), 1.51 (m, 1H), 1.00 (d, *J* = 6.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 218.1, 53.3, 51.0, 44.8, 36.7, 32.3, 29.0, 27.4, 26.0, 25.4, 25.3, 22.4, 18.7. *trans*-**9**: mp 124.5−125.5 °C (cubes); R_f = 0.57 (50% ether/hexanes); IR ($CHCl_3$) 1738 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.17 (ddd, *J* = 2.8, 11.8, 14.3 Hz, 1H), 2.92 (ddd, *J* = 3.0, 11.4, 14.3 Hz, 1H), 2.72 (m, 2H), 2.52 (dt, *J* = 2.6, 14.0, 1H), 2.42−1.88 (m, 10H), 1.81 (ddd, *J* = 3.2, 14.0, 13.6, 1H), 1.43 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 217.2, 54.5, 52.3, 45.7, 37.5, 32.8, 28.7, 26.1, 25.7, 25.5, 25.3, 22.3, 12.4.

trans-**9** was converted to *cis*-**9** by acid-catalyzed equilibration. A solution of *p*-toluenesulfonic acid (0.240 g, 1.26 mmol) in benzene (140 mL) was refluxed for 1.5 h over a Dean−Stark trap and cooled to rt. *trans*-**9** (3.57 g, 12.6 mmol) was added in benzene (35 mL) and refluxed for 30 min. The light pink solution was cooled to rt, neutralized with saturated sodium bicarbonate (60 mL), extracted with ether (350 mL), washed with saturated sodium bicarbonate (80 mL) and brine (2 × 40 mL), dried ($MgSO_4$) and concentrated, and flash chromatography yielded 2.78 g (78% yield) of pure *cis*-**9** along with 0.357 g (10% yield) of *trans*-**9**.

(3a*S*,7*R*,7a*S*)-2,2,7-Trimethyl-4,4′-(1,3-dithiopropyl)indan-1-one (10). A solution of *cis*-**9** (6.97 g, 27.2 mmol) in anhyd THF (420 mL) was added *via* cannula to LDA (1.48 M in cyclohexane, 20.2 mL, 30.0 mmol) diluted with THF (140 mL) at −78 °C. After 20 min of vigorous stirring, methyl iodide (1.86 mL, 30.0 mmol) was added dropwise. After 2 h at this temperature, the solution was gradually warmed (45 min) to −20 °C and maintained for 18 h. Warming to rt drove the reaction to completion, as indicated by a single TLC spot at R_f = 0.59 (50% ether/hexanes). This mixture was added (over a 45 min) to a second aliquot of LDA (1.48 M in cyclohexane, 22.1 mL, 32.7 mmol) in THF (140 mL), again at −78 °C. Ten minutes later, HMPA (5.21 mL, 30.0 mmol) was added dropwise. After an additional 30 min, methyl iodide (2.03 mL,

(42) A small variance in overall yield arises from the relative portions of **31a** and **31b** produced by reduction and the yield of their subsequent conversion to **4**.

32.7 mmol) was added in a one shot fashion. The cooling bath was removed, after 4 h at −78 °C, and the contents warmed to rt. The reaction was quenched with water (200 mL) and extracted with ether (3 × 600 mL) and ethyl acetate (200 mL). The combined organic phases were washed with 10% HCl (300 mL), water (2 × 300 mL), and brine (300 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 7.42 g (96%) of the desired ketone **10**: mp 93−94.5 °C; R_f = 0.63 (50% ether/hexanes); IR ($CHCl_3$) 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.81 (m, 5H), 2.25−2.19 (m, 2H), 2.04−1.84 (m, 5H), 1.69−1.42 (m, 3H), 1.15 (s, 3H), 1.07 (s, 3H), 1.00 (d, J = 6.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 221.9, 53.4, 51.1, 45.0, 41.6, 38.2, 32.1, 29.4, 28.2, 26.4, 26.0, 25.5, 25.4, 25.3, 18.9.

(1*S*,3a*S*,7*R*,7a*S*)-1-Acetoxy-2,2,7-trimethyl-4,4′-(1,3-dithiopropyl)indane (12). At 0 °C, L-Selectride (1.0 M in THF, 81.9 mL, 81.9 mmol) was added to ketone **10** (7.74 g, 27.2 mmol) in anhyd THF (540 mL). The reaction was gradually warmed (over 3 h) to rt. Cautiously, 10% NaOH in water (77 mL) and 30% H_2O_2 (77 mL) were added sequentially at 0 °C. Upon completion, the mixture was warmed to rt, extracted with ether (600 mL) and ethyl acetate (4 × 300 mL), washed with saturated sodium sulfite (350 mL) and brine (2 × 350 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 7.70 g (99% yield) of alcohol **11**: mp 84−85 °C (large cubes); R_f = 0.55 (50% ether/hexanes); IR ($CHCl_3$) 3470 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.87 (d, J = 6.0 Hz, 1H), 2.87 (m, 2H), 2.76 (m, 2H), 2.46 (m, 1H), 2.19−1.91 (m, 5H), 1.81-1.64 (m, 3H), 1.51 (m, 3H), 1.09 (d, J = 7.2 Hz, 3H), 1.06 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 83.8, 52.2, 48.7, 42.7, 40.5, 38.6, 31.7, 31.2, 31.1, 27.5, 26.0, 25.6, 25.6, 25.4, 22.3.

Alcohol **11** (0.914 g, 3.29 mmol) was treated with DMAP (65 mg), Ac_2O (2 mL), and pyridine (15 mL), overnight at rt. The reaction mixture was poured over cold 5% HCl (40 mL), extracted with ether (3 × 100 mL), washed with brine (3 × 100 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 1.02 g (95% yield) of acetate **12**: mp 70−71 °C (large cubes); R_f = 0.68 (50% ether/hexanes); IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.86 (d, J = 6.0 Hz, 1H), 2.74 (m, 4H), 2.42 (m, 1H), 2.19−2.04 (m, 1H), 2.01 (s, 3H), 1.95-1.68 (m, 3H), 1.76−1.51 (m, 2H), 1.50−1.53 (m, 3H), 1.03 (s, 3H), 0.96 (s, 6H), 0.89 (d, J = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 171.4, 83.7, 52.0, 47.2, 43.0, 41.0, 38.6, 32.1, 31.5, 31.4, 28.3, 26.7, 26.4, 26.0, 25.9, 22.0, 21.4; CI-HRMS m/e calcd for $C_{17}H_{28}O_2S_2$ 328.1531, found 328.1649. The relative configuration was proven by X-ray crystallographic analysis after single recrystallization from an ether/petroleum ether diffusion-crystallization chamber.[43]

(1*R*,7*R*)-1-Acetoxy-2,3,4,5,6,7-hexahydro-2,2,7-trimethyl-1*H*-inden-4-one (13). Ceric ammonium nitrate (1.20 g, 2.2 mmol) was added to acetate **12** (180 mg, 0.55 mmol) in 25% aqueous acetonitrile (7 mL) at rt. After 3 min, the reaction mixture was poured onto water (200 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated. Purification by centrifugal chromatography (ether/hexanes) yielded 65 mg (50%) of yellow oil **13**: R_f = 0.50 (50% ether/hexanes); IR (neat) 1720, 1660, 1545 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.53 (s, 1H), 2.50−2.08 (m, 6H), 2.02 (s, 3H), 1.05 (s, 3H), 1.04 (d J = 6.3 Hz, 3H), 0.90 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 198.9, 171.1, 162.8, 139.2, 85.2, 42.9, 41.0, 36.1, 31.3, 28.8, 28.2, 22.9, 20.9, 17.5; UV (EtOH) γ_{max} 240 nm; EI-HRMS m/e calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1411.

