Studies on the Synthesis of Acanthodoral and Nanaimoal: Evaluation of Cationic Cyclization Routes

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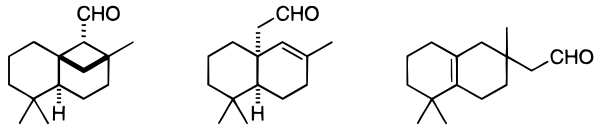
Intramolecular Lewis acid-promoted reactions of α,β-unsaturated ketone **6** and aldehydes **7** and **8** were examined as potential routes to acanthodoral (**1**), a structurally interesting natural product. Ketone **6** afforded ene product **22** exclusively, and both **7** and **8** gave mixtures of bicyclic aldehydes **3** and **26** and tricyclic aldehyde **25**. The latter most likely results from **7** by intramolecular cyclization of the alkene onto the Lewis acid-activated carbonyl moiety affording carbocation **31** followed by a 1,2-hydride shift and ring closure. Starting from **8**, tricyclic aldehyde **25** apparently forms by cyclization to cation **35** and ring closure to cyclobutane **36**, followed by ring opening to **31**, the same cation as formed in reactions of **7**. Nanaimoal (**3**) results from loss of H^+ from **31**, and bicyclic aldehyde **26** may be formed in a similar manner or by a concerted ene reaction. The configuration of **25** establishes that the stereochemistry of the initial cyclization to **31** precludes the possible use of this strategy for the synthesis of acanthodoral. However, acid-promoted cyclization of allylic alcohol **23** efficiently gives diene **29** which undergoes selective hydroboration/oxidation to afford nanaimoal.

Introduction

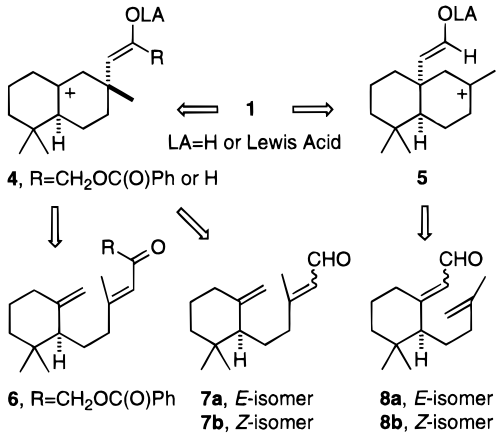
Acanthodoral (**1**), isoacanthodoral (**2**), and nanaimoal (**3**) are structurally interesting isomeric sesquiterpenoid aldehydes isolated from the nudibranch *Acanthodoris nanaimoensis*.[1a] A mixture of **1**−**3** isolated from the natural source exhibited antibacterial and antifungal activities.[1b] Our attention was drawn to **1** because of its unusual structure coupled with our interest in Lewis acid-promoted 2 + 2 cycloadditions as routes to functionalized cyclobutanes.[2] Indeed, a proposed biosynthesis suggests that aldehydes **2/3** may arise from **1**, formed presumably via some type of formal 2 + 2 process.[1] Herein we report our studies directed toward the preparation of **1** using a biogenetic approach exploring intramolecular Lewis or protic acid-promoted cycloadditions of alkenes with α,β-unsaturated aldehydes or α,β-benzoyloxyenones. In the course of these studies, a short synthesis of nanaimoal was also developed.[2,3]



1 **2** **3**

Our synthetic plan is shown in Scheme 1. Studies on Ti(IV)-mediated 2 + 2 cycloadditions of α′-alkoxy α,β-enones with alkenes[2,4] suggested that similar reactions of ketone **6** may produce a 2 + 2 product that could be converted to **1**. In addition, studies by Gassman and Lottes[5a] and Majetich[5c] on Lewis acid-promoted 2 + 2 cycloadditions of acrolein acetals and α,β-unsaturated

Scheme 1



enones with simple unactivated alkenes further suggested that treatment of aldehydes **7** and/or **8** with Lewis or protic acids may generate cations **4** or **5** which may then proceed on to **1**. The latter studies built on earlier work of Snider and others.[6,7] Ionic 2 + 2 cycloadditions of this type complement photochemical 2 + 2 processes which are usually not efficient due to rotational deactivation of the excited state of acyclic enones or enals.[8]

Results

A brief examination of intermolecular Lewis acid-promoted reactions of enones **9a**−**c** with methylenecyclohexane was undertaken as a feasibility study (Scheme 2). Promotion of reactions of methoxymethyl vinyl ketone

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) (a) Ayer, S. W.; Andersen, R. J.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1984**, *49*, 2653−2654. (b) Ayer, S. W. Ph.D. Thesis, the University of British Columbia, B.C., Canada, 1985. (c) Graziani, E. I.; Andersen, R. J. *J. Am. Chem. Soc.* **1996**, *118*, 4701−4702.

(2) (a) Engler, T. A.; Ali, M. H.; Vander Velde, D. *Tetrahedron Lett.* **1989**, *30*, 1761−1764.

(3) (a) For a previous synthesis of **2**, see: Liu, H.-J.; Ulíbarri, G.; Nelson, L. A. K. *J. Chem. Soc., Chem. Commun.* **1990**, 1419−1421. (b) For a previous synthesis of **3**, see: Ayer, S. W.; Hellou, J.; Tischler, M.; Andersen, R. J. *Tetrahedron Lett.* **1984**, *25*, 141−144.

(4) (a) Engler, T. A.; Combrink, K. D.; Letavic, M. A.; Lynch, K. O., Jr.; Ray, J. E. *J. Org. Chem.* **1994**, *59*, 6567−6587. (b) Engler, T. A.; Wei, D.; Letavic, M. A.; Combrink, K. D.; Reddy, J. P. *J. Org. Chem.* **1994**, *59*, 6588−6599. (c) Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068−5070.

(5) (a) Gassman, P. G.; Lottes, A. C. *Tetrahedron Lett.* **1992**, *33*, 157−160. See also: (b) Gassman, P. G.; Chavan, S. P.; Fertel, L. B. *Tetrahedron Lett.* **1990**, *31*, 6489−6492. (c) Majetich, G.; Khetani, V. *Tetrahedron Lett.* **1990**, *31*, 2243−2246. For a previous report of 2 + 2 cycloadditions of allyl cations with alkenes, see: (d) Klein, H.; Freyberger, G.; Mayr, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 49.

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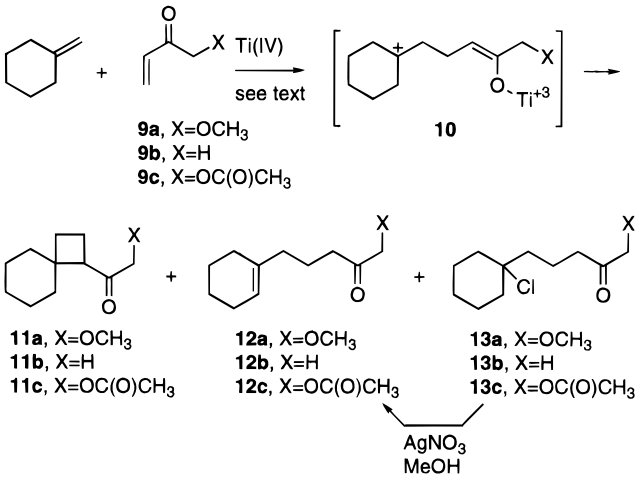
Scheme 2



(**9a**) with 2 equiv of Ti(IV), as a 1:1 mixture of $TiCl_4$:Ti(OiPr)$_4$,[4] at −78 °C followed by warming to −20 °C afforded ene product **12a** and chloro ketone **13a**,[9] in low yields (11−12% and 11−18%, respectively). Reactions of methyl vinyl ketone (**9b**) under the similar conditions were difficult to reproduce, however, and cyclobutane **11b** and ene product **12b** were found in very low yields (<10%), if at all. Reactions of acetoxymethyl vinyl ketone (**9c**) were more encouraging. With 2.5 equiv of Ti(IV), as a 1.9:1 mixture of $TiCl_4$:Ti(OiPr)$_4$, as promoter, cyclobutane **11c** was formed in 34% yield along with ene product **12c** in 45% yield. With $TiCl_4$ as promoter, small amounts of the desired cyclobutane **11c** (8%) were found, accompanied by chloroenone **13c** (62%) as the major product.

