Total Syntheses of the Cytotoxic Marine Natural Product, Aplysiapyranoid C

Michael E. Jung,* Bruce T. Fahr, and Derin C. D'Amico
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

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The first total syntheses of the cytotoxic marine natural product, alysiapyranoid C, 1c, are reported. The Wittig reaction of 4-methyl-3-pentenyltriphenylphosphorane with the THP ether of hydroxyacetate gave in 88% yield the Z-alkene 4 which was hydrolyzed to the alcohol 5 in 72% yield. Sharpless asymmetric epoxidation of 5 afforded the epoxy alcohol 6 in 91% yield and 81% ee. Opening of the epoxide of 6 with ammonium chloride in DMSO gave in 76% yield the chloro diol 7 which was converted to the primary TBS ether 8 in 95% yield. Opening of the epoxy alcohol 6 with HCl and Ti(OiPr)4 afforded the desired chloro diol 7 as the minor product along with the rearranged chloromethyl diol 9. This compound is presumably formed by opening of the protonated epoxide to give a butenyl cation which rearranges to the cyclopropylcarbonyl cation and is then trapped by chloride ion at the unsubstituted cyclopropyl carbon, regenerating the alkene. Cyclization of the TBS ether 8 with tetrabromocyclohexadienone (TBCO) afforded a mixture of all four possible cyclization products, the desired tetrahydropyrans 11a,b and the tetrahydrofurans 12a,b with the former being isolated in 70% yield. Hydrolysis of the TBS ether afforded the primary alcohols from which the desired isomer, 13, could be isolated (24% overall from 8). Swern oxidation furnished the aldehyde 14 which was subjected to the Takai chlorovinylation to give a mixture of alysiapyranoid C 1c and the reduced product, dechloroalysapiapyranoid C 15. This dechlorination under these conditions is quite unusual. A second synthesis of alysiapyranoid C avoided this problem. Selective protection of the more hindered tertiary alcohol of the chloro diol 7 afforded the primary alcohol 16 in which the tertiary alcohol was protected as the triethylsilylether. Swern oxidation, Takai reaction, and desilylation gave the dichloro alkenol 17 in 52% overall yield. In this case, only a small amount of the corresponding dechlorinated product was obtained. Final cyclization of 17 with TBCO afforded alysiapyranoid C 1c as the major product in an isolated yield of 43%. Thus we have completed two total syntheses of alysiapyranoid C 1c from the simple bromide 2 in eight or nine steps and good overall yield.

Introduction

The alysiapyranoids A–D, 1a–d, are four halogenated monoterpenes isolated by Kakisawa and co-workers from the marine mollusc Aplysia kurodai (Scheme 1).3 These compounds, which have an unusual polycyclic halogenated tetrahydropyran structure, show good cytotoxicity against several cell lines. For example, alysiapyranoid D has exhibited an IC₅₀ of 14 μg/mL vs human tumor cells (Moser), while the other alysiapyranoids are somewhat less active (IC₅₀’s of 19 – 96 μg/mL vs standard cancer cell lines, e.g., Vero, MDCK, and B₁₆ cells). We have previously reported the synthesis of the alysiapyranoids A and D, 1a,d, from simple achiral allylic alcohols.4 The approach in those syntheses involved as key steps: (1) a Sharpless asymmetric epoxidation to give an epoxide alcohol, from which all three of the required stereocenters are ultimately derived; and (2) a stereoselective bromoetherification to furnish a product that is normally disfavored sterically but is favored in these cases due to a strong inductive effect on the homoallylic halogen atom.

Scheme 1

\[
\begin{align*}
 & 1a \quad X = H \quad Y = Br \\
 & 1c \quad X = Cl \quad Y = Cl \\
 & 1b \quad X = H \quad Y = Br \\
 & 1d \quad X = Cl \quad Y = H 
\end{align*}
\]

