[8] Crystal data for **1**·2Cl ($[Cu_{28}L_{20}(OAc)_{10}Cl_6(MeOH)_{11}(H_2O)_{23}]$): $M_W = 5952.09$, monoclinic, space group $P2_1$, $a = 14.2512$, $b = 26.9615(19)$, $c = 34.476(3)$ Å, $\alpha = 90.00$, $\beta = 90.049(2)$, $\gamma = 90.00°$, $V = 13246.8(16)$ Å^3, $Z = 2$; $\rho_{calcd} = 1.492$ g cm^{-3}; $2.73 < \theta < 28.34°$; crystal dimensions $0.24 \times 0.38 \times 0.42$ mm^3; $\mu = 23.35$ cm^{-1}; $T = 123(2)$ K; 172045 reflections collected; 63307 unique reflections and 2727 parameters were used for the full-matrix least-squares refinement on F^2; $R1 = 0.0394$, $wR2 = 0.1012$.

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[10] Crystal data for **2**·2Cl ($[Cu_{28}L_{20}(OAc)_{10}Cl_6(MeOH)_{15}(H_2O)_{20}]$): $M_W = 6026.21$, monoclinic, space group $P2_1$, $a = 14.1740(12)$, $b = 26.753(2)$, $c = 34.535(3)$ Å, $\alpha = 90.00$, $\beta = 90.314(3)$, $\gamma = 90.00°$, $V = 13095.7(19)$ Å^3, $Z = 2$; $\rho_{calcd} = 1.528$ g cm^{-3}; $2.70 < \theta < 22.78°$; crystal dimensions $0.10 \times 0.14 \times 0.22$ mm^3; $\mu = 23.63$ cm^{-1}; $T = 150(2)$ K; 84037 reflections collected; 34295 unique reflections and 2767 parameters were used for the full-matrix least-squares refinement on F^2; $R1 = 0.0651$, $wR2 = 0.1270$. Note that **2**·2Cl differs from **1**·2Cl in that the bound solvent composition is 6MeOH and $2H_2O$ for the former and 5MeOH and $3H_2O$ for the latter.

[11] Here we define a "supermolecule" (see ref. [1c]) as composed of receptors (that is, α-aminohydroxamic anions and acetates) and substrates (copper and chloride ions) held together weakly by intermolecular forces, thus giving a larger discreet superstructure.

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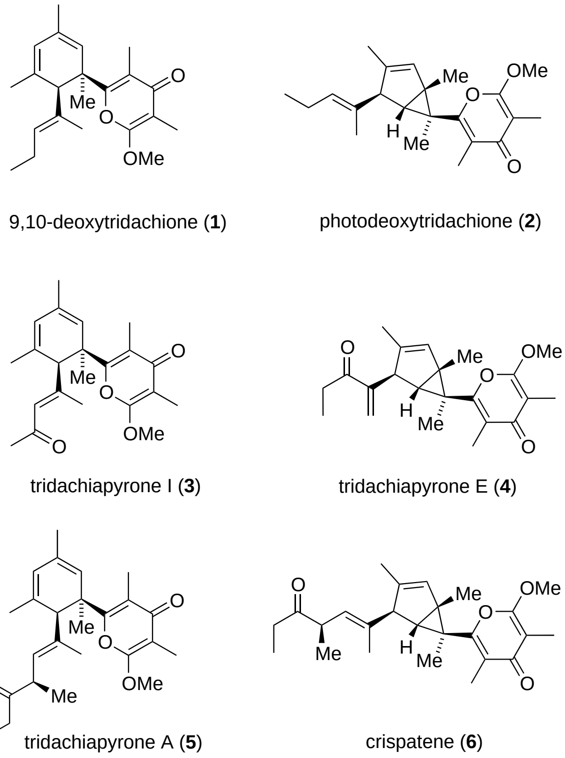
Lewis Acids in Total Synthesis

Total Synthesis of (±)-Photodeoxytridachione through a Lewis Acid Catalyzed Cyclization**

*Aubry K. Miller and Dirk Trauner**

Certain sacoglossan molluscs sequester active chloroplasts from algae and use these organelles to carry out photosynthesis in their own tissues.[1] These fascinating animals lack a protective shell and thus rely on chemical defense against predators. Not surprisingly, they have yielded a range of interesting biologically active natural products.[2] Many of these are highly unsaturated polypropionates that feature an α-methoxy-γ-pyrone moiety (Scheme 1).