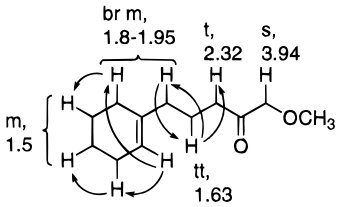


Figure 1. $^1H-^1H$ couplings from a COSY Experiment on **12a** (chemical shifts are in ppm).

The structure of cyclobutane **11c** was assigned from IR, NMR, and mass spectral data. The molecular ion indicated a 1:1 adduct, and lack of signals in the NMR attributable to an olefinic moiety is consistent with the structural assignment. The position of the C=C in ene product **12a** was established by a COSY experiment, the results of which are summarized in Figure 1; the structure of **12c** was assigned by spectral comparison to **12a**. The structures shown for chloro ketones **13a/c** are supported by MS and $^1H/^{13}C$ NMR data and by the conversion of **13c** to **12c** on treatment with $AgNO_3$/MeOH.

Formation of products **11/13** likely occurs via alkylation of the Ti(IV)-activated enone by the alkene[6] to give cation **10** followed by ring closure or reaction with chloride ion. Whether or not the ene products **12** originate directly from a concerted process, from cation **10** formed directly from the alkene and the enone, or from ring opening of initially formed cyclobutanes **11** to give **10** is not clear. The formation of ene product **12c** from **13c** on treatment with $AgNO_3$ indicates the possibility that cation **10** may be an intermediate to the ene products.

Although the yields of cyclobutane products from the model experiments described above were modest, we reasoned that intramolecular variants might be more successful and our attention turned to a study of reactions of **6**−**8**. Lewis acid-promoted reactions of (benzoyloxy)methyl enone **6** were examined initially. Enone **6** was prepared as shown in Scheme 3. Preparation of α-(phenylsulfoxy) keto esters **14a/15a**, as mixtures of diastereomers, was accomplished by the method of Leyendecker [treatment of 3-methyl-2-cyclohexenone with $LiCu(CH_3)_2$ and reaction of the resulting enolate with methyl or ethyl α-(phenylsulfinyl)acrylate][10] and reduction with Raney nickel or aluminum amalgam gave keto esters **14b/15b**, respectively. Chemoselective methyl-

(6) (a) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872−5880. (b) Snider, B. B.; Deutsch, E. A. *J. Org. Chem.* **1983**, *48*, 1822−1829. (c) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1981**, *46*, 2563−2566. For an early example, see: (d) Büchi, G.; Koller, E.; Perry, C. W. *J. Am. Chem. Soc.* **1964**, *86*, 5646−5654. For early reports of intramolecular addition of alkenes to Lewis acid-activated carbonyl compounds, see: (e) Stork, G.; Burgstahler, A. *J. Am. Chem. Soc.* **1951** *73*, 3544−3546. (f) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, *91*, 2371−2373. (g) Corey, E. J.; Balanson, R. D. *Tetrahedron Lett.* **1973**, 3153−3156. (h) Naegeli, P. *Tetrahedron Lett.* **1978**, *24*, 2127−2130. (i) Cookson, R. C.; Smith, S. A. *J. Chem. Soc., Chem. Commun.* **1979**, 145−146. (j) Naegeli, P.; Wetli, M. *Tetrahedron* **1981**, *37*, Supplement No. 1, 247−255. (k) Baldwin, J. E.; Lusch, M. J. *J. Org. Chem.* **1979**, *44*, 1923−1927.

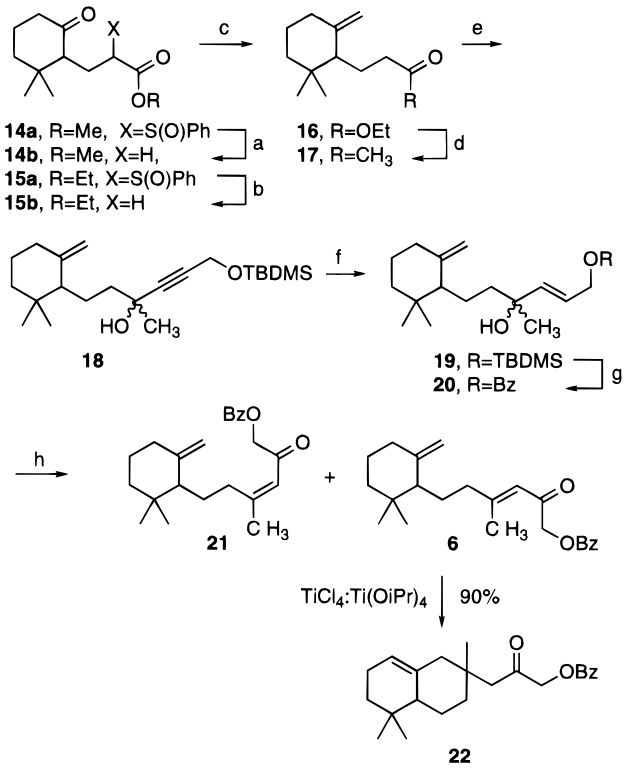
(7) Lewis acid-promoted 2 + 2 cycloaddition reactions of allenes and alkynes with alkenes have been more extensively explored. (a) Snider, B. B. *J. Org. Chem.* **1976**, *41*, 3061−3062. (b) Lukas, J. H.; Baardman, F.; Kouwenhoven, A. P. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 369−370. (c) Snider, B. B.; Brown, L. A.; Conn, R. S. E.; Killinger, T. A. *Tetrahedron Lett.* **1977**, 2831−2834. (d) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283−5293. (e) Fienemann, H.; Hoffmann, H. M. R. *J. Org. Chem.* **1979**, *44*, 2802−2803. (f) Snider, B. B.; Roush, D. M. *J. Am. Chem. Soc.* **1979**, *101*, 1906−1907. (g) Snider, B. B.; Roush, D. M.; Rodini, D. J.; Gonzalez, D.; Spindell, D. *J. Org. Chem.* **1980**, *45*, 2773−2785. (h) Snider, B. B.; Kirk, T. C.; Roush, D. M.; Gonzalez, D. *J. Org. Chem.* **1980**, *45*, 5015−5017. (i) Snider, B. B.; Spindell, D. K. *J. Org. Chem.* **1980**, *45*, 5017−5020. (j) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 2735−2738. (k) Hoffmann, H. M. R.; Ismail, Z. M.; Weber, A. *Tetrahedron Lett.* **1981**, *22*, 1953−1956. (l) Rosenblum, M.; Scheck, D. *Organometallics* **1982**, *1*, 397−400. (m) Fadel, A.; Salaün, J.; Conia, J. M. *Tetrahedron* **1983**, *39*, 1567−1573. (n) Snider, B. B.; Ron, E. *J. Org. Chem.* **1986**, *51*, 3643−3652. (o) Jenner, G.; Papadopoulos, M. *Tetrahedron Lett.* **1996**, *37*, 1417−1420. Lewis acid-promoted cycloaddition reactions of electron-rich alkenes with electron-deficient alkenes have been well-documented; for selected examples, see: (p) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248−255. (q) McCulloch, A. W.; McInnes, A. G. *Tetrahedron Lett.* **1979**, 1963−1966. (r) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 747−759. (s) Takeda, T.; Fujii, T.; Morita, K.; Fujiwara, T. *Chem. Lett.* **1986**, 1311−1314. (t) Quendo, A.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 6443−6446. (u) Fétizon, M.; Goulaouic, P.; Hanna, I.; Prange, T. *J. Org. Chem.* **1988**, *53*, 5672−5679. (v) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Bal Reddy, K. *Tetrahedron Lett.* **1987**, *28*, 1501−1504. (w) Ichikawa, Y.-i.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919−1921. (x) Narasaka, K.; Kusama, H.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1471−1478. (y) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869−8885. (z) Hojo, M.; Tomita, K.; Hirohara, Y.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 8123−8126. (aa) Monti, H.; Audran, G.; Léandri, G.; Monti, J.-P. *Tetrahedron Lett.* **1994**, *35*, 3073−3076.