(1*R*,7*R*)-2,3,4,5,6,7-hexahydro-1-hydroxy-2,2,7-trimethyl-1*H*-inden-4-one (14). Potassium carbonate (250 mg, 1.81 mmol) was added to acetoxy enone **13** (415 mg, 1.76 mmol) in 10% aqueous methanol (20 mL) and left overnight at rt. The methanol was rotary evaporated and the resulting residue diluted with brine (50 mL), extracted with ether (4 × 50 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Radial chromatography (ether/hexanes) gave 331 mg (97%) of hydroxy enone **14** as a yellow oil: R_f = 0.22 (50% ether/hexanes); IR ($CHCl_3$) 3425, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.31 (d, J = 5.0 Hz, 1H), 2.70−2.50 (m, 2H), 2.50−2.20 (m, 3H), 2.20−2.00 (m, 2H), 1.75−1.60 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 1.04 (s, 3H), 0.94 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 199.9, 166.9, 136.3, 84.9, 41.9, 41.9, 36.1, 31.4, 28.8, 22.8, 22.3, 17.9.

8,9-Deoxy-12-noralliacolide (16) and *epi*-8,9-Deoxy-12-noralliacolide (17) *via* Tandem Addition−Displacement. A solution of hydroxy enone **14** (188 mg, 0.969 mmol) and triethylamine (0.268 mL, 1.92 mmol) in anhyd THF (5 mL) was treated with methanesulfonyl chloride (0.110 mL, 1.42 mmol) for 30 min at rt. Concurrently, a solution of dilithium acetate was being prepared to react with the above mesylate. *n*-Butyllithium (2.32 M in hexane, 4.24 mL, 9.89 mmol) was added to *N*,*N*-diisopropylamine (1.32 mL, 10.7 mmol) in anhyd THF (7 mL) at 0 °C. To this solution, dry acetic acid (0.282 mL, 4.93 mmol) was added followed by HMPA (0.857 mL, 4.93 mmol). The resulting solution was stirred at rt for 30 min. This suspension of dilithium acetate was added to the above mesylate, at 0 °C. The solution was slowly warmed to rt and stirred overnight. During which, the starting material disappeared (*via* TLC analysis) and product lactones gradually formed (one spot on TLC). The reaction mixture was diluted with saturated ammonium chloride solution (50 mL), extracted with ether (4 × 50 mL), washed with saturated ammonium chloride solution (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. Radial chromatography (ether/hexanes) gave 107.5 mg (47%) of a 1:1 mixture of **16** and **17** which was determined by comparison of the C-8 vinyl hydrogen's integration: R_f = 0.53 (50% ethyl acetate/hexanes); IR ($CHCl_3$) 3450, 2925, 2850, 1770, 1460 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) **16**: δ 5.63 (s, 1H), **17**: 5.55 (d, J =2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ175.3, 175.3, 145.4, 142.4, 140.0, 138.5, 99.5, 99.5, 74.6, 45.6, 45.3, 44.2, 42.6, 42.4, 35.7, 30.9, 30.2, 29.9, 29.6, 29.6, 29.4, 29.2, 29.0, 26.6, 20.0, 18.5, 18.3.

(1*S*,7*R*,7a*S*)-1-Hydroxy-2,2,7-trimethylindan-4-one (18). Solid trimethyloxonium tetrafluoroborate (13.1 g, 88.5 mmol) was added to dithiane **11** (6.96 g, 21.9 mmol) in anhyd methylene chloride (375 mL) at rt. This slurry was stirred until the starting material disappeared (approximately 1.2 h). The reaction was quenched by the addition of saturated sodium bicarbonate (35 mL) and allowed to stir for 20 min. The resulting mixture was diluted with saturated sodium bicarbonate (150 mL), extracted with methylene chloride (4 × 300 mL), washed with water (60 mL) and brine (2 × 75 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 3.50 g (87%) of a mixture of diastereomeric γ-hydroxy ketones **18** (chromatography and recrystallization always provided ~5:1 mixture of two diastereomers): mp 94−96 °C (opaque cubes); R_f = 0.39 and 0.32 (50% ether/hexanes); IR ($CHCl_3$) 3450 (broad), 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) major isomer: δ 3.71 (d, J = 4 Hz, 1H), 2.96 (dt, J = 13.6, 9.6 Hz, 1H), 2.45−2.25 (m, 2H), 2.16−1.95 (m, 2H), 1.75 (dd, J = 10.5, 13.6 Hz, 1H), 1.60−1.38 (m, 3H), 1.50 (dd, J = 8.6, 13.6 Hz, 1H), 1.07 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.00 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 213.0, 80.6, 57.4, 52.4, 41.1, 40.0, 36.0, 31.2, 30.6, 24.1, 18.2, 13.9; minor isomer: δ 3.35 (d, J = 4 Hz, 1H), 2.96 (dt, J = 13.4, 9.8 Hz, 1H), 2.45−2.25 (m, 2H), 2.16−1.95 (m, 2H), 1.80−1.38 (m, 5H), 1.07 (s, 3H,), 1.07 (d, 3H), 0.95 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 213.5, 80.3, 60.2, 52.0, 47.6, 41.1, 38.4, 30.2, 28.4, 26.8, 22.8, 20.7. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.41; H, 10.28. Found: C, 73.52; H, 10.48.

(1*S*,3a*R*,7*R*,7a*S*)-1-Acetoxy-3a-hydroxy-2,2,7-trimethylindan-4-one (21). Freshly-distilled acetic anhydride (18.1 mL, 19.6 g, 191 mmol) was added at 0 °C to a mixture of γ-hydroxy ketones **18** (3.50 g, 19.1 mmol) in benzene (480 mL) and carbon tetrachloride (48 mL). After 15 min, 70% perchloric acid (~70 drops) was added until a slight yellow color appeared. Thirty minutes later, the bath was removed. After TLC indication of completion, the solution was cooled to 0 °C, saturated sodium bicarbonate (70 mL) was added, and the solution was stirred until gas evolution ceased (~10 min). The

(43) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

resulting solution was extracted with ether (3 × 350 mL) and ethyl acetate (140 mL), washed with saturated sodium bicarbonate (2 × 75 mL) and brine (75 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (SiO_2, hexanes to 8% ethyl acetate/hexanes) yielded 5.12 g (96%) of enol acetate **19**: mp 109–113 °C (wax); R_f = 0.59 (50% ethyl acetate/hexanes); IR ($CHCl_3$) 1760–1720 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.04 (d, J = 4.8 Hz, 1H), 2.52 (m, 1H), 2.15 (m, 3H), 2.10 (s, 3H), 2.08–1.95 (m, 2H), 2.04 (s, 3H), 1.80 (m, 1H), 1.45 (m, 1H), 1.03 (s, 3H), 0.95 (s, 3H), 0.92 (d, J = 6.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.9, 169.0, 140.9, 127.3, 81.7, 50.6, 41.4, 49.5, 31.4, 28.5, 27.9, 26.7, 23.6, 20.5, 20.5, 19.4.