9,10-deoxytridachione (**1**)
photodeoxytridachione (**2**)
tridachiapyrone I (**3**)
tridachiapyrone E (**4**)
tridachiapyrone A (**5**)
crispatene (**6**)

Scheme 1. Molluscan polypropionates. The absolute stereochemistry shown is arbitrary.

Architecturally, these natural products, which have been largely ignored by the synthetic community,[3] fall into two categories. Whereas 9,10-deoxytridachione (**1**), tridachiapyrone I (**3**), and tridachiapyrone A (**5**) are cyclohexadiene derivatives, photodeoxytridachione (**2**), tridachiapyrone E (**4**), and crispatene (**6**) feature a bicyclo[3.1.0]hexene core. The isomeric nature of these ring systems raises questions about their mutual biogenetic relationship.[4] In 1979, Ireland and Scheuer demonstrated that 9,10-deoxytridachione (**1**) can be photochemically converted in vivo and in vitro into photodeoxytridachione (**2**).[1] This transformation could proceed through conrotatory photochemical retro-electrocyclization followed by a "photochemical Diels–Alder reaction"—that is a $[_{\pi}4_a+_{\pi}2_s]$ cycloaddition.[5] However, since no racemization occurs, the reaction was proposed to proceed as a photochemical $[_{\sigma}2_a+_{\pi}2_a]$ rearrangement.[4]

Although these results suggest that **2** is biosynthesized via **1**, it is also, at least in principle, conceivable that both compounds are *directly* derived from a common acyclic precursor **7** (Scheme 2). The cyclohexadiene **1** may originate from this hypothetical intermediate through thermal disrotatory 6π electrocyclization. In contrast, the bicyclo[3.1.0]hexene **2** could arise in one step from a thermal $[_{\pi}4_a+_{\pi}2_a]$ cycloaddition of the same precursor. Provided that such a reaction could be realized in the laboratory, a unified synthetic approach toward both classes would be possible, since 6π electrocyclizations of hexatrienes are well-prece-

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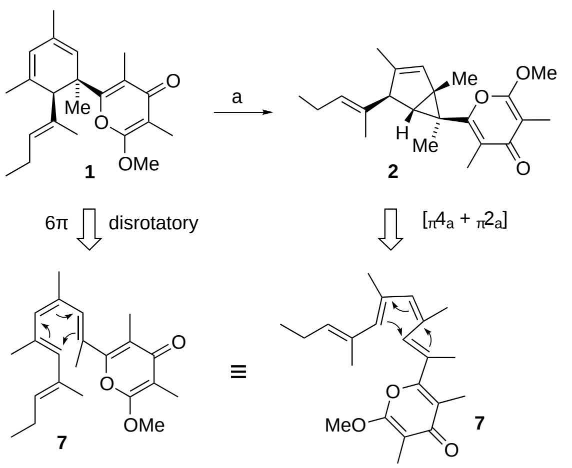
[**] The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a sponsoring member and Novartis as a supporting member.