(8) For reviews of photochemical 2 + 2 cycloadditions, see: (a) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453−1473. (b) Baldwin, S. W. In *Organic Photochemistry*; Padwa, A., Ed.; Dekker: New York, 1981: Vol. 5, pp 123−225. (c) Wender, P. A. In *Photochemistry in Organic Synthesis*; Coyle, J. D., Ed.; The Royal Society of Chemistry: London, 1986; pp 163−188

(9) Initially, compound **13b** was mistakenly identified as the desired cyclobutane product **11b**.[2] Unfortunately, all attempts to isolate the latter product have failed despite considerable effort in which the ratio and equivalents of $TiCl_4$:Ti(OiPr)$_4$ and reaction temperature were varied.

(10) (a) Leyendecker, F.; Comte, M.-T. *Tetrahedron* **1986**, *42*, 1413−1421. (b) Leyendecker, F.; Comte, M.-T. *Tetrahedron* **1987**, *43*, 85−92. (c) Leyendecker, F.; Comte, M.-T. *Tetrahedron Lett.* **1982**, *23*, 5031−5034.

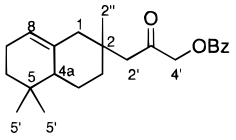
Scheme 3[a]



[a] (a) Al(Hg)/H_2O, 74%. (b) Al(Hg)/H_2O, 75% or RaNi/H_2O, 98%. (c) $TiCl_4$/Zn/CH_2Br_2, 71%. (d) i. $LiAlH_4$, 98%; ii. DMSO/ClC(O)-C(O)Cl, Et_3N, 96%; iii. MeMgCl, 100%; iv. DMSO/ClC(O)C(O)Cl, Et_3N, 98%. (e) LiC≡$CCH_2OTBDMS$, 100%. (f) Red-Al/H_3O^+, 94%. (g) $Bu_4N^+F^-$/PhC(O)Cl, DMAP, 97%. (h) PCC, 67%.

enylation of the ketone carbonyl in **15b** was effected with the Nozaki−Lombardo reagent,[11] and the product **16** was converted to ketone **17** in 92% overall yield by the sequence shown. Enone **6** then resulted from ketone **17** by the following sequence. Addition of lithium [(*tert*-butyldimethylsilyloxy)methyl]acetylide gave alcohol **18** as an *ca.* 1:1 mixture of diastereomers (by ^{13}C NMR), and hydroalumination of this mixture followed by protonation of the resultant alkenylaluminum species gave trans allylic alcohol **19**, again as a mixture of diastereomers. Fluoride-mediated desilylation of **19** and treatment with benzoyl chloride/DMAP gave benzoates **20**. Finally, PCC oxidation of the mixture produced a 4:1 mixture of enones **6** and **21**, respectively, in 67% yield, and the major isomer was separated by flash chromatography.[12]

Treatment of **6** with excess amounts (4 equiv) of Ti(IV), initially as a 1:1 mixture of $TiCl_4$:$Ti(OiPr)_4$, followed by additional $TiCl_4$ to complete the reaction, resulted only in ene product **22** in 90% yield; no other products were detected by carefully monitoring the reactions by TLC. Use of lesser amounts of Ti(IV), i.e., 1 equiv of $TiCl_4$ or 1.5 equiv of a 3:1 mixture of $TiCl_4$:$Ti(OiPr)_4$, failed to give any products; other Lewis acids were not examined. The position of the carbon−carbon double bond in **22** was established by $^1H-^1H$ decoupling, HETCOR, and HMBC NMR experiments. Thus, the hydrogens attached to C-2′ appeared as two doublets at 2.38 and 2.30 ppm (J = 15 Hz) in the ^1H NMR spectrum, and the C-2′ resonance was assigned by a HETCOR experiment. An HMBC experiment (Figure 2) then revealed coupling between the hydrogens attached to C-2′ and four sp^3 carbons. Similarly, the C-2″ methyl hydrogens were coupled to four sp^3 carbons. Other notable $^2J/^3J$ C−H couplings are also shown in Figure 2; that the methine carbon is coupled to the hydrogens of the *gem*-dimethyl substituents and the C-1 hydrogens indicated with certainty the position of the C=C. Unfortunately, we have been unable to obtain X-ray quality crystals of **22** or a derivative, which has prevented assignment of the relative stereochemistry of the two stereogenic centers.



C-2"	28.5	C-4a	47.1	H-2"	1.08	H-2'	2.30/2.38
C-5'	24.6/28.5	C-1	48.8	H-4a	1.58	H-8	5.36
C-2	35.8	C-8	121	H-1	1.85/2.12	H-4'	4.82
C-3	37.8	C-8a	137	H-7	1.95		(ABq, J=17)
C-2'	43.5	C-4'	69.7				

Chemical shifts (ppm) of selected ^1H and ^{13}C signals.

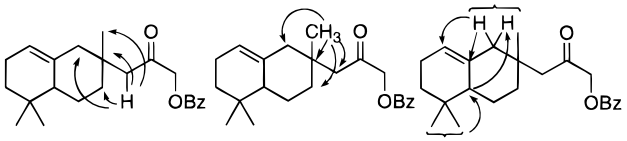
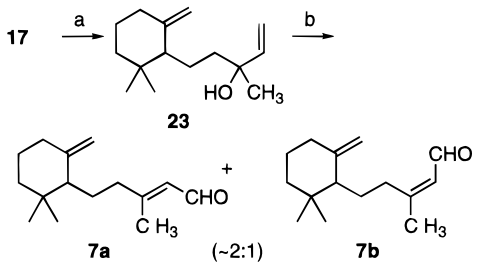


Figure 2. Summary of HMBC NMR data on **22**.

Scheme 4[a]

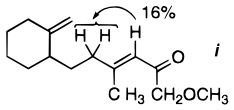


[a] (a) CH_2=CHMgBr, 100%. (b) PCC, 92%.

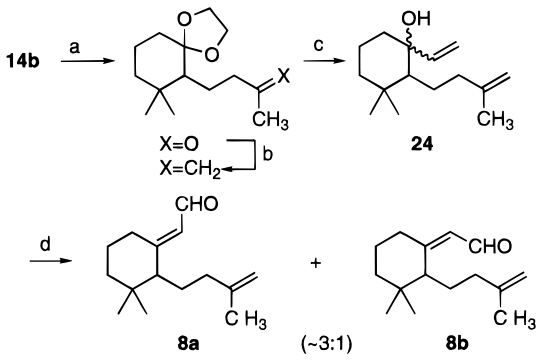
The syntheses of aldehydes **7/8** are shown in Schemes 4 and 5. Addition of vinylmagnesium bromide to ketone **17** followed by PCC oxidation gave an *ca.*2:1 mixture of aldehydes **7a/7b**, respectively, in 92% yield. In this sequence, compound **23** was found and used as a mixture of diastereomers, and the final aldehydes **7a/b** were separated by careful flash chromatography. Aldehydes **8** were prepared from keto ester **14b** in 38% overall yield by a straightforward sequence involving (i) ketalization, (ii) $LiAlH_4$ reduction, (ii) perruthenate oxidation, (iii) methyl Grignard addition, (iv) a second perruthenate oxidation, (v) Wittig methylenylation, (vi) deketalization, and (vii) addition of vinylmagnesium bromide followed by (viii) PCC oxidation. Again, in this sequence, compound **24** and intermediates leading to it were handled as mixtures of diastereomers (*ca.* 1:1), and aldehydes

(11) Lombardo, L. *Org. Synth.* **1987**, *65*, 81−89.

(12) The stereochemistry in **6** was assigned on the basis of a comparison of its $^1H/^{13}C$ NMR spectra with those of *i*, a compound prepared in our lab in connection with a related project (Ali, M. H, Ph.D. Dissertation, University of Kansas, 1993). The stereochemistry in *i* was established by a $^1H-^1H$ NOE experiment, the results of which are shown.