Dry sodium bicarbonate (8.10 g, 96.4 mmol) was added to enol acetate **19** (2.70 g, 9.64 mmol) in anhyd methylene chloride (490 mL). m-CPBA (4.41 g, 21.7 mmol, 85% pure) was added to the slurry at 0 °C. After 3 h at 0 °C, temperature was raised to 10 °C, and directly extracted on ether (3 × 250 mL) and water (160 mL). The aqueous layer was further extracted methylene chloride (270 mL). The combined organic phases were washed with saturated sodium bicarbonate (3 × 160 mL) and brine (160 mL), dried ($MgSO_4$), filtered through silica gel (to remove residual m-CPBA), and concentrated; yielding 3.61 g (in ~80% purity) of solid **20**: R_f = 0.50 (50% ether/hexanes); IR ($CHCl_3$) 1760–1735 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.16 (d, J = 4.8 Hz, 1H), 2.35 (dd, J = 4.0, 13.6 Hz, 1H), 2.19–2.00 (m, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 2.04 (d, J = 14.6 Hz, 1H), 1.95 (dd, J = 4.8, 10.8 Hz, 1H), 1.53 (d, J = 14.6 Hz, 1H), 1.54–1.37 (m, 2H), 1.45 (s, 3H), 0.97 (s, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 170.9, 169.6, 85.7, 81.2, 70.5, 50.9, 41.4, 40.9, 28.5, 27.4, 26.6, 26.3, 22.6, 20.8, 20.4, 19.8.

Aqueous KOH (0.05 M, 48 mL) was added to crude epoxy acetate **20** (6.70 g, ~21.1 mmol) in methylene chloride (700 mL) at rt. Methanol (~200 mL) was slowly added until the cloudy suspension became homogeneous. After approximately 1 h, the reaction mixture was partitioned between ether (300 mL) and water (100 mL) and extracted. The aqueous layer was further extracted with ethyl acetate (4 × 200 mL). The combined organic phases were washed with saturated sodium bicarbonate (100 mL) and brine (80 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) and recrystallization (hexanes with a trace of methylene chloride) yielded 4.58 g (~95% yield) of pure α-hydroxy ketone **21**: mp 80.5–82.0 °C (large cubes); R_f = 0.35 (50% ether/hexanes); IR ($CHCl_3$) 3480, 1740–1718 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.26 (d, J = 5.6 Hz, 1H), 3.09 (s, 1H, D_2O washed out), 2.58–2.42 (m, 2H), 2.31 (dd, J = 6.0, 10.0 Hz, 1H), 2.28 (d, J = 13.8, 1H), 2.05 (s, 3H), 1.89 (m, 1H), 1.82–1.60 (m, 2H), 1.45 (d, J = 13.8 Hz, 1H), 1.23 (s, 3H), 1.02 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 212.1, 170.6, 82.9, 82.7, 60.3, 48.3, 40.6, 35.7, 32.3, 29.8, 29.0, 25.1, 21.0, 20.6. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.10; H, 8.72. Found: C, 65.85; H, 8.68.

(1*S*,3a*R*,4*S*,7*R*,7a*S*)-4-(2-Propenyl)-2,2,7-trimethylindan-1,3a,4-triol (22). Allylmagnesium chloride (2.0 M in THF, 0.440 mL, 0.880 mmol) diluted with anhyd THF (5.5 mL) was added over 1 h to α-hydroxy ketone **21** (44.7 mg, 0.1759 mmol) in anhyd THF (17 mL) at −78 °C. The reaction was complete in 15 min and quenched with 10% HCl (15 mL). The resulting solution was extracted with ether (2 × 50 mL) and ethyl acetate (25 mL), washed with water (5 mL), saturated sodium bicarbonate (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to yield 14.9 mg of crude product. A pure sample of triol **22** (37.9 mg, 85%) was obtained by a combination of PTLC (250 μm plate, 60% ether/hexanes) and recrystallization from hexanes with a trace of methylene chloride. Triol **22**: mp 108.5–110 °C (tiny cubes); R_f = 0.12 (50% ether/hexanes); IR ($CHCl_3$) 3480 (broad), 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.91 (m, 1H), 5.18 (d, J = 10.8 Hz, 1H), 5.13 (d, J = 17.6 Hz, 1H), 4.44 (t, J = 6.8 Hz, 1H), 2.44 (dd, J = 9.6, 13.6 Hz, 1H), 2.22 (d, J = 4.0 Hz, 1H), 2.02 (dd, J = 5.6, 13.6 Hz, 1H), 1.81–1.26 (m, 10H), 1.16 (s, 3H), 1.12 (d, J = 6.0 Hz, 3H), 1.06 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 134.3, 119.7, 82.9, 82.4, 73.3, 57.0, 46.8, 40.7, 38.6, 32.8, 32.2, 30.8, 29.9, 26.5, 22.6. The relative configuration was verified by x-ray crystallography.[43]

(1*S*,7*R*,7a*S*)-1-Acetoxy-1,2,5,6,7,7a-hexahydro-2,2,7-trimethyl-4*H*-inden-4-one (23). A solution of *p*-toluenesulfonic acid monohydrate (3.14 g, 16.5 mmol) in benzene (250 mL) was refluxed for 1.5 h over a Dean–Stark trap, cooled to rt, and combined with neat α-hydroxy ketone **21** (1.68 g, 6.61 mmol). Fifteen minutes later, freshly-distilled methanesulfonyl chloride (0.640 mL, 0.947 g, 8.26 mmol) was added dropwise. The reaction was complete in 1.5 h, accompanied by a brilliant yellow color. Saturated sodium bicarbonate (125 mL) was added (the color was bleached). Once gas evolution ceased, the mixture was extracted with ether (3 × 400 mL) and ethyl acetate (400 mL), washed with saturated sodium bicarbonate (80 mL) and brine (80 mL), dried ($MgSO_4$), and concentrated to yield a yellow wax. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 1.50 g (96% yield) of pure enone **23**: mp 121–124 °C (flakes); R_f = 0.39 (UV-active, 50% ether/hexanes); IR ($CHCl_3$)

(1*S*,7*R*,7a*S*)-1,2,5,6,7,7a-Hexahydro-1-hydroxy-2,2,7-trimethyl-4*H*-inden-4-one (24). Powdered potassium carbonate (5.37 g, 38.9 mmol) was added to acetoxy-enone **23** (1.53 g, 6.48 mmol) in 10% aqueous methanol (300 mL). The reaction was allowed to stir at rt for 48 h, concentrated, and extracted with ether (250 mL) and ethyl acetate (4 × 150 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, ethyl acetate/hexanes) yielded 1.18 g (94% conversion, 99% yield based on recovery of **23**) of hydroxy enone **24**: yellow oil; R_f = 0.14 (UV-active, 50% ether/hexanes); IR (neat) 3440 (broad), 1673, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.42 (d, J = 2.4 Hz, 1H), 3.96 (d, J = 3.2 Hz, 1H), 2.72 (ddd, J = 3.2, 4.3, 11.3 Hz, 1H), 2.51 (ddd, J = 2.0, 4.6, 17.7 Hz, 1H), 2.31 (ddd, J = 6.0, 13.6, 17.7 Hz, 1H), 1.95 (m, 2H), 1.89 (m, 1H), 1.57 (m, 1H), 1.19 (s, 3H), 1.10 (d, J = 6.4 Hz, 3H), 1.05 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 199.7, 146.3, 138.2, 81.7, 55.2, 48.6, 39.9, 32.0, 29.5, 23.6, 20.4, 19.4.

