A Stereoselective Synthesis of (±)-11-Hydroxy-*trans*-8-dodecenoic Acid Lactone, a Naturally Occurring Macrolide from *Cephalosporium recifei*

E. J. Corey,* Peter Ulrich, and J. Michael Fitzpatrick

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received June 7, 1975*

Abstract: The naturally occurring macrolide 11-hydroxy-*trans*-8-dodecenoic acid lactone (**7**) has been synthesized stereoselectively. Hydrostannation of the acetylene **1** afforded the *trans*-vinylstannane **2a** as the major product. Conversion of **2a** to the corresponding lithium derivative and pentynyl cuprate and coupling with either 7-iodoheptanonitrile or ethyl 7-iodoheptanoate yielded either the nitrile **4a** or the ester **4b.** Hydrolysis to hydroxy acid **5** and thermal cyclization of thioester **6** produced the racemate of the title compound.

The recent discovery of the "double activation" method[1-3] for the direct synthesis of complex, polyfunctional macrocyclic lactones from the corresponding hydroxy acids has substantially simplified the task of synthesis in this area.[4] We now report the use of this process as a key step in a simple, stereoselective synthesis of (±)-11-hydroxy-*trans*-8-dodecenoic acid lactone, a naturally occurring macrolide isolated[5,6] from the fungus *Cephalosporium recifei.*

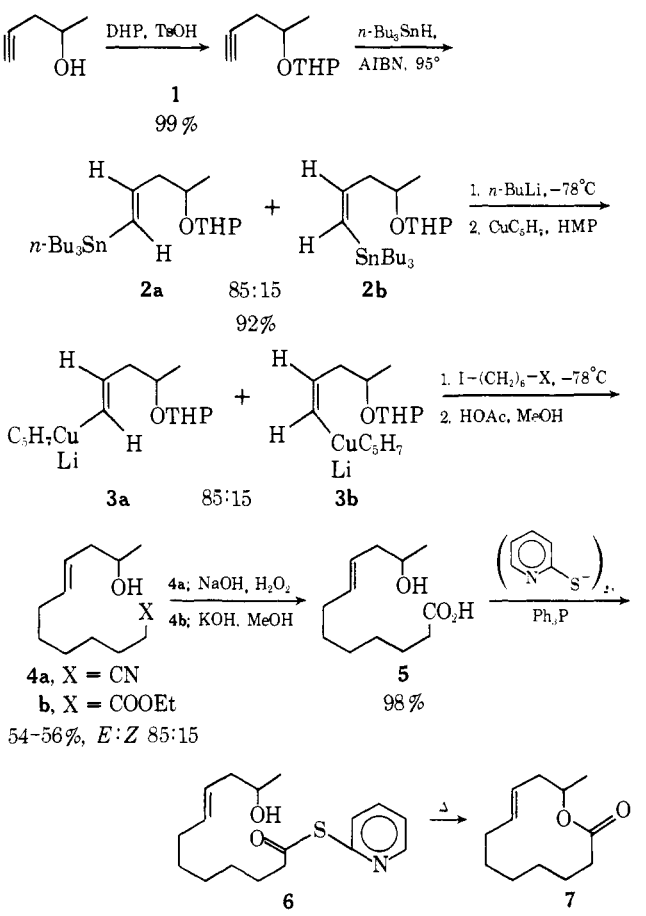
The acetylenic tetrahydropyranyl ether **1** was prepared from 4-pentyn-2-ol in 99% yield by reaction with dihydropyran in methylene chloride containing a catalytic amount of *p*-toluenesulfonic acid, at ambient temperature for 1 hr. Heating acetylene **1** for 3 hr at 95°C with tri-*n*-butyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), followed by distillation at 136–146°C (0.016 mm) effected smooth, stereoselective hydrostannation[7] to vinylstannanes **2a,b** in a ratio of 85:15, respectively (Chart I).