Scheme 5[a]



[a] (a) i. $HOCH_2CH_2OH$/[pTsOH], 86%; ii. $LiAlH_4$, 90%; iii. $(Pr_4N)RuO_4$, 100%; iv. MeMgI, 100%; v. $(Pr_4N)RuO_4$, 100%. (b) Ph_3PCH_2, 94%. (c) i. [pTsOH]/H_2O, 91%; ii. CH_2=$CHMgBr$, 100%. (d) PCC, 58%.

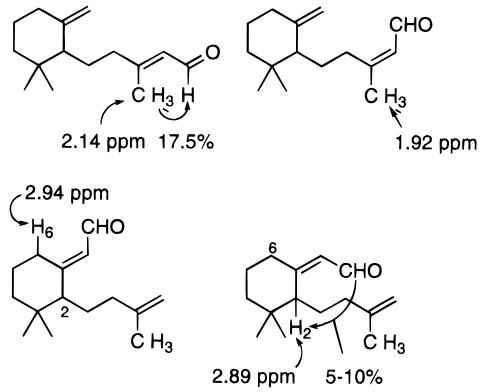


Figure 3. Summary of selected $^1H-^1H$ NMR data on **7/8** and NOE data on **7a/8b**.

8a/b (*ca.* 3:1) could be separated by careful flash chromatography. The double-bond geometry in aldehydes **7** and **8** was determined by data from $^1H-^1H$ NMR experiments (Figure 3). NOE experiments clearly established the (*E*)-geometry in **7a** and **8b**. In addition, the β-methyl group of the enal moiety in **7a** and **7b** appears at 2.14 and 1.92 ppm, respectively, in their ^1H NMR spectra due to deshielding by the proximal aldehyde carbonyl group. A similar deshielding effect is evident in the ^1H NMR spectra of aldehydes **8** in which a ddd (J = 13, 4, 4 Hz; gem/ax-eq/eq-eq) appears at ca. 2.94 ppm in the spectrum of **8a** and a dd (J = 11, 3 Hz) at ca. 2.89 ppm in that of **8b**. These signals are assigned to the equatorial hydrogens at positions 6 and 2, respectively. Deshielding of H-2 in **8b** suggests that the major conformer has this hydrogen in an equatorial position to avoid $A^{(1,3)}$ strain between the aldehyde and the isopentenyl side chain.

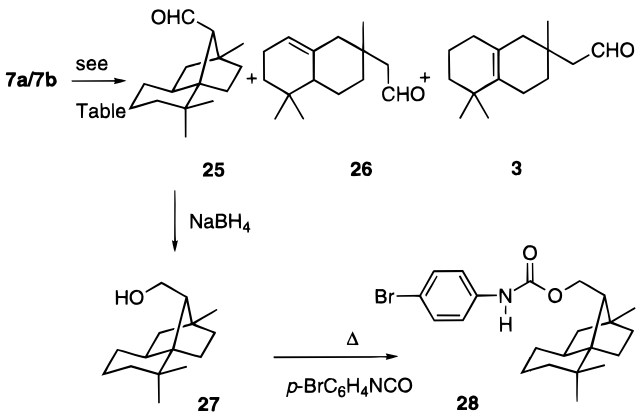
Results of Lewis acid-promoted reactions of **7a/b** are presented in Table 1. Reactions of **7a**, **7b**, or *ca.* 1:1 mixtures of the two produced the same three products **25**, **26**, and **3**, accompanied by small amounts other unidentified olefinic products (Scheme 6). The ratio of the three products varied somewhat with the Lewis acid employed; the best material balance was found with a 1:1 mixture of $B(OMe)_3$:BCl_3 as promoter (2 equiv of boron with respect to starting aldehyde). In these reactions, isomerization of **7a** to **7b** was found to occur by quenching reactions of pure **7a** before completion and recovering mixtures of **7a/b** along with the products. Similarly, in reactions starting from pure **7b**, the presence of isomer **7a** could be detected by TLC during the course of the reaction.

Table 1. Lewis Acid-Promoted Reactions of 7a/7b

aldehyde (ratio)	Lewis acid (equiv/ratio)[a]	temp (°C)	% yields **25**[b]	% yields **3/26**[c] (ratio)[d]
7a/7b (2:3)	$B(OMe)_3$:BCl_3 (1:1)	−78	44	47 (1:2)
7a	BCl_3 (1)	−78	28	39 (1:3)
7b	$B(OMe)_3$:BCl_3 (1.5:0.5)	−78	44	46 (1:2)
7a or **7a/b**	$B(OMe)_3$ (1)	−78	no reaction	
7a	$TiCl_4$:$Ti(OiPr)_4$ (1:0.5)	−78 → 0	18	28 (1:2)
7a	$SnCl_4$ (0.8)	−78 → −20	21	41 (1:2)
7a	$BF_3{\cdot}Et_2O$ (0.5)	−78 → −20	8	56 (1:2)
7a	$BF_3{\cdot}Et_2O$ (2)	−78 → −20	18	43 (2:3)

[a] With respect to aldehyde **7**. [b] Isolated yield. [c] Combined yield, see text. [d] By ^1H NMR.

Scheme 6



Aldehyde **25** was isolated cleanly from the reaction mixtures. Unfortunately, its 500 MHz ^1H NMR spectrum was not sufficiently resolved to identify key resonances and multiplicities necessary to distinguish it from acanthodoral (**1**) or other possible isomers; indeed, the available spectral data (^1H/^{13}C NMR, IR, mass) were consistent with those expected for acanthodoral. At first, we surmised that alkene−aldehyde products **3/26** might have been produced by subsequent acid-catalyzed ring opening of initially formed acanthodoral and that the crude reaction mixture was a combination of the three. However, attempts to effect conversion of product **25** to **3** or **26** by treatment with protic or Lewis acids failed; it was inert. The structure of **25** was ultimately determined with certainty by $NaBH_4$ reduction and conversion of the resultant alcohol **27** to urethane **28**. Single-crystal X-ray analysis revealed its tricyclic structure,[13] which apparently results from a cyclization/rearrangement sequence (see below).

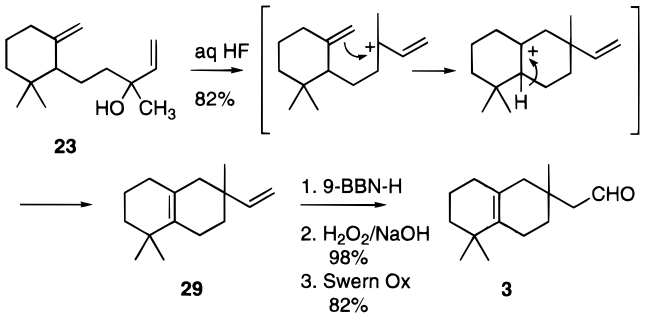
Separation of bicyclic aldehyde products **3** and **26** proved difficult. Preparative GC afforded pure **3**; however, **26** could not be obtained free of impurities. NMR spectral data of aldehyde **3** were identical to those of nanaimoal[14] which was independently synthesized from allylic alcohol **23** in 67% overall yield via acid-catalyzed cyclization to bicyclic diene **29** followed by hydroboration/oxidation (Scheme 7).

Because aldehyde **26** could not be obtained pure, its structural assignment should be regarded as tentative. However, the structure shown is consistent with NMR

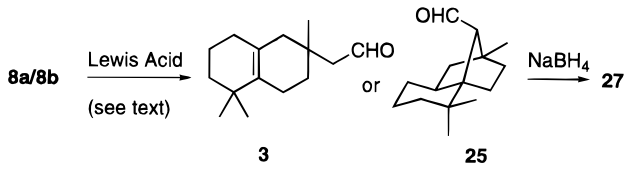
(13) The authors have deposited coordinates for structure **28** with the Cambridge Data Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Data Centre, University Chemical Lab, Lensfield Road, Cambridge, CB2 1EZ, U.K.

(14) We thank Professor R. J. Andersen of The University of British Columbia for copies of ^1H NMR spectra of nanaimoal.