Scheme 2

This causes the normally disfavored opening of the intermediate bromonium ion at the more substituted carbon atom to occur to give the tetrahydropyran product in preference to the tetrahydrofuran product (Scheme 2). Thus, cyclization of the bis-homoallylic alcohol A having either a chlorine or a bromine atom in the homoallylic position with a source of positive bromine atom would afford the bromonium ion B (and its stereoisomer, see below), which could be opened at either the tertiary position to give the tetrahydropyran C or at the secondary center to give the tetrahydrofuran product D. We have shown that the halogen atom is crucial in...
controlling this opening in the desired sense, namely to favor the normally disfavored opening to give mainly the desired product C. We believe that the inversion of the normal opening of bromonium ions of this sort is due to the carbon–halogen dipole (shown in B) which destabilizes the carbocation at the secondary center proximal to the halogen atom and thereby inductively favors opening at the end distal to the halogen. This reaction sequence affords, in the case of aplysiapyranoid D, the all-equatorial isomer and, in the case of aplysiapyranoid A, a less stable isomer having an axial bromine atom. We now report herein the first two total syntheses of A, a less stable isomer having an axial bromine atom.

The syntheses both begin (Scheme 3) with the phosphonium bromide derived from the readily available 5-bromo-2-methyl-2-pentene 2. In the formation of the phosphonium bromide, it was necessary to add a trace amount of tetramethylpiperidine (TMP) to the reaction to suppress migration of the double bond to form a 2-methyl-1-alkene. Although this less substituted double bond isomer would be expected to be less stable, it was found to be necessary to completely suppress its formation using a hindered base, since otherwise inseparable mixtures of products resulted. Under conditions reported by Still for similar substrates, the phosphonium bromide was deprotonated with KHMD5 in THF/HMPA, followed by Wittig reaction with the tetrahydropyranyl ether of hydroxyacetone 3, to give only the Z-alkene 4 in 88% overall yield from 2. The resulting adduct was deprotected using PPTS in ethanol to yield the allylic alcohol 5.\(^\text{7}\) Sharpless epoxidation of 5 was effected in 91% yield using the modification of Zhou, which allows rapid asymmetric epoxidation of cis allylic alcohols, normally poor substrates in the Sharpless epoxidation.\(^\text{8}\) The enantiomeric excess of the epoxy alcohol 6 obtained was determined to be 81% by the method of Alexakis.\(^\text{9}\) The epoxy alcohol was opened by chloride ion using ammonium chloride and titanium tetraisopropoxide in DM- SO\(^\text{10}\) to give the chlorodiol 7, which was the branch point in the two syntheses. For the first synthesis, monoprotection of the diol at the primary alcohol was carried out under the usual conditions to give 8 in 95% yield.

We had observed a novel rearrangement in an earlier attempt to prepare the chlorodiol 7 in the opening of the epoxy alcohol 6 with hydrogen chloride and titanium tetraisopropoxide in dichloromethane rather than with ammonium chloride in dimethyl sulfoxide (Scheme 4). In addition to the desired product 7 (20% yield), we also obtained the rearranged chloromethyl diol 9 as a 2.8:1 mixture of diastereomers in 45% yield. These compounds are presumably formed by protonation of the epoxide to give I which can be opened by chloride ion in an Sn2 process to give 7 or can open via an Sn1 process to give the butenyl cation 11 which is stabilized as the cyclopropylcarbinyl cation III. Opening of this cyclopropylcarbinyl cation with chloride ion at the unsubstituted carbon regenerates the alkene and produces the products 9.


For the first synthesis, the cyclization of 8 was carried out using tetrabromocyclohexadienone (TBCO) in dichloromethane at 40 °C, which yielded four products in good yield (Scheme 5). The two major products were determined on the basis of their 1H NMR spectra to be the stereoisomeric tetrahydropyrans 11a,b. The two other products have been assigned the tetrahydrofuran structures 12a,b, based on comparison of their 1H NMR spectra with those of similar compounds. 