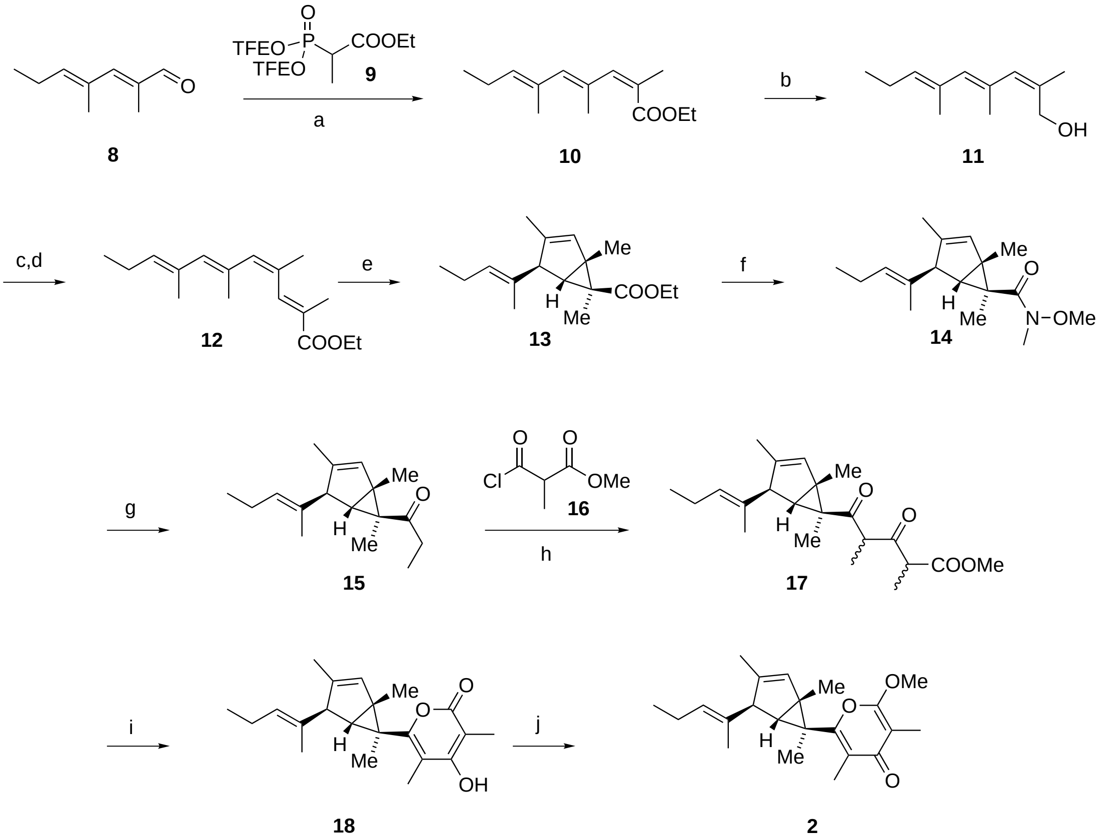
Scheme 2. Biosynthetic relationship and retrosynthetic analysis of **1** and **2**. a) hν.[4]

dented. We present herein the development of a Lewis acid catalyzed cyclization of hexatrienes to bicyclo[3.1.0]hexenes and the application of this novel reaction toward the total synthesis of **2**.

Our synthesis started with the known unsaturated aldehyde **8** (Scheme 3).[6] Still–Gennari condensation with trifluoroethyl phosphonate **9** yielded intermediate (*E,E,Z*)-**10** with excellent diastereoselectivity (≈20:1 in favor of the diastereomer shown).[7] Reduction with DIBAH then afforded alcohol **11**. A subsequent oxidation with TPAP/NMO followed by Horner–Wadsworth–Emmons condensation under Masamune–Roush conditions yielded the tetraenoic ester **12** (see Table 1 for selected data) and set the stage for the key step of the synthesis.[8]

After extensive experimentation (see below) it was found that treatment of **12** with catalytic amounts of dimethylaluminum chloride afforded bicylo[3.1.0]hexene **13** as the only isolated diastereomer in good yield (73 %, Table 1). Thus, the bicyclo[3.1.0]hexene core of the natural product with its two adjacent quaternary stereocenters was formed from an acyclic precursor in a single step.[9]

The installment of the α-methoxy-γ-pyrone moiety proved to be more difficult than anticipated, presumably as a result of steric hindrance of the neopentylic ester function. Despite many attempts, **13** could not directly be converted into the desired tricarbonyl compound **17** by cross-Claisen condensation with a corresponding dianion.[10] To circumvent this obstacle, **13** was transformed into the Weinreb amide **14** and then exposed to ethyl magnesium bromide to afford ethyl ketone **15**. Deprotonation with excess base and addition of malonyl chloride **16** gave **17** in good yield (95 % based on