The ratio of *E* to *Z* products was quite insensitive to temperatures above 90°C (below this temperature the *Z* isomer predominates[7,8]) and to the steric requirement of the alkyl substituents bonded to tin or of the alcohol protecting group. Thus if tricyclohexyltin hydride is employed as the tin source, or if the alcohol is protected as the tribenzylsilyl ether, the ratio of *E* to *Z* isomers is unchanged (see Table I). However, a high degree of selectivity (>98%) has been found when the carbon α to the acetylene is functionalized, for example, the tetrahydropyranyl ether of propargyl alcohol.[7] The apparently small steric requirements of the trialkyltin moiety may be rationalized in terms of the length of the C–Sn bond (ca. 2.2 Å).[9]

The mixture of vinylstannanes was converted stereospecifically to the mixture of cuprates **3a,b** by sequential treatment with *n*-butyllithium at −78 to −10° and pentynylcopper, solublized in tetrahydrofuran with hexamethylphosphorous triamide,[10] at −78° to −45°. Coupling[11] of the cuprates with either 7-iodoheptanonitrile or ethyl 7-iodoheptanoate was effected by dropwise addition of the iodide to a solution of the cuprates at −78°C and warming to 25° over several hours.

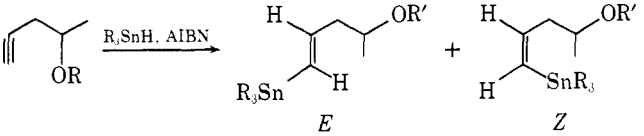
Exposure of the resulting tetrahydropyranyl ethers to 1:1 acetic acid–methanol at 60° for 4–8 hr produced 11-hydroxy-8-dodecenonitrile (**4a**) and ethyl 11-hydroxy-8-dodecenoate (**4b**) in 54–56% yield based upon vinylstannane. The alcohols **4a** and **4b** were formed in each case as an 85:15 mixture, respectively, of trans and cis isomers. Approximately the same trans–cis ratio (4.8) was observed when the lithio derivative from the 85:15 mixture of **2a** and

Chart I



2b was stirred at 25° for 30 min (tetrahydrofuran solution) and then quenched with benzophenone, indicating that at equilibrium sizable amounts of the *cis*-vinyllithium derivative are present. Chromatographic separation of the isomeric esters **4b,** using silica gel plates impregnated with silver nitrate and ether as the eluent, gave the pure trans form.

Isomerically pure (±)-11-hydroxy-*trans*-8-dodecenoic acid (**5**) was obtained in 98% yield by saponification of



trans ethyl ester **4b**. Treatment of hydroxy acid **5** with triphenylphosphine and 2,2′-dipyridyl disulfide[1] in a small amount of xylene gave thioester **6**. Dilution of this mixture with more xylene and slow addition to xylene at reflux gave, after chromatography, the desired macrocyclic lactone **7** (52% yield). The synthetic lactone was chromatographically and spectrally identical with authentic naturally occurring material.[12]

Experimental Section

7-Iodoheptanonitrile. 7-Bromoheptanonitrile (Columbia Organic Chemical Co., Inc., 3.80 g, 20.0 mmol) and sodium iodide (12.0 g, 80.0 mmol) were combined in acetone (25 ml) under argon and stirred 4 hr at 25°. The solid was removed by filtration and washed with acetone (10 ml) and ether (100 ml). The filtrate and washings were combined and again filtered, and this filtrate was concentrated to a yellow oil. This was taken up in ether (100 ml) and washed with water, saturated aqueous sodium thiosulfate (10 ml), and brine (10 ml). The ethereal extract was dried (sodium sulfate) and evaporated to give a yellow oil which was distilled to give 4.52 g (95%) of product: bp 92–100° (0.10 mm); d^{20} 1.465; ir (film) 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–2.2 (m, 8 H), 2.38 (br t, 2 H), 3.20 (br t, 2 H); mass spectrum *m/e* 237.