The formation of tetrahydropyrans 11a,b is normally disfavored in cyclizations of substituted 4-pentenols with respect to the tetrahydrofurans due to the strong steric repulsion (1,3-diaxial-like interactions) in the transition states leading to these products. This mode of cyclization is favored by the inductive effect of the chlorine atom, which destabilizes build-up of positive charge at the proximal end of the bromonium ions 10ab because of repulsion of the two positive dipoles. The major isomer present was the desired tetrahydropyran 11a with both halogens equatorial, due presumably to steric hindrance in the transition state for cyclization leading to 11b with an axial chlorine atom. We have observed both of these inductive and steric effects in similar cyclizations before. Compound 11a could not be separated cleanly, but a mixture of it and compound 12a was isolated in 70% yield from the crude reaction mixture using silica gel chromatography. The synthesis of aplysiaapiryanoid C was finished as follows (Scheme 6). Treatment of the mixture of 11a and 12a with TBAF removed the TBS groups to give, after flash chromatography on silica gel, the desired alcohol 13. This alcohol was converted by a Swern oxidation into the aldehyde 14, which was converted to the vinyl chloride using the method of Takai, namely treatment with TBAF, THF, 0 °C; SiO2, yield of 13 is 24% from 8. (b) (CCl3)2, DMSO, Et3N, CH2Cl2, −78 °C to 0 °C, 98%. (c) CrCl2, CHCl3, THF, 60 °C, 68% of a 5:5:3 mixture of 1c, 15, and 14.

Scheme 6

Scheme 7

(a) DMTrCl, collidine, 0 °C; Et3SiOTf (TESOTf), collidine, CH2Cl2, 40 °C; C2H2SH, CF3COOH, 90% from 7. (b) (COCl)2, DMSO, Et3N, CH2Cl2, −78 °C to −20 °C, 88%. (c) CrCl2, CHCl3, THF, 60 °C, 69%. (d) HF-pyr, pyr, CH2Cl2, −20 °C, 86%. (e) TBCO, CH2-NO2, 25 °C, 43%.

with chromos chloride and chlorofluro. Interestingly, we obtained a 1:1 mixture of aplysiaapiyanoid C 1c along with compound 15, in which the vinyl chloride has been reduced to a simple vinyl group. Presumably compound 15 is formed from 1c in a reductive process carried out by the chromium(II) chloride. Whether the active reducing species is actually chromium(II) chloride or not is unknown. It is possible that the reduction of the vinyl chloride is carried out by a trace contaminant. It is known, for example, that chromium(II) chloride can undergo oxidative addition to vinyl chlorides in the presence of trace amounts of nickel(II) chloride. Further work is underway to determine the cause of this unwanted reduction and to find ways to suppress it.

Thus this completes an eight-step synthesis of aplysiaapiyanoid C from the bromide 2.

However, we have developed a somewhat better synthesis of 1c by inverting the key steps as follows (Scheme 7). Conversion of the diol to the secondary triethylsilyl ether was carried out in a 3-step one-pot procedure by dimethoxytritylation of the primary alcohol, silylation of the tertiary alcohol, and deprotection with acid and dodecanethiol to give 16. Swern oxidation furnished in 88% yield the aldehyde which was subjected to the Takai reaction to give a good yield of the desired E-vinyl chloride (with little interference by an intramolecular ene reaction). Final removal of the silyl ether with HF-pyr afforded the tertiary alcohol 17 in 96% yield. In this case, only a small amount (up to ~10%) of the dechlorinated product was obtained in the chlorovinylation reaction, in marked contrast to the case with the aldehyde 14 above. We believe that the abnormal Takai reaction (to give the dechlorinated product 15) must be due to the severe steric hindrance of this particular aldehyde (1,3-diaxial to a methyl group in a pyran ring system). We have not seen this abnormal process with other simple aldehydes. Cyclication of the dichloro dienol 17 with TBCO in nitromethane gave a mixture of


(14) Takai reports such problems with olefinic aldehydes giving products from ene reactions.
(15) When less pyridine is used for the desilylation, the quaternary fluoride, formed by Markovnikov addition of HF to the trisubstituted alkene, is produced.
(16) The Takai reaction on several aldehydes, e.g., benzaldehyde, dodecanal, and 2-(deoxy)-2-methylpropanal, gave no chlorovinylation with no dechlorinated product observed.
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Experimental Section

General. 1H NMR were recorded at 200, 300, 400, or 500 MHz and are so indicated. 13C NMR were recorded at 90, 100, or 125 MHz, respectively, and are so indicated. Infrared spectra were recorded on a FTIR as a liquid film or as a thin crystalline film. High-resolution mass spectra (MS) were recorded on a Finnigan-MAT 8430 instrument. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 0.2 mm plates. Visualization was accomplished using ultraviolet light or one of the following stains: 1. Phosphomolybdate/arsenate spray. 2. Potassium permanganate for aldehydes and ketones. 3. 10% H2SO4 for aldehydes and ketones. 4. 1% ninhydrin for amines. 5. 2% ninhydrin in 95% ethanol for imines. All other reagents were purified by literature procedures. All reactions were performed under argon unless otherwise noted.