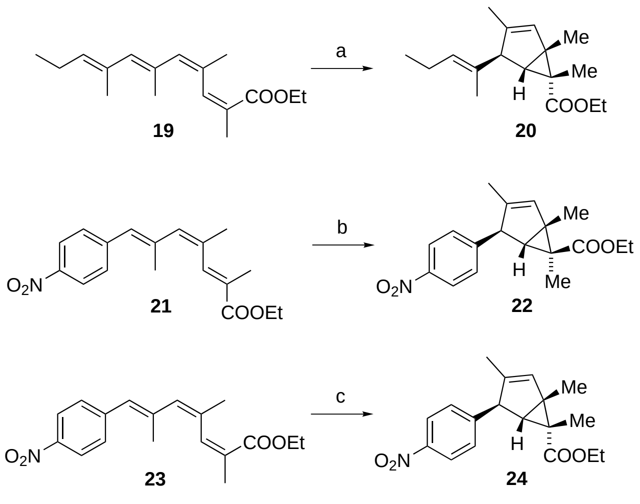


Scheme 3. Total synthesis of **2**. Reagents and conditions: a) **9**, KHMDS, 18[crown]-6, THF, −78 °C, 79 %; b) DIBAH, CH_2Cl_2, 0 °C, 93 %; c) TPAP, NMO, CH_2Cl_2; d) $(EtO)_2P(O)CH(Me)COOEt$, LiCl, DBU, MeCN, 43 % from **11**; e) Me_2AlCl (0.2 equiv), CH_2Cl_2, 73 %; f) MeHNOMe·HCl, *i*PrMgCl, THF, 0 °C, 63 %; g) EtMgBr, THF, 87 %; h) LiHMDS (3 equiv), **16**, THF, hexanes, −78 °C, 59 % (95 % based on recovered starting material); i) DBU, benzene, reflux, 78 %; j) FSO_2OMe, CH_2Cl_2, 77 %. HMDS = hexamethyldisilazide, DIBAH = diisobutylaluminum hydride, TPAP = tetra *n*-propylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFE = trifluoroethyl.

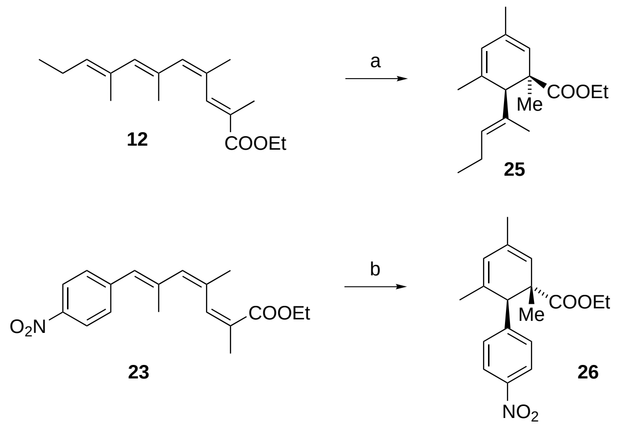
recovered starting material).[11] Cyclization of **17** under basic conditions resulted in the formation of the pyrone **18**.[10] Finally, regioselective methylation of this ambident nucleophile under the conditions of Beak et al. afforded **2**.[12] The NMR spectra of our synthetic material corresponded in all respects to the published data,[2f] and the high-resolution mass spectrum confirmed the molecular formula (Table 1).

To explore the scope and limitations of the key cyclization and to gain more insight into its mechanism, we studied the reactions of several compounds related to **12** in the presence of various Lewis acids. In addition to Me_2AlCl, other catalysts such as $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, and $TiCl_4$ were found to effect the isomerization, albeit in lower yields. Importantly, all reactions were found to proceed stereospecifically (Scheme 4). For instance, tetraenoic ester **19**, a diastereomer of **12**, gave bicyclo[3.1.0]hexene **20**, which is an epimer of **14** (Table 1).[13] Similarly, **21** cyclized to **22**, whereas its isomer **23** afforded **24**.[14]