Scheme 7



Scheme 8



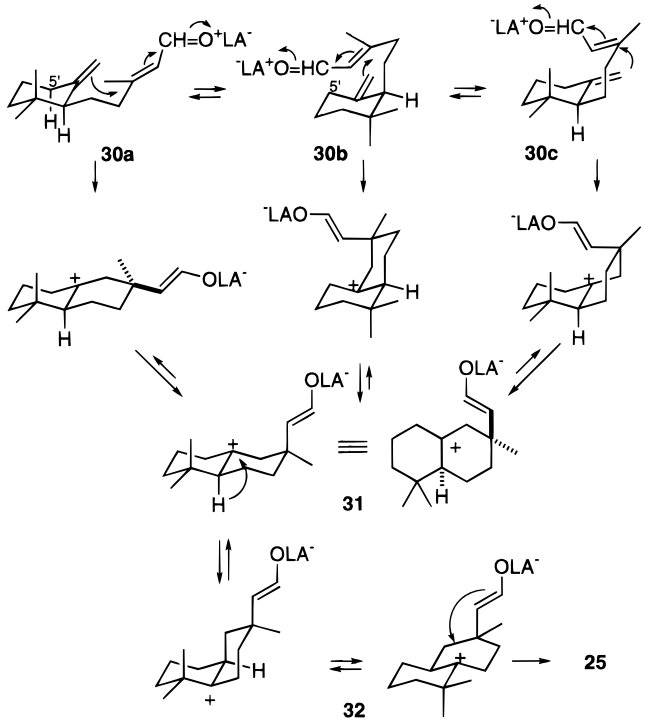
data and is further supported by comparison of its $^{1}H/^{13}C$ NMR spectra to those of the ene product **22**, which show a number of similar features (see Supporting Information). Although formed as a single diastereomer, the relative stereochemistry in **26** was not assigned.

Studies of Lewis acid-promoted reactions of aldehydes **8a/b** were quite interesting and limited to only a few examples, for reasons discussed below. Treatment with BCl_3:$B(OMe)_3$ gave nanaimoal as a major product (20%, Scheme 8) accompanied by recovered starting aldehyde **8a** (28%) and its isomer **8b** (12%), again indicating that the former isomerizes under the reaction conditions as found with aldehydes **7**. Remarkably, reaction of **8a** with $TiCl_4$ at −85 °C and treatment of the crude reaction mixture directly with $NaBH_4$ gave tricyclic alcohol **27** in 55% yield; *the same product as found in treatment of aldehydes* **7** *with Lewis acids followed by reduction of the products*. Alcohol **27** was also found in 23% yield upon treatment with 2.5:1 mixture of aldehydes **8a/b** with a mixture of $TiCl_4$:$Ti(OiPr)_4$ followed by $NaBH_4$ reduction. In the latter reactions, unidentified ene products were also produced in minor amounts. Because the formation of **27** in these reactions was surprising, its structure was again determined by conversion to a *p*-bromourethane derivative; single-crystal X-ray analysis once more revealed structure **28**.

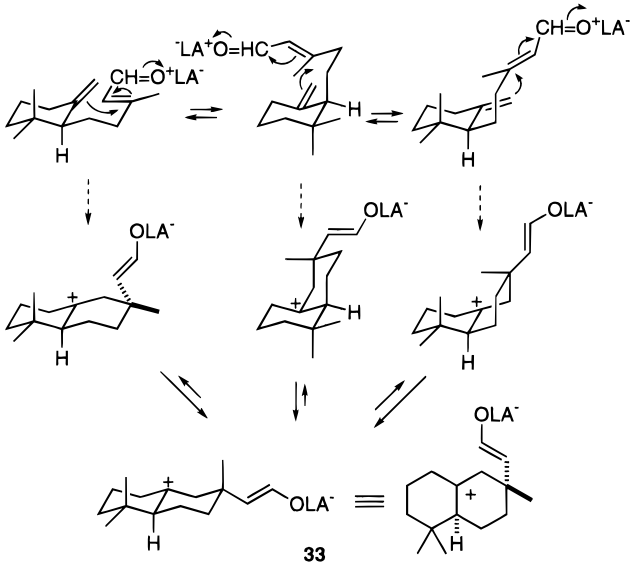
Discussion

The formation of tricyclic aldehyde **25** from *both* enals **7** and **8** was unexpected and indicated a common intermediate, produced presumably through rearrrangement processes. An analysis of possible routes from **7** is shown in Scheme 9. A likely first step is an intramolecular alkylation of the Lewis acid-activated enal moiety in **30** by the carbon−carbon π bond which results in 3° cation **31**.[6] A subsequent 1,2-hydrogen shift produces a second 3° carbocation **32** which undergoes ring closure to tricyclic aldehyde **25**. Interconversion of carbocations **31** and **32** is reasonable since both are 3° carbocations likely to be similar in energy, and a faster rate of 5-membered ring formation than 4-membered ring closure accounts for the formation of **25**. It is conceivable that a cyclobutane carboxaldehyde product might be formed from **31**, but if so, such an intermediate reverts to **31** under the reaction conditions.[6a]

Scheme 9

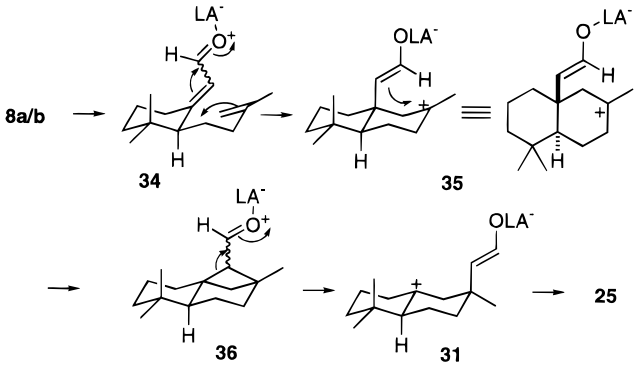


Scheme 10

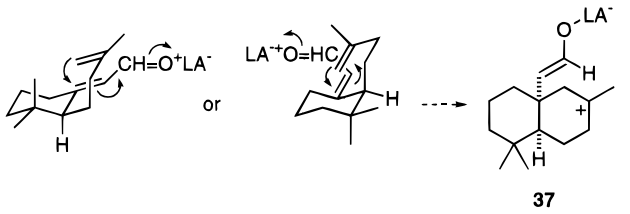


However, the stereochemistry of carbocations **31/32** suggests that the initial alkylation proceeds via a conformation which is not suitable for the production of acanthodoral. Likely conformations for this step are **30a**−**c**. Other possible conformations would lead to the stereoisomeric carbocation **33** (Scheme 10), and it is not obvious how product **25** would result from such an intermediate (although a deprotonation−protonation sequence is conceivable). Of conformations **30a**−**c**, the latter can probably be ruled out because of a relatively highly strained syn-pentane orientation of the enal side chain with respect to the axial methyl group. It is not clear which of the other two gives rise to a lower energy pathway to **31**. Conformer **30a** suffers from a type of $A^{(1,3)}$ strain,[15] two gauche interactions between the enal side chain and the *gem*-dimethyl substituents,[17] and a steric interaction between the β-methyl group of the side chain and the C-5′ axial hydrogen on the ring. On the other

Scheme 11



Scheme 12



hand, **30b** incorporates one less gauche interaction, but an added axial substituent as well as a steric interaction between the enal side chain and the axial C-5′ hydrogen. Both are probably energetically accessible, and the Curtin−Hammett Principle does not allow for a confident prediction of the relative energies between transition states emanating from **30a/b**.

The rationale for studying reactions of enal **8** was that should intramolecular alkylation of the Lewis acid-activated enal moiety by the C=C occur, as apparently occurs in reactions of **7**, then the resultant 3° carbocation should be less prone to 1,2-hydride shifts since such a process could only produce a less stable 2° carbocation intermediate. However, the formation of tricyclic aldehyde **25** suggests the route shown in Scheme 11. Alkylation of the Lewis acid-activated enal moiety in **34** by the carbon−carbon π bond produces 3° carbocation **35**. Ring closure to cyclobutane **36** followed by Lewis acid-promoted ring opening[6a] provides cation **31**, *the same cation formed in reactions of* **7**, which then proceeds on to **25** as discussed previously. Cation **35** again apparently arises via a conformation (**34**) unsuitable for the production of acanthodoral; note that **36** is a stereoisomer of acanthodoral. Other possible conformations for this step would lead to diastereomeric carbocation **37** (Scheme 12), from which it is again not apparent how **25** would be formed.