(E)-2,6-Dimethylhepta-2,5-dien-1-ol, 5. The tetrahydropyranyl ether 4 (3.60 g, 16.0 mmol) was dissolved in 125 mL of absolute ethanol, and a solution of sodium hydroxide (8.6 g, 0.21 mmol) in 30 mL of water was added, and the solution was refluxed for 1.5 h at room temperature. The allylic alcohol (5.15 g, 92%) as a colorless oil was obtained after concentration to an oil. The crude product was dissolved in ether and washed with saturated sodium bicarbonate solution and then with brine, and the flask was capped and heated to 60 °C for 4 h. The solution was cooled to room temperature, and the solvent was removed by rotary evaporation. The crude product was dissolved in ethanol, washed with saturated sodium bicarbonate solution and then with brine, and then dried (MgSO4), filtered, and concentrated by rotary evaporation. The resulting oil was purified by flash chromatography over silica gel (20% ethyl acetate in hexane), followed by recrystallization to provide product 5 (6.4 mmol) as a colorless oil: bp 61–65 °C @0.21 mm Hg. 1H NMR (360 MHz, CDCl3) δ 5.30 (br t, J = 7.5 Hz, 1H), 5.08 (br t, J = 7.1 Hz, 1H), 4.16 (d, J = 5.8 Hz, 2H), 2.75 (dd, J = 7.2, 7.2 Hz, 2H), 1.81 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.18 (br t, J = 5.8 Hz, 1H). 13C NMR (125 MHz, CDCl3) δ 134.2, 130.0, 127.2, 122.7, 61.6, 26.6, 25.6, 21.3, 17.7. IR (neat) 3324, 2971, 1674 cm-1. HRMS calcd for C15H24O (M+ H) 233.1692, found 233.1693.

[2R,3R]-3-Chloro-2,6-dimethyl-5-heptenoic acid-1,2-diol, 7. To a solution of the epoxy alcohol 6 (1.00 g, 6.4 mmol) in dimethyl sulfoxide (DMSO, 64 mL) was added ammonium chloride (0.68 g, 12.7 mmol). Titanium tetraisopropoxide (4.1 mL, 19.2 mmol) and D-(-)-diisopropyl tartrate (5.6 mL, 26.2 mmol) were added, and the solution was stirred for 15 min. A 37% solution of tert-butyl hydroperoxide (7.2 mL, 34.3 mmol) was added, and the reaction was stirred for an additional 15 min while maintaining the temperature between -30 °C and -20 °C. The crude alcohol 5 (2.6 g, 18.5 mmol) was added to the reaction, and the reaction was placed in a -20 °C freezer for 18 h. The reaction was warmed to 0 °C, and a solution of sodium hydroxide (8.6 g, 0.21 mmol) in 30 mL of brine was added to the reaction, followed by addition of 30% hydrogen peroxide (21 mL, 0.19 mmol). After the reaction had stirred for 2 h, the reaction was warmed to room temperature and stirred for an additional 7 h. The solution was diluted with brine, and Na2SO4 was added. The aqueous layer was washed with methylene chloride. The combined organic layers were dried (MgSO4), filtered, and concentrated to an oil. Flash chromatography over silica gel (30% ethyl acetate in hexane) provided the epoxy alcohol 6 (1.00 g, 6.4 mmol) in 98% yield. The crude product was dissolved in a minimum amount of warm hexane, allowing the solution to cool and filtering off the triphenylphosphine oxide crystals. The resulting hexane solution was concentrated by rotary evaporation. Flash chromatography over silica gel (5% ethyl acetate in hexane) afforded the 2-alkene 4 (1.74 g, 88%) as a colorless oil. 1H NMR (360 MHz, CDCl3) δ 5.34 (br t, J = 7.2 Hz, 1H), 5.07 (t, J = 7.1 Hz, 1H), 4.59 (s, 2H), 2.73 (m, 4H), 1.61 (s, 3H), 1.15 (m, 1H), 3.51 (m, 1H), 2.76 (dd, J = 7.3, 7.3 Hz, 2H), 1.9–1.5 (m, 6H), 1.83 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 131.7, 131.6, 128.2, 122.8, 97.4, 65.3, 62.1, 30.6, 26.8, 25.6, 25.5, 21.7, 19.5, 17.6. IR (neat) 2942, 1453 cm-1. HRMS calcd for C7H12O2 (M+ H) 163.0896, found 163.0897.