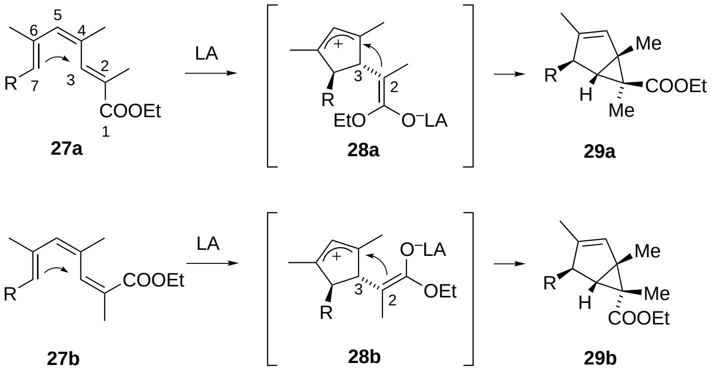
Notably, in the absence of a Lewis acid these substrates underwent regular disrotatory 6π electrocyclization to afford cyclohexadienes (Scheme 5).[14] Compound **25** may serve as an intermediate in the total synthesis of **1** and its congeners.



Scheme 4. Stereospecific formation of bicyclo[3.1.0]hexenes. Reagents and conditions: Me_2AlCl (0.2 equiv), CH_2Cl_2; a) 61 %; b) 84 %; c) 68 %.



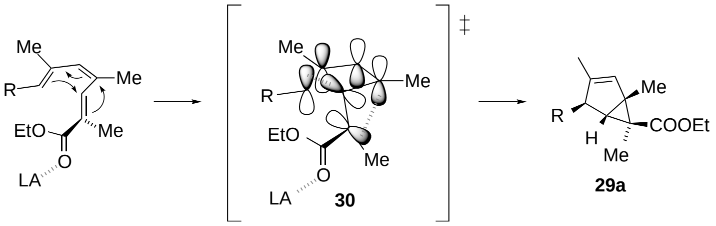
Scheme 5. Stereospecific formation of cyclohexadienes. Conditions: a) benzene, 80 °C, 95 %; b) toluene, 60 °C, 98 %.



Scheme 6. Proposed stepwise mechanism.

Mechanistically, the Lewis acid catalyzed cyclization could either proceed in a stepwise fashion or as a concerted cycloaddition. In the stepwise mechanism, coordination of the Lewis acid (LA) to the carbonyl group of trienoic ester **27a** or its isomer **27b** triggers a stereoselective ring formation, placing the two substituents *anti* with respect to each other (Scheme 6). The resulting zwitterionic intermediates **28a**/**28b** stabilize themselves by C–C-bond formation to yield bicyclo[3.1.0]hexenes **29a** or **29b**. Provided that this last step is considerably faster than rotation around the C2–C3 bond, the reactions could proceed stereospecifically.

Alternatively, a concerted cycloaddition mechanism that involves only one transition state **30** could be formulated (Scheme 7). The severe A^{1,3} strain between the methyl groups at C2 and C4 forces the triene to adopt a conformation in which it is effectively dissected into a diene and a dienophile moiety. Assisted by the C6 methyl group, the diene can assume an s-*cis* conformation, which allows for an intramolecular $[_{\pi}4_{a}+_{\pi}2_{a}]$ cycloaddition.[5a,15] The highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile are oriented more or less perpendicular to each other and overlap in such a way that bond formation occurs in an antarafacial sense with respect to both components. Coordination of a Lewis acid to the carbonyl group decreases the energy level of the LUMO, enabling this reaction to compete effectively with a 6π electrocyclization. The stereospecificity of the reaction is nicely explained by this concerted mechanism. Nevertheless, based on the currently available experimental data, no firm conclusion can be drawn as to the actual mechanism of the reaction.



Scheme 7. Proposed concerted mechanism.

Table 1: Selected physical properties of **12**, **13**, **20**, and **2**.