Formation of nanaimoal from aldehydes **7** or **8** may occur via loss of H^+ from cations **31/32** or also possibly **33/37**. If the latter are formed, however, they apparently do not close to acanthodoral (**1**) or if they do, reversion/conversion to **33** occurs under the reaction conditions. Finally, formation of aldehyde **26** from **7** may also result from cation **31**, or an intramolecular ene reaction; ene product **22** may be formed in a similar manner from ketone **6**. Since we have been unable to assign the relative stereochemistry in **22/26**, it is not possible to determine which of the various pathways lead to them at this time.

Thus, a stepwise 2 + 2 process is apparently occurring in reactions of **8** and may also be involved in those of **7**, but the stereochemistry of the initial alkylations to produce cation intermediates **31/35** suggests that these approaches are not practical for synthesis of acanthodoral, or isoacanthodoral. A new approach is planned.

Experimental Section[18]

Enones **9a/c** were prepared by literature methods.[19] Because of their largely routine nature, experimental details for the preparation of **6**, **7a/b**, and **8a/b** are included in the Supporting Information.

Titanium(IV)-Catalyzed Reaction of Methylenecyclohexane with Methoxymethyl Vinyl Ketone (9a). $TiCl_4$ (0.24 mL, 2.20 mmol) was added to a solution of $Ti(OiPr)_4$ (0.66 mL, 2.20 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 5 min, the mixture was cooled to −78 °C and ketone **9a** (218 mg, 2.18 mmol) was added, producing a bright yellow solution. After 15 min, methylenecyclohexane (215 mg, 2.23 mmol) was added and the reaction mixture was stirred for 3 h at −78 °C. The mixture was then warmed to −20 °C and allowed to stand for 16 h. Solid sodium bicarbonate (ca. 1 g) was added followed by 2-propanol (2 mL). The mixture was poured into saturated aqueous sodium bicarbonate and the resultant mixture extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried (K_2CO_3), and filtered. Concentration of the filtrate provided a light yellow oil, and flash chromatography with 15% EtOAc/hexane as eluent produced products **12a** (57 mg, 13%) and **13a** (57 mg, 11%), both as colorless oils.

Physical and spectral data for **12a:** R_f 0.41 (20% EtOAc/hexane); ^{1}H NMR (300 MHz) 1.5−1.6 (m, 4H), 1.71 (dt, J = 7, 2, 2H), 1.8−1.95 (m, 6H), 2.40 (t, J = 7.2, 2H), 3.42 (s, 3H), 4.00 (s, 2H), 5.32 (br s, 1H); ^{13}C NMR (75 MHz) 21.15, 22.46, 22.89, 25.19, 27.97, 37.33, 38.14, 59.26, 77.60, 121.77, 136.76, 208.64; HRMS 196.1453 (calcd for $C_{12}H_{20}O_2$, 196.1463).

Physical and spectral data for **13a:** R_f 0.31 (20% EtOAc/hexane); ^{1}H NMR (300 MHz) 1.18−1.20 (m, 1H), 1.5−1.90 (m, 13H), 2.48 (t, J = 7, 2H), 3.42 (s, 3H), 4.02 (s, 2H); ^{13}C NMR (75 MHz) 17.69, 22.25, 25.39, 38.67, 39.56, 44.52, 59.27, 75.61, 77.59, 208.30; HRMS 196.1465 [calcd for $C_{12}H_{20}O_2$ (M^+ − HCl), 196.1462].

Titanium(IV)-Catalyzed Reactions of Methylenecyclohexane with Acetoxymethyl Vinyl Ketone (9c). $TiCl_4$ (0.14 mL, 1.27 mmol) was added to a solution of $Ti(OiPr)_4$ (0.20

(15) The ΔG for interconversion of chair conformers of 2-methylmethylenecyclohexane is *ca.* 1.0 kcal/mol versus 1.7−1.8 kcal/mol for methylcyclohexane, indicating $A^{(1,3)}$ strain in the former raises the energy of the equatorial conformer by *ca.* 0.7 kcal/mol.[16] In conformer **30a**, however, greater $A^{(1,3)}$ strain is expected because of the way the enal appendage must fold for reaction with the exo-methylene moiety.

(16) Lessard, J.; Tan, P. V. M.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015−1023.

(17) However, the cumulative effect of two gauche interactions of this type are not additive; it is less than expected, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 705.

(18) All compounds were prepared as racemic mixtures. All experiments were carried out in oven- or flame-dried glassware, under a positive pressure of dry nitrogen or argon and were magnetically stirred, unless otherwise noted. All solvents and reagents were distilled from appropriate drying agents before use. Samples for NMR were dissolved in $CDCl_3$, and chemical shifts are expressed as ppm (δ) relative to tetramethylsilane, residual $CHCl_3$, or $CDCl_3$ as internal standards. Samples for NOE experiments were degassed by freeze−thaw techniques under a nitrogen atmosphere immediately before the experiments. Chromatographic separations were carried out either by flash chromatography using MN-Kieselgel 60 silica gel (0.04−0.063 mm mesh size) or by PCTLC (preparative centrifugal thin-layer chromatography) with silica gel (Merck no. 7749) on a Chromatotron Model 7924T. Analytical thin-layer chromatography was done on precoated silica gel plates with a 254 nm fluorescent indicator (Merck no. 5715) and developed in the indicated solvent systems. Compounds were visualized under a UV lamp and/or by staining with either *p*-anisaldehyde/sulfuric acid or phosphomolybdic acid solutions. R_f's refer to TLC experiments. GC analyses were obtained on a 25 m × 0.22 mm BP20 capillary column from Scientific Glass Engineering. Preparative GC was done on a 6 ft × $^1/_4$ in. Carbowax or FFAP column.

(19) (a) Hennion, G. F.; Kupiecki, F. P. *J. Org. Chem.* **1953**, *18*, 1601−1609. (b) Wenkert, E.; Golob, N. F.; Sathe, S. S.; Smith, R. A. J. *Synth. Commun.* **1973**, *3*, 205−209.

mL, 0.67 mmol) in CH_2Cl_2 (10 mL) at −35 °C. After 15 min, the reaction mixture was cooled to −78 °C and ketone **9c** (100 mg, 0.78 mmol) was added, producing a bright orange solution. After 30 min, methylenecyclohexane (100 mg, 1.04 mmol) was added. The reaction mixture was stirred for 0.5 h at −78 °C, and solid sodium bicarbonate (about 1 g) followed by 2-propanol (2 mL) was then added. Workup as described in the previous experiment produced a yellow oil. Flash chromatography with 20% EtOAc/hexane as eluent produced compound **11c** (60 mg, 34%) and compound **12c** (79 mg, 45%).

Spectral and physical data for **11c**: R_f(50% ether/hexane) 0.5; ^{1}H NMR (500 MHz) 1.10−1.20 (m, 2H), 1.21−1.35 (m, 2H), 1.50−1.82 (m, 9H), 2.17 (s, 3H), 2.33−2.42 (m, 1H), 2.94 (dd, J = 8, 8, 1H), 4.59 (ABq, J = 17, 2H); ^{13}C NMR (75 MHz) 15.61, 20.54, 21.88, 22.77, 25.74, 28.77, 31.85, 40.34, 45.27, 51.37, 68.76, 170.19, 203.15; HRMS 224.1405 (calcd for $C_{13}H_{20}O_3$, 224.1412).

Spectral and physical data for compound **12c**: R_f(50% ether/hexane) 0.45; ^{1}H NMR (500 MHz) 1.50−1.65 (m, 4H), 1.68−1.76 (dt, J = 11, 2H), 1.85−2.00 (m, 6H), 2.17 (s, 3H), 2.37 (dd, J = 8, 8, 2H), 4.64 (s, 2H), 5.39 (br s, 1H); ^{13}C NMR (75 MHz) 20.53, 21.07, 22.48, 22.91, 25.22, 27.96, 37.23, 38.08, 67.99, 122.02, 136.62, 171.20, 203.91; HRMS 225.1462 (M^+ + 1) [calcd for $C_{13}H_{21}O_3$, 225.1490].