[2R,3S]-2-Methyl-3-(2-methyl-3-butenyl)oxiranemethanol, 6. The stirred solution of the alcohol 5 (1.00 g, 6.4 mmol) in dimethyl sulfoxide (DMSO, 64 mL) was added ammonium chloride (0.68 g, 12.7 mmol). Titanium tetraisopropoxide (4.1 mL, 19.2 mmol) and D-(-)-diisopropyl tartrate (5.6 mL, 26.2 mmol) were added, and the solution was stirred for 15 min. A 37% solution of tert-butyl hydroperoxide (7.2 mL, 34.3 mmol) was added, and the reaction was stirred for an additional 15 min while maintaining the temperature between -30 °C and -20 °C. The crude alcohol 5 (2.6 g, 18.5 mmol) was added to the reaction, and the reaction was placed in a -20 °C freezer for 18 h. The reaction was warmed to 0 °C, and a solution of sodium hydroxide (8.6 g, 0.21 mmol) in 30 mL of brine was added to the reaction, followed by addition of 30% hydrogen peroxide (21 mL, 0.19 mmol). After the reaction had stirred for 2 h, the reaction was warmed to room temperature and stirred for an additional 7 h. The solution was diluted with brine, and Na2SO4 was added. The aqueous layer was washed with methylene chloride. The combined organic layers were dried (MgSO4), filtered, and concentrated to an oil. Flash chromatography over silica gel (30% ethyl acetate in hexane) provided the epoxy alcohol 6 (1.00 g, 6.4 mmol) in 98% yield. The crude product was dissolved in a minimum amount of warm hexane, allowing the solution to cool and filtering off the triphenylphosphine oxide crystals. The resulting hexane solution was concentrated by rotary evaporation. Flash chromatography over silica gel (5% ethyl acetate in hexane) afforded the 2-alkene 4 (1.74 g, 88%) as a colorless oil. 1H NMR (360 MHz, CDCl3) δ 5.34 (br t, J = 7.2 Hz, 1H), 5.07 (t, J = 7.1 Hz, 1H), 4.59 (s, 2H), 2.73 (m, 4H), 1.61 (s, 3H), 1.15 (m, 1H), 3.51 (m, 1H), 2.76 (dd, J = 7.3, 7.3 Hz, 2H), 1.9–1.5 (m, 6H), 1.83 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 131.7, 131.6, 128.2, 122.8, 97.4, 65.3, 62.1, 30.6, 26.8, 25.6, 25.5, 21.7, 19.5, 17.6. IR (neat) 2942, 1453 cm-1. HRMS calcd for C7H12O2 (M+ H) 163.0896, found 163.0897.

(E)-2,6-Dimethylhepta-2,5-dien-1-ol, 5. The tetrahydropyranyl ether 4 (3.60 g, 16.0 mmol) was dissolved in 125 mL of absolute ethanol, and a solution of sodium hydroxide (8.6 g, 0.21 mmol) in 30 mL of water was added, and the solution was stirred for 1.5 h at room temperature, ethanol (120 mL) was added, followed by slow addition of 5% H2SO4 (60 mL). After the layers separated, the aqueous layer was extracted with ether, and the organic layers were dried