12: $R_f = 0.45$ (silica, 5% Et_2O in hexanes); IR (thin film): $\tilde{\nu} = 2954, 2932, 2873, 1709\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.45$ (s, 1 H), 6.01 (s, 1 H), 5.78 (s, 1 H), 5.34 (t, $J = 7.2$ Hz, 1 H), 4.20 (q, $J = 7.2$ Hz, 2 H), 2.10 (quint, $J = 7.2$ Hz, 2 H), 1.95 (s, 3 H), 1.89 (d, $J = 1.2$ Hz, 3 H), 1.83 (s, 3 H), 1.73 (s, 3 H), 1.29 (t, $J = 7.2$ Hz, 3 H), 0.98 ppm (t, $J = 7.2$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 168.9$, 140.6, 137.5, 136.4, 133.4, 132.3, 132.1, 131.1, 127.2, 60.7, 31.8, 24.2, 21.8, 18.4, 17.0, 14.4, 14.2 ppm; HRMS (EI): calcd for $C_{17}H_{26}O_2$ $[M^+]$: 262.1933, found: 262.1931

13: $R_f = 0.34$ (silica, 5% Et_2O in hexanes); IR (thin film): $\tilde{\nu} = 2961, 2930, 2872, 1717\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.25$ (m, 2 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 2.60 (s, 1 H), 2.02 (quint, $J = 7.6$ Hz, 2 H), 1.92 (s, 1 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.30 (s, 3 H), 1.26 (t, $J = 7.2$ Hz, 3 H), 1.05 (s, 3 H), 0.96 ppm (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 174.2$, 144.1, 134.1, 129.3, 128.9, 60.5, 59.1, 43.1, 37.9, 33.6, 21.4, 14.6, 14.5, 14.5, 13.8, 12.5, 10.1 ppm; HRMS (EI): calcd for $C_{17}H_{26}O_2$ $[M^+]$: 262.1933, found: 262.1937; elemental analysis: calcd for $C_{17}H_{26}O_2$: C 77.82, H 9.99; found: C 78.16, H 10.20

20: $R_f = 0.34$ (silica, 5% Et_2O in hexanes); IR (thin film): $\tilde{\nu} = 2961, 2928, 2872, 1729\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.30$ (t, $J = 7.2$ Hz, 1 H), 5.28 (s, 1 H), 4.08 (dq, $J = 10.8, 7.2$ Hz, 1 H), 3.99 (dq, $J = 10.8, 7.2$ Hz, 1 H), 3.24 (s, 1 H), 2.01 (dq, $J = 7.6, 7.2$ Hz, 2 H), 1.43 (s, 6 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 1.18 (t, $J = 7.2$ Hz, 3 H), 0.97 (s, 1 H), 0.95 ppm (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 173.0$, 140.5, 134.9, 131.2, 128.7, 60.1, 59.3, 39.4, 39.1, 36.1, 29.9, 21.4, 18.2, 14.6, 14.0, 13.9, 12.2 ppm; HRMS (EI): calcd for $C_{17}H_{26}O_2$ $[M^+]$: 262.1933, found: 262.1928

2: $R_f = 0.50$ (silica, 5% MeOH in CH_2Cl_2); IR (thin film): $\tilde{\nu} = 1661\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 5.33$ (s, 1 H), 5.30 (t, $J = 7.2$ Hz, 1 H), 3.96 (s, 3 H), 2.73 (s, 1 H), 2.04 (dq, $J = 7.6, 7.2$ Hz, 2 H), 1.97 (s, 3 H), 1.84 (s, 3 H), 1.57 (s, 3 H), 1.48 (s, 3 H), 1.42 (s, 1 H), 1.19 (s, 3 H), 1.10 (s, 3 H), 0.97 ppm (t, $J = 7.6$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 181.8$, 162.5, 160.7, 144.2, 134.2, 129.0, 128.8, 120.6, 99.7, 58.6, 55.5, 40.9, 37.0, 32.0, 21.4, 17.3, 14.5, 13.9, 12.9, 11.0, 7.1 ppm; HRMS (EI): calcd for $C_{21}H_{30}O_3$ $[M^+]$: 343.2229, found: 343.2248

In summary, a new Lewis acid catalyzed cyclization has been developed and applied to a concise total synthesis of photodeoxytridachione (ten steps from the known aldehyde **8**). Future work will focus on the scope and limitations of the reaction and the development of a catalytic asymmetric version using a chiral Lewis acid. Concurrently, the detailed mechanism of the reaction will be further investigated experimentally and computationally. Total syntheses of other molluscan polypropionates are well underway in our laboratories and will be reported in due course.

Received: September 18, 2002
Revised: October 15, 2002 [Z50192]

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