Benzyl (1*S*,4*S*,7*R*,7a*S*)-2-(1-Acetoxy-4-hydroxy-1,2,5,6,7,-7a-hexahydro-2,2,7-trimethyl-4*H*-inden-4-yl)acetate (26). A solution of benzyl acetate (0.456 mL, 0.474 g, 3.07 mmol) in anhyd THF (1 mL) was added to LDA (1.21 M in cyclohexane, 2.61 mL, 3.16 mmol) diluted with anhyd THF (6 mL) at −78 °C. Forty-five minutes later, a portion (1 mL, ~0.34 mmol) of the above solution was added to enone **23** (20.7 mg, 0.0877 mmol) in THF (5 mL) at −78 °C. The reaction was complete within 30 min. 5% HCl (5 mL) was added, and the mixture was rapidly warmed to 0 °C. This solution was poured onto ether (30 mL) and water (10 mL) and extracted. The aqueous layer was further extracted with ethyl acetate (2 × 30 mL), washed with 5% HCl solution (10 mL) and brine (2 × 10 mL), dried ($MgSO_4$), and concentrated. A combination of radial chromatography (50% ether/hexanes) and recrystallization (twice from ether/pentane) yielded 12.7 mg (36%) of pure benzyl ester **26**: mp 152–152.5 °C (needles); R_f = 0.64 (50% ethyl acetate/hexanes); IR ($CHCl_3$) 3500, 3020, 1729, 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.31–7.40 (m, 5H), 5.38 (d, J = 2.4 Hz, 1H), 5.18 (d, J = 6.4 Hz, 1H), 5.17 (d, J = 12.4 Hz, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.20 (s, 1H), 2.73 (d, J = 14.8 Hz, 1H), 2.53 (d, J = 14.8 Hz, 1H), 2.46 (ddd, J = 2.5, 5.8, 6.8 Hz, 1H), 2.05 (s, 3H), 1.83–1.73 (m, 3H), 1.65–1.57 (m, 2H), 1.19 (m, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.2, 171.0, 143.2, 132.3, 128.9, 128.8, 128.7, 80.2, 71.5, 66.6, 52.7, 47.4, 42.5, 38.1, 31.6, 31.5, 26.0, 21.1, 20.5, 19.8. The relative configuration was verified by X-ray crystallographic analysis.[43]

***tert*-Butyl-(1*S*,4*S*,7*R*,7a*S*)-2-(1,4-dihydroxy-1,2,5,6,7,7a-hexahydro-2,2,7-trimethyl-4*H*-inden-4-yl)acetate (27).** A solution of lithium *tert*-butyl acetate (0.05 M) was generated by the addition of LDA (1.33 M in cyclohexane, 15.8 mL, 21.0 mmol) to *tert*-butyl acetate (2.62 mL, 19.4 mmol) in anhyd THF (21.4 mL), at −78 °C. Enolate formation was secured by warming to rt (over 3 h) prior to use. A portion of this solution (0.05 M, 30.4 mL, 15.2 mmol) was added rapidly at −78 °C to hydroxy enone **24** (0.843 g, 4.34 mmol) in HMPA (5.3 mL) and anhyd THF (140 mL). The reaction was stirred for 1 h at −78 °C. Extended reaction times produced increasing amounts of acetylated product **28**. The reaction was quenched at −78 °C by the addition of 14% ammonium chloride solution (65 mL)

and warmed to rt. This mixture was extracted with ether (2 × 250 mL) and ethyl acetate (3 × 350 mL), washed with 14% ammonium chloride (85 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (SiO_2, hexanes to 60% ether/hexanes) yielded 1.26 g (95% yield) of desired ester **27**: mp 67–67.5 and 118–119 °C (cubes); R_f = 0.21 (50% ether/hexanes); IR ($CHCl_3$) 3440 (broad), 3025, 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.44 (d, J = 2.4 Hz, 1H), 4.72 (s, 1H), 3.80 (dd, J = 5.0, 9.4 Hz, 1H), 2.54 (d, J = 15.6 Hz, 1H), 2.41 (d, J = 15.2 Hz, 1H), 2.38 (ddd, J = 2.8, 5.2, 11.4 Hz, 1H), 1.81–1.64 (m, 3H), 1.57 (m, 1H), 1.45 (s, 9H), 1.24 (d, J = 9.6, 1H), 1.20 (m, 1H), 1.12 (s, 3H), 1.01 (d, J = 6.0 Hz, 3H), 0.94 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.1, 143.4, 131.7, 81.9, 80.0, 71.3, 54.0, 47.6, 43.1, 38.4, 31.3, 31.2, 28.0 (3C's), 26.1, 21.3, 20.0. Along with the desired product **27**, there was a small amount (42.1 mg, 3% yield) of acetoxy ester **28**: mp 110–111 °C (needles); R_f = 0.44 (50% ether/hexanes); IR ($CHCl_3$) 3445 (broad), 1740, 1709 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.44 (d, J = 2.4 Hz, 1H), 5.20 (d, J = 6.0 Hz, 1H), 4.66 (s, 1H), 2.55 (d, J = 15.2 Hz, 1H), 2.41 (d, J = 15.2 Hz, 1H), 2.48 (ddd, J = 2.4, 6.0, 11.1 Hz, 1H), 2.05 (s, 3H), 1.81–1.64 (m, 2H), 1.68–1.57 (m, 2H), 1.45 (s, 9H), 1.18 (m, 1H), 1.00 (s, 6H), 0.86 (d, J = 6.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.0, 171.1, 143.4, 132.0, 81.9, 80.3, 71.3, 52.7, 47.3, 42.9, 38.3, 31.6, 31.5, 28.0 (3C's), 26.4, 21.3, 20.5, 19.8. Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 67.96; H, 9.06. Compound **28** could be converted to **27** by treatment with 3.2 equiv of L-Selectride in THF.

***tert*-Butyl (4*S*,7*R*,7a*S*)-2-(4-Hydroxy-1,2,5,6,7,7a-hexahydro-2,2,7-trimethyl-1-oxo-4*H*-inden-4-yl)acetate (29).** A solution of dimethyl sulfoxide (1.34 mL, 17.4 mmol) in methylene chloride (50 mL) was added over 5 min at −55 °C to oxalyl chloride (2.0 M in methylene chloride, 5.92 mL, 11.8 mmol) diluted with methylene chloride (175 mL). After an additional 2–3 min, the substrate **27** (1.23 g, 3.95 mmol) in methylene chloride (90 mL) was added *via* cannula. Thirty minutes afterwards, triethylamine (5.50 mL, 39.5 mmol) was added dropwise. Stirring was maintained for an additional 1 h at the above temperature, after which it was gradually warmed 0 °C (over ~1 h). The reaction was quenched with water (60 mL), extracted with methylene chloride (4 × 100 mL), washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (SiO_2, hexanes to 33% ether/hexanes) yielded 1.06 g (87% yield) of desired β,γ-unsaturated ketone **29**: mp 215.5–216.5 °C (needles); R_f = 0.40 (50% ether/hexanes); IR ($CHCl_3$) 3480 (broad), 3035, 1747, 1714 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.87 (d, J = 2.0 Hz, 1H), 4.53 (s, 1H), 2.68 (d, J = 15.2 Hz, 1H), 2.47 (d, J = 15.2 Hz, 1H), 2.38 (dd, J = 2.0, 11.2 Hz, 1H), 1.86 (td, J = 3.2, 13.2 Hz, 1H), 1.75 (ddd, J = 3.6, 3.6, 14.0 Hz, 1H), 1.63–1.39 (m, 2H), 1.44 (s, 9H), 1.26 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 222.1, 171.9, 143.9, 130.0, 82.1, 71.9, 55.6, 49.8, 42.0, 39.0, 37.0, 32.6, 28.0 (3C's), 24.5, 24.3, 19.2.