Ethyl 7-Iodoheptanoate was likewise prepared from ethyl 7-bromoheptanoate (Chemicals Procurement Laboratories) in 95% yield; bp 88–95° (0.20 mm) [lit.[13] bp 113–119° (5–6 mm)]; ir (film) 1734, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H), 1.1–2.0 (m, 8 H), 2.30 (br t, 2 H), 3.18 (t, 2 H), 4.12 (q, 2 H).

Tetrahydropyranyl Ether of 4-Pentyn-2-ol (1). 4-Pentyn-2-ol (Farchan Division, Story Chemical Corp., 2.10 g, 25.0 mmol) and 2,3-dihydropyran (2.50 g, 29.5 mmol) were combined in dichloromethane (20 ml) containing ca. 2 mg of *p*-toluenesulfonic acid. The solution was stirred 1 hr at ambient temperature, then washed with saturated aqueous sodium bicarbonate (10 ml) and brine (10 ml), dried (potassium carbonate), and concentrated to a light yellow oil which was distilled to a colorless oil (4.18 g, 99%): bp 56–58° (1.65 mm); ir (film) 3295, 2120, 1125, 1075, 1034, 1022, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (2 d, 3 H), 1.3–1.9 (m, 6 H), 2.0 (2 t, 1 H), 2.15–2.7 (m, 2 H), 3.46 (m, 1 H), 3.88 (m, 2 H), 4.59 (m, 1 H); mass spectrum *m/e* 168.

Tetrahydropyranyl Ether of 5-Tributylstannyl-4-penten-2-ol (2). Alkyne **1** (2.10 g, 12.5 mmol) and tributyltin hydride[14] (4.07 g, 14.0 mmol) were stirred 3 hr at 95° in the presence of a catalytic amount of azobisisobutyronitrile (50 mg initially, 20 mg more after 2 hr) under argon. The resulting colorless oil was distilled under high vacuum giving, after a small forerun, 5.25 g (92%) of colorless oil: bp 136–146° (0.016 mm); ir (film) 1603, 1024 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–2.1 (m, 36 H), 2.3 (m, 2 H), 3.5 (m, 1 H), 3.9 (m, 2 H), 4.7 (m, 1 H), 5.98 (m with satellites, trans HC=CH), 5.88 (br d, partly obscured, cis SnCH=C), 6.5 (dt, partly obscured, SnC=CH), total vinyl integration = 2 H; careful inspection of the integration of the vinylic region indicates a trans-cis ratio of 84 ± 3:16 ± 3. Assignments in this region are by comparison with data reported by Seyferth and Vaughan for *cis*- and *trans*-propenyltrimethyltin.[15]

Ethyl 11-Hydroxy-*trans*-8-dodecenoate (4b). A solution of the protected stannylpentenol (**2**) (2.29 g, 5.00 mmol, trans:cis = ca. 85:15) in tetrahydrofuran (8 ml) under argon at −78° was treated with *n*-butyllithium (2.46 *M* in hexane, 2.04 ml, 5.00 mmol). The very pale yellow solution was stirred 2 hr at −78° and 1 hr at −10°. A second solution was prepared from 1-pentynylcopper[16] (0.710 g, 5.25 mmol) and hexamethylphosphorous triamide (1.715 g, 10.5 mmol) in tetrahydrofuran (8 ml) under argon by stirring 5 min at 25°; this was transferred by syringe to the first solution (cooled to −78°). After stirring 2 hr at −78° and 1 hr at −45°, the tan-yellow cuprate solution was treated with ethyl 7-iodoheptanoate (1.42 g, 5.00 mmol), and was then stirred 4 hr at −78°, allowed to reach −35° over 1 hr, kept at −35° for 1 hr, and then allowed to reach 25° over 6 hr. The yellow solution was diluted with ether and washed alternately with concentrated ammonia–ammonium chloride buffer and acetic acid–sodium acetate buffer until the ammonia washes were colorless. The dried (sodium sulfate) ether layer was concentrated and the residue stirred with acetic acid–methanol (1:1, 55 ml) at 60° under argon for 8 hr to effect THP removal. The solution was evaporated to give 3.0 g of yellow oil. This was chromatographed on a silica gel column (50 g, 2.5 × 20 cm) with pentane containing successively greater percentages of ether (5 to 70%). Tetrabutyltin (1.645 g, 95%) was eluted with 5% ether; unreacted ethyl 7-iodoheptanoate (0.245 g, 18%) was eluted with 10% ether. Elution with 50% ether gave ethyl 11-hydroxy-8-decenoate (**4b**) (0.653 g, 54% based on **2**, 66% conversion based on recovered iodo ester) as a pale yellow oil: ir (film) 3440, 2933, 1738, 1187, 973, 728 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0–1.8 (m, 14 H), 1.8–2.4 (m, 7 H), 3.8 (2 unresolved sextets with ratio δ 3.78:δ 3.81 = ca. 5:1, 1 H), 4.12 (q, 2 H), 5.46 (m, 2 H); mass spectrum *m/e* 242.