In another experiment, ketone **9c** (162 mg, 1.26 mmol) was added to a solution of $TiCl_4$ (0.125 mL, 1.14 mmol) in CH_2Cl_2 (20 mL) at −78 °C to produce a bright red solution. After 15 min, methylenecyclohexane (114 mg, 1.19 mmol) was added. The reaction mixture was stirred for 45 min and worked up as described above to produce a yellow oil. PCTLC using 10% EtOAc/hexane as eluent produced compound **11c** (20 mg, 8%), compound **13c** (186 mg, 62%), and unreacted enone (14 mg) as clear liquids.

Spectral data for **13c**: ^{1}H NMR (300 MHz) 1.10−1.22 (m, 1H), 1.40−1.90 (m, 13H), 2.10 (s, 3H), 2.41 (dd, J = 7, 7, 2H), 4.59 (s, 2H); ^{13}C NMR (75 MHz) 17.47, 20.26, 22.07, 25.23, 38.41, 39.89, 44.23, 67.77, 75.41, 170.00, 203.38; HRMS 261.1265 (M^+ + 1) [calcd for $C_{13}H_{22}O_3Cl$, 261.1257].

Reaction of 13c with Silver Nitrate. Chloro ketone **13c** (55 mg, 0.21 mmol) was dissolved in a concentrated solution of silver nitrate in methanol (5 mL), and the mixture was stirred for 3 h at rt. The mixture was filtered to remove a white solid, and the filtrate was concentrated under vacuum. Flash chromatography on silica gel with 10% EtOAc/hexane as eluent gave **12c** as a colorless oil (45 mg, 95%).

2-Oxo-3-(2,5,5-trimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalen-2-yl)propyl Benzoate (22). $TiCl_4$ (0.015 mL, 0.14 mmol) was added to a solution of $Ti(OiPr)_4$ (0.04 mL, 0.14 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was warmed to −10 °C and recooled to −78 °C, and a solution of **6** (50 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 4 h, the reaction mixture was warmed to −20 °C and allowed to stand for 16 h. The reaction mixture was cooled to −78 °C, and additional $TiCl_4$ (0.015 mL, 0.136 mmol) was added. The reaction mixture was then warmed to −20 °C, and another aliquot of $TiCl_4$ (0.015 mL, 0.14 mmol) was added. The reaction mixture was slowly warmed to 0 °C, and solid sodium bicarbonate (ca. 1 g) was added followed by 2-propanol (5 mL). The mixture was extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate produced a yellow oil, and PCTLC using 5% ether/hexane as eluent afforded **22** (45 mg, 90%): ^{1}H NMR (500 MHz) 0.83 (s, 3H), 0.91 (s, 3H), 1.08 (s, 3H), 1.17−1.37 (m, 4H), 1.53−1.71 (m, 2H), 1.78−2.00 (m, 4H), 2.12 (dd, J = 3, 14, 1H), 2.30 (d, J = 15, 1H), 2.38 (d, J = 15, 1H), 4.81 (d, J = 17, 1H), 4.82 (d, J = 17, 1H), 5.36 (br s, 1H), 7.45 (t, J = 8, 2H), 7.56 (t, J = 8, 1H), 8.08 (d, J = 8, 2H); ^{13}C NMR (125 MHz) 22.62, 23.97, 24.65, 28.44, 28.56, 31.22, 34.89, 35.79, 37.82, 43.47, 47.14, 48.82, 69.72, 120.99, 128.39, 129.34, 129.86, 133.30, 136.99, 165.82, 203.68; HRMS 354.2197 (calcd for $C_{23}H_{30}O_3$, 354.2195).

Lewis Acid-Promoted Reaction of 7b. Trimethyl borate (0.11 mL, 0.97 mmol) was added dropwise to a solution of **7b** (136 mg, 0.62 mmol) in CH_2Cl_2 (5 mL). After 1 h, a 1.0 M solution of boron trichloride in THF (0.50 mL, 0.5 mmol) was added and, after 15 min, solid sodium bicarbonate (ca. 1 g) was added followed by 2-propanol (5 mL). The mixture was slowly warmed to rt and water was added, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic solutions were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under a flow of nitrogen (to avoid evaporation of volatile products under vacuum[1a]), and the residue was flash chromatographed using 2% ether/pentane as eluent to produce **25** (59 mg, 44%) as a colorless oil and a (1:2) mixture of ene products **3** and **26** (63 mg) containing some undetermined olefinic compounds by ^{1}H NMR. Compounds **3** (t_R 9.5 min) and **26** (t_R 11 min) were partially separated by preparative GC [$^1/_4$in. × 6 ft FFAP, column and detector temperature 200 °C, injector temperature 240 °C, 4 μL, 20 mL/min].

Spectral and physical data for **25**: R_f(20% ether/hexane) 0.79; ^{1}H NMR (500 MHz) 0.87(s, 3H), 0.98 (s, 3H), 1.09 (s, 3H), 1.20−1.65 (m, 9H), 1.76-1.93 (m, 4H), 2.08 (d, J = 6, 1H), 10.14 (d, J = 6, 1H); ^{13}C NMR (125 MHz) 19.61, 21.11, 25.16, 26.55, 33.41, 33.86, 35.18, 37.63, 39.20, 40.75, 44.83, 48.12, 61.83, 67.53, 207.35; HRMS 220.1833 (calcd for $C_{15}H_{24}O$, 220.1827).

Spectral and physical data for **3**: R_f(25% ether/hexane) 0.58; ^{1}H NMR (500 MHz) 0.96 (s, 6H), 1.04 (s, 3H), 1.40−1.65 (m, 6H), 1.74−1.85 (m, 4H), 1.94−2.05 (m, 2H), 2.22 (dd, J = 3, 14.5, 1H), 2.28 (dd, J = 3, 14.5, 1H), 9.84 (dd, J = 3, 1H); ^{13}C NMR (125 MHz) 19.28, 21.24, 25.91, 27.82, 27.86, 31.52, 32.08, 33.54, 34.70, 39.64, 43.57, 53.58, 125.22, 133.67, 203.93; HRMS 220.1835 (calcd for $C_{15}H_{24}O$, 220.1827).

Spectral data for **26**: ^{1}H NMR (500 MHz) 0.84 (s, 3H), 0.91 (s, 3H), 1.07 (s, 3H), 1.20−1.38 (m, 4H), 1.64−1.74 (m, 4H), 1.88−2.02 (m, 2H), 2.08 (dd, J = 3, 13.5, 1H), 2.23 (dd, J = 3, 15, 1H), 2.28 (dd, J = 3, 15, 1H), 5.36 (br s, 1H), 9.81 (dd, J = 3, 1H); ^{13}C NMR (125 MHz) 22.63, 23.80, 28.44, 28.88, 31.24, 35.50, 37.04, 38.22, 44.07, 47.07, 48.93, 49.29, 121.18, 136.57, 204.08.

(2,5,5-Trimethyloctahydro-2,4a-methanonaphthalen-9-yl)methanol (27). Sodium borohydride (60 mg, 1.6 mmol) was added to a solution of **25** (40 mg, 0.18 mmol) in methanol (10 mL). After 0.5 h at rt, the mixture was treated with saturated aqueous ammonium chloride. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate and flash chromatography of the residue using 5% ether/hexane as eluent yielded **27** (38 mg, 94%) as a white solid: mp 72−73 °C; R_f(25% ether/hexane) 0.23. ^{1}H NMR (500 MHz) 0.85 (s, 3H), 1.00 (s, 3H), 1.10 (s, 3H), 1.20−1.85 (m, 15H), 3.75 (dd, J = 11, 9, 1H), 4.04 (dd, J = 11, 2, 1H); ^{13}C NMR (125 MHz) 20.45, 21.25, 26.14, 26.44, 33.07, 33.72, 34.84, 36.32, 39.45, 40.52, 44.56, 45.14, 54.05, 58.81, 61.95; HRMS 222.1981 (calcd for $C_{15}H_{26}O$, 222.1984).