***tert*-Butyl (4*S*,7*R*)-2-(4-Hydroxy-2,3,4,5,6,7-hexahydro-2,2,7-trimethyl-1-oxo-1*H*-inden-4-yl)acetate (30).** Sodium (280 mg, 12.2 mmol) was cautiously reacted with anhyd methanol (9 mL). At 0 °C, the β,γ-unsaturated ketone **29** (752 mg, 2.43 mmol), in anhyd THF (75 mL), was added dropwise *via* cannula. The reaction was complete within 30 min and diluted with saturated sodium bicarbonate (55 mL). The methanol was evaporated via rotary evaporation. The resulting solution was extracted with ether (2 × 150 mL) and ethyl acetate (5 × 50 mL), washed with brine (2 × 90 mL), dried ($MgSO_4$), and concentrated. Radial chromatography (hexanes to 50% ether/hexanes) yielded 739 mg (98% yield) of desired enone **30**: yellow oil; R_f = 0.36 (UV-active, 50% ether/hexanes); IR (neat) 3450 (broad), 1731, 1700, 1621 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.23 (s, 1H), 2.66 (d, J = 15.6 Hz, 1H), 2.60 (dd, J = 3.0, 17.8 Hz, 1H), 2.52 (m, 1H), 2.47 (d, J = 15.6 Hz, 1H), 2.29 (dd, J = 1.6, 17.8 Hz, 1H), 2.04–1.89 (m, 2H), 1.80 (m, 1H), 1.49 (s, 9H), 1.38 (m, 1H), 1.10 (s, 3H), 1.08 (d, 3H), 1.07 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 214.0, 172.0, 167.9, 141.2, 82.2, 69.6, 43.2, 43.1, 41.1, 33.2, 27.8 (3C's), 26.9, 25.8, 25.2, 24.4, 17.7.

***tert*-Butyl (1*S*,4*S*,7*R*)-2-(1,4-Dihydroxy-2,3,4,5,6,7-hexahydro-2,2,7-trimethyl-1*H*-indenyl)acetate (31a) and *tert*-Butyl (1*R*,4*S*,7*R*)-2-(1,4-Dihydroxy-2,3,4,5,6,7-hexahydro-2,2,7-trimethyl-1*H*-indenyl)acetate (31b).** DIBAL-H (1.0 M in hexane, 8.29 mL, 8.29 mmol) was added at −78 °C to α,β-unsaturated ketone **30** (730 mg, 2.37 mmol) in anhyd toluene (120 mL). Upon TLC evidence for completion (~1.5 h), excess reagent was destroyed with absolute methanol (2.5 mL) and then diluted with water (80 mL). Surplus methanol was removed by evaporation, and the resulting solution was suction-filtered to remove aluminum salts. Optimum yield was obtained by washing the collected precipitate with each extraction aliquot. The filtrant was extracted with ether (2 × 100 mL) and ethyl acetate (4 × 100 mL), and the combined organic phases were washed with brine (70 mL), dried ($MgSO_4$), and concentrated. PTLC (1000 μm silica gel plate with 66% ether/hexanes) yielded 355 mg (48% yield) of α-diol **31a** and 357.5 mg (48% yield) of β-diol **31b**. α-Diol **31a**: mp 195.5–197.5 °C (needles); R_f = 0.35 (50% ether/hexanes); IR ($CHCl_3$) 3450 (broad), 3375 (broad), 1703 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.00 (s, 1H), 3.84 (s, 1H), 2.59 (d, J = 15.2 Hz, 1H), 2.37 (d, J = 15.2 Hz, 1H), 2.34 (m, 1H), 2.17 (d, J = 1.6, 2H), 1.98–1.83 (m, 2H), 1.73 (ddd, J = 3.0, 8.0, 13.0 Hz, 1H), 1.57 (s, 1H), 1.48 (s, 9H), 1.33 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.7, 143.6, 140.7, 87.3, 81.7, 69.3, 44.1, 42.6, 41.0, 33.6, 30.2, 28.3, 27.9 (3C's), 27.8, 22.1, 19.3. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.63; H, 9.75. Found: C, 69.20; H, 9.64. β-Diol **31B**: mp 123–125.5 °C (prisms); R_f = 0.11 (50% ether/hexanes); IR ($CHCl_3$) 3375 (broad), 1719 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.06 (s, 1H), 4.00 (s, 1H), 2.55 (d, J = 15.2 Hz, 1H), 2.33 (d, J = 15.2 Hz, 1H), 2.44–2.34 (m, 2H), 2.00–1.92 (m, 2H), 1.85 (ddd, J = 3.0, 8.4, 13.4 Hz, 1H), 1.72 (ddd, J = 3.2, 9.6, 13.0 Hz, 1H), 1.47 (s, 9H), 1.35 (m, 2H), 1.05 (s, 3H), 1.02 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.6, 144.0, 139.4, 84.4, 81.7, 69.4, 43.7, 43.4, 40.3, 33.9, 28.1, 27.9 (4C's), 27.2, 22.3, 17.8. Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.63; H, 9.75. Found: C, 69.57; H, 9.64.

Hydrolysis and Mesylation of β-Hydroxy *tert*-Butyl Ester 31b. Granular potassium carbonate (51.0 mg, 0.369 mmol) was added to **31b** (22.9 mg, 0.0738 mmol) in 10% aqueous methanol (4 mL). This solution was allowed to stir for 5 d at rt. The solution was concentrated, taken up in absolute methanol, and filtered to remove the excess inorganic salts. The crude carboxylate was dried by repetitive evaporation of benzene (3 × 4 mL). Triethylamine (57.0 μL, 41.4 mg, 0.409 mmol) and methanesulfonyl chloride (16.0 μL, 27.3 mg, 0.238 mmol) were added sequentially to the crude carboxylate suspended in THF (2 mL). The reaction was allowed to stir for 2 h at −10 °C and overnight at rt (~12 h). Saturated ammonium chloride (5 mL) was added. The mixture was extracted with ether (50 mL) and ethyl acetate (2 × 50 mL), washed with brine (25 mL), dried ($MgSO_4$), and concentrated. PTLC (50% ethyl acetate/hexanes) yielded 14.7 mg (65%) of the starting β-hydroxy *tert*-butyl ester **31b**, 3.6 mg (21% yield) of 8,9-deoxy-12-noralliacolide (**16**), and 9.3 mg of crude **34**. 8,9-Deoxy-12-noralliacolide (**16**): R_f = 0.52 (UV-active, 50% ethyl acetate/hexanes); IR ($CHCl_3$) 3440 (broad), 1771 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.68 (s, 1H), 2.75 (d, J = 16.8 Hz), 2.70 (m, 1H), 2.50 (d, J = 16.8 Hz, 1H), 2.07 (m, 1H), 1.81–1.43 (m, 6H), 1.10 (s, 3H), 1.13 (d, J = 6.2 Hz, 3H), 1.11 (s, 3H). A pure sample of **34** was obtained by repetitive PTLC. Diene **34**: R_f = 0.73 (50% ethyl acetate/hexanes); IR (neat) 3350 (broad), 3180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.77 (s, 1H), 4.74 (s, 1H), 4.20 (d, J = 8.4 Hz, 1H), 2.49 (m, 1H), 2.44–2.37 (m, 1H), 2.34 (d, J = 15.6 Hz, 1H), 2.27 (m, 1H), 2.18 (d, J = 15.6 Hz, 1H), 1.87 (ddd, J = 4.4, 8.4, 16.8 Hz, 1H), 1.42 (dddd, J = 3.7, 7.0, 9.4, 13.0 Hz, 1H), 1.19 (d, J = 8.4 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 1.07 (s, 6H).