Table I. Hydrostannation Isomer Distribution

R	R′	*E*/*Z*	Temp, °C
n-Bu	$Si(CH_2Ph)_3$	85:15	90–250
n-Bu	THP	85:15	200
Cyclohexyl	THP	85:15	200

The trans isomer of **4b** was purified by the following method. Preparative layer plates (20 × 20 × 0.2 cm, EM Laboratories precoated plates, Silica Gel 60, F-254) were immersed briefly in a 10% (w/v) solution of silver nitrate in acetonitrile and allowed to air-dry in the dark overnight. Elution of 80–100 mg of a mixture of the trans and cis isomers of ethyl 11-hydroxy-8-dodecenoate with ether on one such plate allowed separation of the isomers (trans, R_f 0.5; cis, R_f 0.3).

11-Hydroxy-8-dodecenonitrile (4a) was prepared in an analogous manner from 7-iodoheptanonitrile and was purified by partitioning the two-phase crude product between pentane and acetonitrile and subjecting the residue from the acetonitrile extracts to preparative layer chromatography (20 × 20 × 0.2 cm layer of silica gel, ether), giving a yellow oil (R_f 0.45) in 56% yield: analytical TLC (silver nitrate treated silica gel, ethyl acetate) R_f 0.27 (major, assigned to trans), R_f 0.17 (minor, assigned to cis); ir (film) 3430, 2930, 2252, 972, 728 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17, 1.20 (2 d, 3 H, δ 1.17; δ 1.20 = ca. 5:1), 1.2–1.85 (m, 8 H), 1.88 (s, 1 H), 1.9–2.5 (m, 6 H), 3.79, 3.82 (2 unresolved sextets, δ 3.79; δ 3.82 = ca. 5:1, 1 H), 5.48 (m, 2 H); mass spectrum *m/e* 195.

11-Hydroxy-*trans*-8-dodecenoic Acid (5). A. From 4a. A solution of hydroxynitrile **4a** (110 mg, 0.56 mmol) in 95% ethanol (1 ml) was combined with 30% aqueous potassium hydroxide (1 ml, 5.2 mmol) and 30% hydrogen peroxide (0.28 ml, 2.5 mmol). A continuous stream of nitrogen was bubbled through the solution while it was heated to 40–45° for 1 hr; after this time it was refluxed until the effluent gases no longer contained ammonia (4 hr). The mixture was cooled to 0°, saturated with salt, and acidified with 12 *N* hydrochloric acid. The aqueous layer was extracted several times with ether, and the combined organic layers were washed with brine and dried over magnesium sulfate. Concentration yielded 115 mg (98%) of a colorless oil, pure by ^1H NMR and TLC: ir (film) 3450–2400 (broad), 1710, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, 3 H), 1.34 (m, 11 H), 2.20 (m, 6 H), 3.80 (m, 1 H), 5.47 (m, 2 H), 7.10 (m, 2 H); mass spectrum *m/e* 214 (weak), 196 (strong); exact mass 214.1575 (calcd for $C_{12}H_{22}O_3$: 214.1569).