***p*-Bromourethane 28.** A mixture of **27** (37.8 mg, 0.17 mmol), *p*-bromophenyl isocyanate (32 mg, 0.16 mmol), and benzene (4 mL) was refluxed for 8 h and cooled to rt, and the solvent was removed under vacuum to produce a white solid. PCTLC using 5% ether/hexane as eluent produced **28** (67 mg, 100%) as a white solid. Recrystallization from 5% ether/hexane gave long thin needle-shaped crystals: mp 134−136 °C; R_f(25% ether/hexane) 0.54. ^{1}H NMR (500 MHz) 0.87 (s, 3H), 1.04 (s, 6H), 0.90−1.80 (m, 14H), 4.18−4.22 (dd, J = 11, 11, 1H), 4.60−4.67 (dd, J = 11, 2, 1H), 6.61 (br s, 1H). 7.30 (d, J = 8, 2H), 7.4 (d, J = 8, 2H); ^{13}C NMR (125 MHz) 20.24, 21.13, 26.09, 26.37, 32.99, 33.73, 34.95, 36.25, 39.40, 40.39, 44.38, 45.40, 54.24, 54.37, 64.71, 115.76, 120.13, 131.93, 137.13, 153.43; HRMS 419.1449 (calcd for $C_{22}H_{30}O_2NBr$, 419.1460).

1,1,6-Trimethyl-6-vinyl-1,2,3,4,5,6,7,8-octahydronaphthalene (29). A 48% aqueous hydrogen fluoride solution (0.5 mL) was added to a solution of alcohols **23** (195 mg, 0.87 mmol) in acetonitrile (4 mL). After 1 h, $CHCl_3$ (5 mL) was added and the organic phase was separated. The aqueous phase was extracted with $CHCl_3$, and the combined $CHCl_3$ solutions were washed with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and filtered. PCTLC with pentane as eluent gave **29** (145 mg, 82%) as a clear oil: R_f(hexane) 0.7. ^{1}H NMR (500 MHz) 0.96 (s, 3H), 0.97 (s, 3H), 0.99 (s, 3H), 1.36−1.71 (m, 7H), 1.80−2.00 (m, 5H), 4.85−4.86 (dd, J = 1.5, 10.5, 1H),

4.90−4.93 (dd, J = 1.5, 18, 1H), 5.74−5.85 (dd, J = 10.5, 18, 1H); ^{13}C NMR (75 MHz) 19.45, 21.71, 25.67, 27.89 (2 CH_3's), 31.61, 33.52, 34.48, 35.09, 39.83, 42.34, 110.04, 125.42, 133.58, 147.79; HRMS 204.1870 (calcd for $C_{15}H_{24}$, 204.1878).

Hydroboration−Oxidation of 29: 2-(2,5,5-trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanol. A 0.5 M solution of 9-BBN-H in THF (0.60 mL, 0.90 mmol) was added dropwise to a solution of **29** (54 mg, 0.26 mmol) in THF (5 mL). After 4 h, the reaction mixture was treated with water (5 mL) followed by a 3 M aqueous sodium hydroxide (0.20 mL, 0.60 mmol). A solution of 30% aqueous hydrogen peroxide (0.20 mL) was added, and the reaction mixture was warmed to 50 °C using a hot water bath. After 0.5 h, the reaction mixture was cooled to rt and saturated aqueous sodium bicarbonate was added. The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic solutions were washed with brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate and flash chromatography of the residue with 10% ether/hexane as eluent gave the title compound (58 mg, 98%) as a clear oil: ^{1}H NMR (500 MHz) 0.87 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.20−1.32 (m, 2H), 1.36 (t, J = 6.5, 2H), 1.38−1.46 (m, 2H), 1.48−1.64 (m, 5H), 1.77−1.80 (m, 2H), 1.96−2.00 (br s, 1H), 3.69−3.74 (m, 2H); ^{13}C NMR 19.40, 21.34, 24.83, 27.78, 27.99, 30.73, 31.70, 33.49, 34.68, 39.77, 43.83, 43.95, 59.63, 125.46, 133.34; HRMS 222.1975 (calcd for $C_{15}H_{26}O$, 222.1984).

Nanaimoal (3). DMSO (0.056 mL, 0.79 mmol) was added dropwise to a solution of oxalyl chloride (0.035 mL, 0.40 mmol) in CH_2Cl_2 (5 mL) at −70 °C over a period of 5 min. After 10 min, a solution of the alcohol prepared in the previous experiment (53 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added dropwise followed after 15 min by triethylamine (1.0 mL, 7.17 mmol). The reaction mixture was slowly warmed to 0 °C, and water was added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (Na_2SO_4), and filtered. Concentration of the filtrate and PCTLC of the residue with 5% ether/pentane produced **3** (43 mg, 82%) as a colorless liquid.

Lewis Acid-Promoted Reactions of 8a/b. (a) Promotion with BCl_3:$B(OMe)_3$. A solution of **8a** (100 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) was added to a solution of trimethyl borate (0.56 mL, 0.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 30 min, a 1.0 M solution of boron trichloride in hexane (0.5 mL, 0.5 mmol) was added dropwise. After 2 h, the reaction mixture was warmed to −20 °C, saturated aqueous sodium bicarbonate was added, and the reaction mixture was allowed to warm to rt. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was concentrated under vacuum. Flash chromatography of the residue with ether/hexanes (1:17) as eluent gave **3** (20 mg, 20%), along with unreacted **8a** (28 mg, 28%) and isomer **8b** (12 mg, 12%).

(b) Promotion with $TiCl_4$. A solution of **8a** (40 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of $TiCl_4$ (0.055 mL, 0.50 mmol) in a mixture of CH_2Cl_2 (5 mL) and pentane (1 mL) cooled to −85 °C. After 10 min, solid sodium bicarbonate (ca. 1 g) was added to the orange reaction mixture followed by methanol (5 mL, the orange color faded). The reaction mixture was allowed to warm to −20 °C, and solid sodium borohydride (125 mg, 3.3 mmol) was added. The reaction mixture was allowed to warm to rt, and water was added to destroy the excess borohydride. The solvent was removed, and the residue was redissolved in CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic solutions were washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography of this residue with 10% ether/hexanes as eluent gave **27** (22 mg, 55% yield).

(c) Promotion with $TiCl_4$:$Ti(OiPr)_4$. $TiCl_4$ (0.03 mL, 0.27 mmol) was added to a solution of $Ti(OiPr)_4$ (0.07 mL, 0.25 mmol) in CH_2Cl_2 (10 mL) at −78 °C, followed by the dropwise addition of a 2.5:1 mixture of **8a** and **8b** (85 mg, 0.39 mmol) in CH_2Cl_2 (5 mL). After 1 h, additional $TiCl_4$ (0.03 mL, 0.27 mmol) was added and the mixture turned dark orange immediately. After 1.5 h, another portion of $TiCl_4$ (0.03 mL, 0.27 mmol) was added, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was warmed to −40 °C, and solid sodium bicarbonate (1 g) was added followed by 2-propanol (1 mL). The reaction mixture was allowed to warm to rt and filtered, and the filtrate was concentrated under a flow of nitrogen. The residue was dissolved in methanol (10 mL) and sodium borohydride (216 mg, 5.5 mmol) added. After 30 min, saturated aqueous ammonium chloride was added and the reaction mixture was diluted with brine and CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic solutions were washed with brine, dried ($MgSO_4$), filtered, and concentrated under vacuum. Flash chromatography of the residue with 10% ether/hexanes as eluent gave **27** (11 mg, 23% yield).

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Supporting Information Available: ORTEP drawing of **28**; ^{1}H and ^{13}C NMR spectra for all new compounds; experimental procedures for synthesis of **15a** (the procedures used were identical to those used for **14a**[10]), **6**, **7a/b**, **8a/b**, and spectral data for all intermediates; IR and mass spectral data for **3**, **11c**, **12a/c**, **13a/c**, **22**, **25**−**29**, and 2-(2,5,5-trimethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanol (the hydroboration/oxidation product of **29** (103 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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