For comparison purposes **34** was also prepared from enone **14**. At 0 °C, *n*-butyllithium (2.46 M in hexanes, 0.119 mL, 0.292 mmol) was added to methyltriphenylphosphonium bromide (0.108 g, 0.302 mmol) in anhyd THF (7 mL) and gradually warmed to rt. Enone **14** (12.0 mg, 0.0618 mmol) dissolved in anhyd THF (6 mL) was added at 0 °C. After 2 h at rt, water (8 mL) was added, the product was extracted with ether (4 × 50 mL) and ethyl acetate (40 mL). The combined organic layers were washed with 10% NaOH solution (2 × 10 mL) and water (2 × 10 mL), dried ($MgSO_4$), and concentrated.

PTLC (50% ethyl acetate/hexanes) provided 8.2 mg (68% yield) of the desired diene **34**, identical in all respects to the above material.

***tert*-Butyl (4*S*,7*R*)-2-(4,5,6,7-Tetrahydro-2,2,7-trimethyl-2*H*-indenyl)acetate (33).** Triethylamine (28.4 μL, 20.6 mg, 0.204 mmol) was added to β-hydroxy *tert*-butyl ester **31b** (21.1 mg, 0.0680 mmol) in anhyd THF (2.5 mL) at −10 °C. Fifteen minutes later, freshly-distilled methanesulfonyl chloride (7.9 μL, 11.7 mg, 0.102 mmol) was added over 2 min. After 14 h at rt, the mixture was flushed through a 10 g pad of silica gel (with 10−15 mL of ethyl acetate) and concentrated. PTLC (50% ethyl acetate/hexanes) provided 14.1 mg (71% yield) of diene **33**: yellow oil; R_f = 0.74 (UV-active, 50% ethyl acetate/hexanes; IR (neat) 3500 (broad), 3050, 1712, 1622 (weak) cm^{-1}; UV-Vis (hexane) λ_{max} 259.4 nm (E = 9685); ^{1}H-NMR ($CDCl_3$) δ 6.12 (d, J = 2.4 Hz, 1H), 5.79 (t, J = 2.4 Hz, 1H), 4.63 (s, 1H), 2.60 (d, J = 15.6 Hz), 2.50 (d, J = 15.6 Hz, 1H), 2.46 (m, 1H), 2.04−1.89 (m, 3H), 1.46 (s, 9H), 1.24−1.09 (m, 1H), 1.14 (s, 3H), 1.13 (d, J = 5.6 Hz, 3H), 1.10 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.7, 145.0, 144.2, 141.1, 138.9, 81.6, 69.9, 50.8, 45.8, 36.2, 30.3, 29.4, 28.0 (3C's), 22.7, 22.2, 20.0.

(1*S*,4*S*,7*R*)-1-(Chloroacetoxy)-2,3,4,5,6,7-hexahydro-4-(2-hydroxyethyl)-2,2,7-trimethyl-1*H*-inden-4-ol (37a). Lithium aluminum hydride (56.9 mg, 1.50 mmol) was added to α-diol **31a** (150 mg, 0.484 mmol) in dry ether (24 mL) at 0 °C. After 3 h at rt, saturated ammonium chloride (8 mL) was added *cautiously* at 0 °C. Once gas evolution ceased, the suspension was extracted with ethyl acetate (4 × 85 mL), washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Decomposition of triol **35a** ($t_{1/2} \approx$ 2 days) forced chromatography to immediately precede its use. PTLC (one-half of a 1000 μm plate, ethyl acetate) yielded 79.9 mg (69% conversion, 92% yield based on recovery of **31a**) of desired triol **35a**: mp 118−119.5 °C (granular); R_f = 0.08 (50% ethyl acetate/hexanes); IR (neat) 3380 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.00 (m, 1H), 3.99 (d, J = 7.2 Hz, 1H), 3.80 (dd, J = 5.0, 11.0 Hz, 1H), 2.51 (dd, J = 3.8, 6.2 Hz, 1H), 2.32 (d, J = 15.2 Hz), 2.32 (m, 1H), 2.20−2.04 (m, 3H), 1.95−1.83 (m, 2H), 1.77−1.72 (m, 1H), 1.62 (td, J = 4.4, 15.6 Hz, 1H), 1.37 (m, 1H), 1.19 (d, J = 7.2 Hz, 1H), 1.12 (d, J = 6.8 Hz, 3H), 1.07 (s, 3H), 1.01 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 143.1, 142.1, 87.4, 71.7, 59.6, 42.6, 41.0, 40.0, 32.9, 30.2, 28.3, 27.8, 22.1, 19.4.

Pyridine (65.3 μL, 63.9 mg, 0,808 mmol) was added along with a catalytic amount (~2 mg) of DMAP to a solution of triol **35a** (77.6 mg, 0.323 mmol) in anhyd methylene chloride (13 mL). At −78 °C, chloroacetic anhydride (113 mg, 0.662 mmol) in anhyd methylene chloride (1.5 mL) was added over 5 min. The ice bath was removed, and the reaction mixture was allowed to just reach rt. Alcohol **36a** (123 mg, 97% yield) was recovered by filtering through a 10 g pad of silica gel with methylene chloride, concentrating, and immediately purifying by PTLC (one-half of a 1000 μm plate, 50% ethyl acetate/hexanes). Alcohol **36a**: oil; R_f = 0.55 (50% ethyl acetate/hexanes); IR (neat) 3480 (broad), 3025, 1759, 1747, 1739 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.40 (s, 1H), 4.66 (m, 2H), 4.15 (s, 1H), 4.07 (s, 2H), 4.05 (d, J = 1.2 Hz, 2H), 2.33 (d, J = 15.6 Hz, 1H), 2.29 (m, 1H), 2.20 (dd, J = 2.2, 15.6 Hz, 1H), 2.04 (m, 1H), 1.98−1.82 (m, 2H), 1.64 (ddd, J = 2.4, 7.6, 13.2 Hz, 1H), 1.39 (m, 1H), 1.25 (dt, J = 3.8, 7.0 Hz, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 167.6 (2C's), 145.3, 139.4, 90.0, 70.0, 62.5, 43.3, 40.9, 40.7, 39.7, 37.2, 32.5, 29.8, 28.0, 27.8, 22.2, 18.6.