(17) We thank Dr. Darko Kantoci of Loma Linda University for his assistance in this separation.
(MgSO₄), filtered, and concentrated. Flash chromatography over silica gel (40% ethyl; acetate in hexane) provided the chloro diol 7 as white crystals (0.93 g, 76%): mp 36–37 °C. [α]D²⁰ = +33.9 (c 0.66, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.23 (br. t, J = 6.2 Hz, 4H), 4.16 (dd, J = 10.6, 3.0 Hz, 1H), 3.62 (dd, J = 6.5, 2.0 Hz, 2H, 2.51 (m, 1H), 2.49 (s, 1H), 2.35 (m, 1H), 2.60 (t, J = 6.5 Hz, 1H), 1.74 (s, 3H), 1.64 (s, 3H), 1.25 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 80.0, 77.5, 58.6, 52.9, 37.6, 29.3, 23.2, 22.4. IR (neat) 2988, 1736 cm⁻¹. HRMS calc for C₁₉H₂₄O₃Si (M⁺ + H) 268.9944, found 268.9934.

Aplpysiapyranoid C, 1c, and (2R,3R,5S)-5-Bromo-3-chloro-2-ethenyl-2,6,6-trimethyltetrahydropyran, 15. To a glass ampule containing chromium(II) chloride (27 mg, 0.22 mmol) was added the aldehyde 14 (9.9 mg, 0.06 mmol) in THF (0.4 mL) under argon. Chromium(II) chloride was dissolved (7 µL, 0.083 mmol), and the ampule was sealed under argon. The solution was placed in an oil bath at 60 °C for 56 h, at which point the reaction was cooled to room temperature and opened, and the reaction was quenched with ether (2 mL) and water (2 mL). After the layers had separated, the aqueous layer was extracted with ether, and the organic layers were dried (MgSO₄), filtered, and concentrated to give a yellow oil (7.7 mg, 70% yield). The reaction was quenched with hexane and water. The organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. Flash chromatography of the crude product over silica gel (5% ethyl acetate in hexane) provided 0.72 g of the alcohol 3 as a colorless oil (95%): [α]D²⁰ = +22.8 (c 0.62, CHCl₃). ¹H NMR (200 MHz, CDCl₃) δ 5.23 (m, 1H), 4.04 (dd, J = 10.7, 2.9 Hz, 1H), 3.61 (d, J = 9.9 Hz, 1H), 3.60 (d, J = 9.9 Hz, 1H), 2.52 (m, 1H), 1.74 (s, 3H), 1.63 (s, 3H), 1.25 (s, 3H), 0.93 (s, 9H), 0.08 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 134.1, 120.9, 74.4, 70.0, 67.9, 31.5, 25.82, 25.77, 21.3, 18.2, 18.0, −5.51, −5.35. IR (neat) 3567, 2955, 1464 cm⁻¹. HRMS calc for C₁₀H₁₄O₂Si (M⁺ − H) 220.0760, found 220.0763.
To a mixture of chromium(II) chloride (0.37 g, 3.0 mmol) in THF (1.5 mL) under argon was added chloroform (23 mL) and cooled to 0 °C in a polyethylene bottle. The reaction was stirred at room temperature for 12 h. The reaction was quenched with water (6 mL). Using centrifugation to separate the layers, the organic layer was removed and the aqueous layer was extracted with ethereal. The organic layers were dried (MgSO₄), filtered, and concentrated to an oil. The oil was dissolved in hexane and filtered through a plug of silica gel using 5% ethyl acetate in hexane. The resulting solution was concentrated, and flash chromatography of the resulting oil (10% benzene in hexane) provided a lysoisapyanoid C, 1c.

Aplysiapyranoid C, 1c. To a solution of the dichloroalkanol 17 (36.0 mg, 0.161 mmol) in nitromethane (1.1 mL) was added TBCO (135 mg, 0.33 mmol). The flask was covered with aluminum foil, and the reaction was stirred at room temperature under argon for 12 h. The reaction was diluted with dichloromethane (3 mL), then washed with sodium hydroxide solution (1 N). The organic solution was dried (MgSO₄), filtered, and concentrated to an oil. The oil was dissolved in hexane and filtered through a plug of silica gel using 5% ethyl acetate in hexane. The resulting solution was concentrated, and flash chromatography of the resulting oil (10% benzene in hexane) provided a lysoisapyanoid C, 1c.

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Supporting Information Available: Copies of NMR spectra (23 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.