B. From 4b. Hydroxy ester **4b** (242 mg, 1.00 mmol) was dissolved in 6 *N* methanolic potassium hydroxide (2 ml, 12 mmol). The mixture was diluted with water (1 ml) and stirred at 25° for 1 hr. More water (5 ml) was added, and the solution was extracted several times with ether. The aqueous layer was cooled to 0°, acidified with 12 *N* hydrochloric acid, saturated with salt, and extracted several times with ether. The combined organic layers were washed with saturated brine and dried over magnesium sulfate. Concentration yielded 210 mg (0.98 mmol, 93%) of the oily hydroxy acid **5**.

11-Hydroxy-*trans*-8-dodecenoic Acid Lactone (7). Hydroxy acid **5** (107 mg, 0.50 mmol), 2,2′-dipyridyl disulfide (165 mg, 0.75 mmol), and triphenylphosphine (197 mg, 0.75 mmol) were dissolved in dry, oxygen-free xylene (1 ml) and stirred at 25° for 5 hr. The reaction mixture containing the 2-pyridinethiol ester was diluted with 10 ml of dry oxygen-free xylene and the resulting solution was added slowly from a mechanically driven syringe over 24 hr to 100 ml of dry xylene at reflux under argon. Reflux was continued for 36 hr following addition. The bulk of the xylene was distilled until approximately 1 ml of solvent remained. The residue

was applied directly to a preparative layer plate (20 × 20 × 0.2 cm layer of silica gel) and eluted with 20% ether in petroleum ether (R_f 0.8). Isolation yielded 53 mg (0.27 mmol, 52%) of lactone **7**; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 7 Hz), 1.50 (m, 8 H), 2.30 (m, 6 H), 5.18 (m, 1 H), 5.35 (m, 2 H).

Vapor phase chromatographic comparisons were performed with a Hewlett-Packard 5750 flame ionization instrument using a 6 ft × ⅛ in. column of 3% OV-17 on 80–100 mesh Chromosorb W at a temperature of 145° and a nitrogen flow rate of 60 ml/min; a retention time of 14 min was observed for synthetic and naturally derived lactone **7**.

Acknowledgment. This research was assisted financially by the National Institutes of Health and the National Science Foundation.

References and Notes

(1) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
(2) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 653, 654 (1975).
(3) E. J. Corey, K. C. Nicolaou, and T. Toru, *J. Am. Chem. Soc.*, **97**, 2287 (1975).
(4) A number of noteworthy syntheses of biologically active macrocyclic lactones have been reported over the past few years. See (a) D. Taub, N. N. Girotra, R. D. Hofsommer, C. H. Kuo, H. L. Slates, W. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968); I. Vlattas, I. T. Harrison, L. Tokes, J. H. Fried, and A. D. Cross, *J. Org. Chem.*, **33**, 4176 (1968) (zearalenone); (b) E. W. Colvin, T. A. Purcell, and R. A. Raphael, *Chem. Commun.*, 1031 (1972) (pyrenophorin).
(5) R. F. Vesonder, F. H. Stodola, L. J. Wickerham, J. J. Ellis, and W. K. Rohwedder, *Can. J. Chem.*, **49**, 2029 (1971).
(6) See also R. F. Vesonder, F. H. Stodola, and W. K. Rohwedder, *Can. J. Biochem.*, **50**, 363 (1972).
(7) E. J. Corey and R. H. Wollenberg, *J. Org. Chem.*, **40**, 2265 (1975).
(8) A. J. Leusink, H. A. Budding, and J. W. Marsman, *J. Organomet. Chem.*, **9**, 285 (1967).
(9) D. D. Davis, A. J. Surmatis, and G. L. Robertson, *J. Organomet. Chem.*, **46**, C9 (1972).
(10) E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(11) G. H. Posner, *Org. React.*, **22**, 253 (1975).
(12) We are grateful to Dr. F. H. Stodola, National Regional Research Laboratory, U.S. Department of Agriculture, Peoria, Ill., for the reference sample.
(13) N. J. Leonard, R. C. Fox, and M. Oki, *J. Am. Chem. Soc.*, **76**, 5708 (1954).
(14) K. Hiyashi, J. Iyoda, and I. Shiihara, *J. Organomet. Chem.*, **10**, 81 (1967).
(15) D. Seyferth and L. G. Vaughan, *J. Organomet. Chem.*, **1**, 138 (1963).
(16) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966).