Freshly-standardized aqueous KOH (0.05 M, 5.08 mL, 0.252 mmol) was added dropwise to **36a** (98.6 mg, 0.2514 mmol) in THF (35 mL, containing ca. 0.5% BHT) at 0 °C. Within 15 min, the reaction was complete. Twenty milliliters of brine was added, and the reaction was extracted with ethyl acetate (4 × 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. PTLC (one-half of a 1000 μm plate, 60% ethyl acetate/hexanes) provided 77.6 mg (97% yield) of desired diol **37a**: clear oil; R_f = 0.21 (50% ethyl acetate/hexanes); IR (neat) 3475 (broad), 2950, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.40 (s, 1H), 4.40 (d, J = 2 Hz, 2H), 4.00 (m, 1H), 3.82 (m, 1H), 2.39 (d, J = 15.6 Hz, 1H), 2.50 (dd, J = 1.8, 15.6 Hz, 1H), 2.50−2.24 (m, 2H), 2.08 (ddd, J = 4.8, 9.6, 12 Hz, 1H), 1.96 (ddd, 3.0, 9.6, 12.6 Hz, 1H), 1.85 (m, 1H), 1.77−1.64 (m, 2H), 1.36 (m, 1H), 1.26 (t, 7.2 Hz, 1H), 1.09 (s, 3H), 1.01 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 167.6, 146.5, 138.2, 90.1, 71.8, 59.5, 43.6, 40.9, 40.7, 39.7, 33.1, 30.1, 28.5, 27.9, 22.2, 18.8. DCI-HRMS *m/e* calcd for $C_{16}H_{25}O_4Cl$ (M − H_2O): 298.1414, found 298.1412.

(1*R*,4*S*,7*R*)-1-(Chloroacetoxy)-2,3,4,5,6,7-hexahydro-4-(2-hydroxyethyl)-2,2,7-trimethyl-1*H*-inden-4-ol (37b). Conditions similar to that used for the conversion of **31a** to **37a** (167 mg, 0.543 mmol). Addition of slightly increased portion of $LiAlH_4$ (3.6 equiv) provided triol **35b** (118 mg, 87% conversion, 97% yield): $t_{1/2} \approx$ 3.2 days; oil; R_f = 0.02 (50% ethyl acetate/hexanes); IR (neat) 3350 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.07 (s, 1H), 3.96 (m, 1H), 3.76 (m, 1H), 2.79 (m-broad, 2H), 2.37 (d, J = 14.2 Hz, 1H), 2.37 (m, 1H), 2.20−2.04 (m, 3H), 2.10 (d, J = 14.2, 1H), 2.01 (m, 1H), 1.79−1.68 (m, 1H), 1.55 (td, J = 4.4, 14.8, 1H), 1.35 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 143.2, 140.9, 84.3, 71.9, 59.5, 43.3, 40.4, 39.7, 33.3, 28.0, 28.0, 27.2, 22.2, 17.9.

Acylation of triol **35b** (47.2 mg, 0.197 mmol) under the established conditions provided alcohol **36b** (76.1 mg, 98% yield): oil; R_f = 0.59 (50% ethyl acetate/hexanes); IR (neat) 3540 (broad), 3010, 1767, 1760, 1751 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.46 (s, 1H), 4.34 (t, J = 6.8 Hz, 2H), 4.14 (s, 1H), 4.07 (s, 2H), 4.06 (s, 2H), 2.45 (d, J = 15.8 Hz, 1H), 2.18 (m, 1H), 2.13 (d, J = 15.8 Hz, 1H), 2.04 (m, 1H), 1.95−1.81 (m, 2H), 1.64 (t, J = 9.4 Hz, 1H), 1.39 (m, 1H), 1.25 (dt, J = 4.2, 7.1 Hz, 1H), 1.13 (s, 3H), 1.02 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 167.7, 167.6, 143.9, 139.9, 87.4, 70.0, 62.4, 44.0, 40.8, 40.6, 40.1, 37.0, 32.9, 28.2, 27.6, 27.1, 22.5, 17.8.

Hydrolysis of alcohol **36b** (164 mg, 0.419 mmol) provided 117 mg (88% yield) of desired diol **37b**: oil; R_f = 0.21 (50% ethyl acetate/hexanes); IR (neat) 3380 (broad), 1750, 1731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.46 (s, 1H), 4.62 (s, 2H), 3.98 (m, 1H), 3.97 (m, 1H), 3.79 (m, 1H), 2.49 (td, J = 1.6, 15.6 Hz, 1H), 2.50 (d, J = 15.6 Hz, 1H), 2.04 (ddd, H = 4.8, 9.5, 14.3 Hz, 1H), 1.98−1.86 (m, 2H), 1.72 (m, 1H), 1.59 (ddd, J = 4.0, 4.8, 14.4 Hz, 1H), 1.33 (m, 1H), 1.17−0.84 (m, 2H), 1.12 (s, 3H), 1.02 (s, 3H), 0.96 (d, J = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 167.7, 145.1, 138.7, 87.6, 71.9, 59.4, 44.3, 40.8, 40.1, 39.5, 33.4, 28.3, 28.1, 27.4, 22.6, 18.1.

8,9-Deoxy-10-deoxo-12-noralliacolide (38) from 37a. Chloroacetoxy diol **37a** (28.3 mg, 0.0895 mmol), anhydrous magnesium sulfate (84.9 mg), and *N,N*-diisopropylethylamine (70.2 μL, 52.1 mg, 0.4027 mmol) were refluxed in degassed anhyd toluene (4.2 mL) for 24 h. Upon disappearance of starting material, the lightly yellow suspension was cooled to rt, filtered (the solids were washed with methylene chloride), and concentrated. Immediate PTLC (250 μm plate, 50% ethyl acetate/hexanes) and recrystallization from pentane provided a crystalline sample of **38** (16.9 mg, 85% yield): mp 88.5−90 °C (cubes); R_f = 0.61 (charred, eluted with 50% ethyl acetate/hexanes); IR ($CHCl_3$) 3620, 3440 (broad) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.50 (s, 1H), 3.84 (m, 2H), 2.60 (m, 1H), 2.12−1.97 (m, 3H), 1.91 (ddd, J = 3.7, 8.1, 11.9 Hz, 1H), 1.73 (m, 1H), 1.60 (s, 1H), 1.47 (m, 2H), 1.24−1.09 (m, 1H), 1.16 (d, J = 7.2 Hz, 3H, 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 141.8, 141.4, 111.7, 93.5, 62.7, 45.1, 41.7, 38.3, 30.2, 29.6, 27.8, 20.2. CI-HRMS *m/e* calcd for $C_{14}H_{22}O_2$ 222.1698, found 222.1655.

8,9-Deoxy-10-deoxo-12-noralliacolide (38) from 37b. Diol **37b** (8.1 mg, 0.0256 mmol) and HMPA (7.8 μL, 0.897 mmol) were dissolved in anhyd THF (3 mL). LDA (1.23 M in cyclohexane, 0.0210 mL, 0.0259 mmol) was added over 10 min at −78 °C, maintained for 2 h, and then warmed to rt. After 42 h at rt, saturated ammonium chloride (5 mL) was added, extracted with ether (4 × 40 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Immediate PTLC (100 μm plate, 50% ethyl acetate/hexanes) provided 5.1 mg (89% yield) of **38**. Spectral properties were identical in all respects to that produced from **37a**.