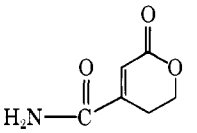
Total Synthesis of Gentiocrucine, an Unusual Alkaloid Containing a Stable Primary Enamide

Bruce Ganem

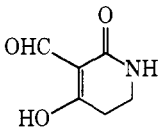
Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14853. *Received April 19, 1975*

Abstract: A total synthesis of the naturally occurring alkaloid gentiocrucine is reported which unambiguously confirms its structure **3a**, **3b** as the first example of a stable primary enamide. Treatment of methyl 2-(methoxymethylene)acetoacetate (**4**) with aniline produced methyl 2-(*N*-phenylaminomethylene)acetoacetate (**5**). Addition of *n*-butyllithium (2 equiv) to **5** at −78° followed by gaseous formaldehyde afforded a 60% yield of *N*-phenylgentiocrucine **8**, mp 116–118.5°. Stirring **8** in liquid ammonia produced gentiocrucine (66%, mp 144–145°), identical with an authentic sample. The reactivity of this substance as well as factors responsible for its stability is discussed.

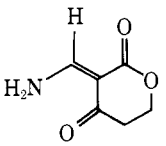
Gentiocrucine, a terpene alkaloid derivative first isolated from *Gentiana cruciata*, was assigned structure **1** by Popov and Marekov on the basis of its spectral and chemical properties.[1] These workers also demonstrated that gentianaine,[2] previously thought to be **2**, was identical with gentiocrucine.[3] Recently the same substance was discovered in another plant, *Enicostemma hyssopifolium*, and its structure reinvestigated.[4] During this work, comprehensive spectroscopic studies ruled out **1** and **2** in favor of the isomeric enamides **3a** and **3b**. If structurally correct, this pair of isomers would represent the first examples, naturally occurring or synthetic, of a stable primary enamide. This article discloses a short total synthesis of gentiocrucine which unambiguously confirms the revised structure **3a, 3b** and establishes a simple new approach to substituted 3-keto-δ-valerolactones.



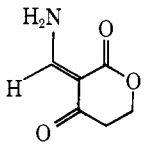
1



2



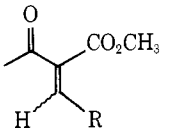
3a



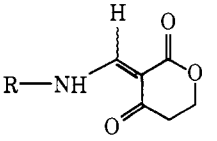
3b

Results

Treatment of methyl 2-(methoxymethylene)acetoacetate (**4**)[5] with two equiv of aniline in $CHCl_3$ produced the corresponding enaminoketoester **5** in 97% yield as a mixture of isomers.[6,7] Addition of *n*-butyllithium (2 mol equiv) to **5** at −78° followed immediately by passage of anhydrous gaseous formaldehyde (1.5 equiv, generated from paraformaldehyde) into the clear orange dianion solution using a stream of nitrogen resulted in a rapid uptake of the gas at −78° and concomitant disappearance of color. After warm-



4, R = OCH_3
5, R = NHPh
6, R = NH_2
7, R = $NHCH_2Ph$



8, R = Ph
9, R = $PhCH_2$