10-Deoxo-12-noralliacolide (40). *m*-Chloroperbenzoic acid (21.2 mg, 80% w/w, 0.0983 mmol) was added to a cooled solution (−78 °C) containing **38** (10.4 mg, 0.0468 mmol) and dry sodium bicarbonate (21.2 mg, 0.251 mmol) in anhyd methylene chloride (5.2 mL). The reaction was complete after gradual (over 2 h) warming to rt. Three drops of brine and a small amount of $MgSO_4$ were added sequentially. The result-

ing solution was filtered through a 10 g pad of silica gel (10 mL of CH_2Cl_2) and purified *via* PTLC (100 μm plate, 50% ethyl acetate/hexanes) to provide 10.9 mg (98% yield) of **40**: mp 71.5–73 °C (cubes); R_f = 0.59 (50% ethyl acetate/hexanes); IR ($CHCl_3$) 3480, 1463, 1442, 1380 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.83 (dd, J = 6.8, 8.0 Hz, 2H), 3.15 (s, 1H), 2.22 (s, 1H), 2.07–1.90 (m), 1.74 (m, 1H), 1.65 (m, 1H), 1.57 (m, 1H), 1.47 (m, 1H), 1.26 (m, 1H), 1.17 (d, J = 7.6 Hz, 3H), 1.10 (s, 3H), 1.09 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 88.6, 78.8, 69.6, 69.3, 63.5, 39.3, 38.3, 37.9, 32.1, 31.4, 25.6, 24.3, 24.0, 16.6.

(±)-12-Noralliacolide (4). Sodium bicarbonate (0.115 g, 1.36 mmol) and sodium metaperiodate (0.243 g, 1.14 mmol) were added sequentially to **40** (50.1 mg, 0.210 mmol) dissolved in carbon tetrachloride (0.54 mL), acetonitrile (0.54 mL), and water (0.54 mL). After 15 min of vigorous stirring, hydrated ruthenium trichloride (16.6 mg) was added, providing a yellow-white suspension. After 4 days, brine (5 mL) was added, and the mixture was extracted with methylene chloride (4 × 40 mL), dried ($MgSO_4$), and concentrated. PTLC (100 μm plate, 50% ethyl acetate/hexanes) provided 51.8 mg (98% yield) of **4**: mp 160–161 °C (stars); R_f = 0.43 (charred, eluted with 50% ethyl acetate/hexanes); IR ($CHCl_3$) 3500 (broad), 3030, 1768, 1470 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.23 (s, 1H), 2.79 (d, J = 17.4 Hz, 1H), 2.56 (d, J = 17.4 Hz, 1H), 2.00–1.82 (m, 5H), 1.98 (d, J = 14.2 Hz, 1H), 1.35–1.28 (m, 1H), 1.33 (d, J = 14.2 Hz, 1H), 1.16 (d, J = 7.2 Hz, 3H), 1.141 (s, 3H), 1.136 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 174.1, 94.6, 75.8, 69.1, 68.7, 43.1, 41.6, 39.0, 35.5, 31.6, 26.0, 24.4, 24.1, 18.2.

(±)-Alliacol A (2). Danishefsky's procedure was used with modification.[41] *n*-Butyllithium (2.75 M in hexanes, 0.57 mL, 1.59 mmol) was added to a solution of 2,2,6,6-tetramethylpiperidine (0.270 mL, 1.61 mmol) and anhyd THF (2.5 mL) at −20 °C. After stirring for 30 min, a solution of **4** (24.0 mg, 0.0953 mmol) in THF (0.7 mL) and HMPA (0.3 mL) was added over 20 min. The reaction mixture was stirred for 1.5 h with slow warming to 0 °C, after which, Eschenmoser's salt (0.353 g, 1.91 mmol) in anhyd THF (1.2 mL) was added at −40 °C. The reaction mixture was allowed to warm slowly to rt and stirred overnight. The solution was diluted with 10% HCl (5 mL) and ethyl acetate (15 mL), and the layers were separated. The aqueous layer was saved for further treatment. The combined organic layers were washed with saturated sodium bicarbonate (2 × 3 mL) and brine (3 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by PTLC (100 μm plate, 50% ethyl acetate/hexanes) to yield 15.3 mg of **2**.

Additional material was recovered by adding potassium carbonate to the initial acidic extract until slightly basic; extracting with ethyl acetate (3 × 10 mL) and concentrating produced a yellow oil. This crude material was refluxed overnight in 1,4-dioxane (0.7 mL) and methyl iodide (3.5 mL). The crude mixture was concentrated and partitioned between ethyl acetate (20 mL) and water (3 mL) containing sodium bicarbonate (~30 mg). The layers were separated, and the aqueous phase was further extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with saturated sodium sulfite solution (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Purification with PTLC (100 μm plate, 50% ethyl acetate/hexanes) yielded an additional 6.8 mg of **2** (total yield 22.1 mg, 88%): R_f = 0.53 (50% ethyl acetate/hexanes); IR ($CHCl_3$) 2951, 1761, 1260, 1125 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.36 (s, 1H), 5.90 (s, 1H), 3.19 (s, 1H), 1.88 (d, J = 14.1 Hz, 1H), 1.21 (d, J = 14.1 Hz, 1H), 1.13 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.09 (s, 3H); ^{13}C-NMR δ 168.8, 143.0, 124.7, 95.0, 76.7, 69.5, 67.2, 41.8, 39.3, 38.7, 31.6, 26.4, 24.5, 24.2, 19.4; CI-HRMS *m/e* calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1366.

(±)-Alliacolide (1). (±)-Alliacol A (**2**) (5.1 mg, 0.019 mmol) was shaken with 10% Pd-on-C (10 mg) in methanol (50 mL) under hydrogen (30 psi) for 2 h. The solvent was evaporated under reduced pressure, and the residue was purified by PTLC (100 μm plate, 50% ethyl acetate/hexanes) to give 4.6 mg (90%) of **1**. Recrystallization from methylene chloride and hexanes provided a pure sample: mp 191–192 °C; R_f = 0.53 (50% ethyl acetate/hexanes); IR ($CHCl_3$) 3000, 2950, 1775, 1502, 1417 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.22 (s, 1H), 2.69 (q, J = 7.5 Hz), 2.15 (s, 1H), 1.93 and 1.27 (d, J = 14 Hz, 2H), 1.16 (d, J = 7.5 Hz, 3H), 1.14 (d, J = 7.5 Hz, 3H), 1.10 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 176.6, 92.6, 69.0, 68.8, 45.3, 41.2, 38.8, 31.6, 28.5, 25.4, 24.4, 24.2, 17.3, 7.7; EI-MS *m/e* 266, 238, 211, 210, 193, 182, 151, 142, 134, 125.

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Supporting Information Available: Copies of relevant ^{1}H-NMR, ^{13}C-NMR, and COSY spectra of synthetic and natural alliacolide (**1**), alliacol A (**2**), **4**, **7**–**14**, **16**–**24**, **26**, **27**, **29**–**31**, **33**–**40** (68 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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