Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Two-Directional Synthesis of (+)-Ancepsenolide

Z. -J. Yao [a] , Q. Yu [a] & Y. -L. Wu [a]
[a] State Key Laboratory of Bioorganic and Natural Products Chemistry Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences , Shanghai, 200032, China
Published online: 21 Aug 2006.

To cite this article: Z. -J. Yao , Q. Yu & Y. -L. Wu (1996) Two-Directional Synthesis of (+)-Ancepsenolide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:19, 3613-3617, DOI: 10.1080/00397919608003773

To link to this article: http://dx.doi.org/10.1080/00397919608003773

SYNTHETIC COMMUNICATIONS, 26(19), 3613-3617 (1996)

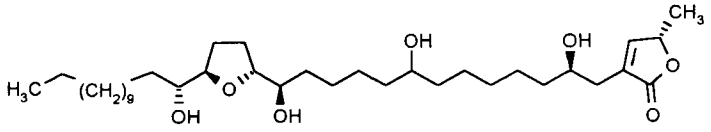
TWO-DIRECTIONAL SYNTHESIS OF (+)-ANCEPSENOLIDE

Zhu-Jun Yao Qian Yu Yu-Lin Wu*

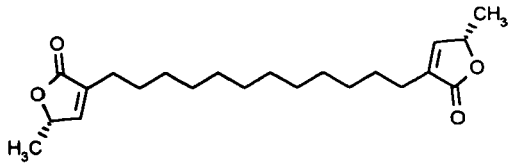
State Key Laboratory of Bioorganic and Natural Products Chemistry
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
Shanghai 200032, CHINA

ABSTRACT A two-directional strategy developed for the synthesis of (+)-ancepsenolide was described.

A growing class of biologically interesting natural products named annonaceous acetogenins have generated great attention in recent years.[1] Their structures typically possess a terminal butenolide attached to a long aliphatic chain punctuated by oxygenated functional groups such as annonacin.[2] One of the earliest and simplest acetogenin, (+)-ancepsenolide had its plane structure established for 25 years,[3] while its absolute configuration was just revealed recently by the synthetic method.[4] As part of our research interests, we developed a practical approach to construct the butenolide subunit and was applied in the synthesis of acetogenins.[5] Herein, we wish to report the synthesis of (+)-ancepsenolide utilizing this method.

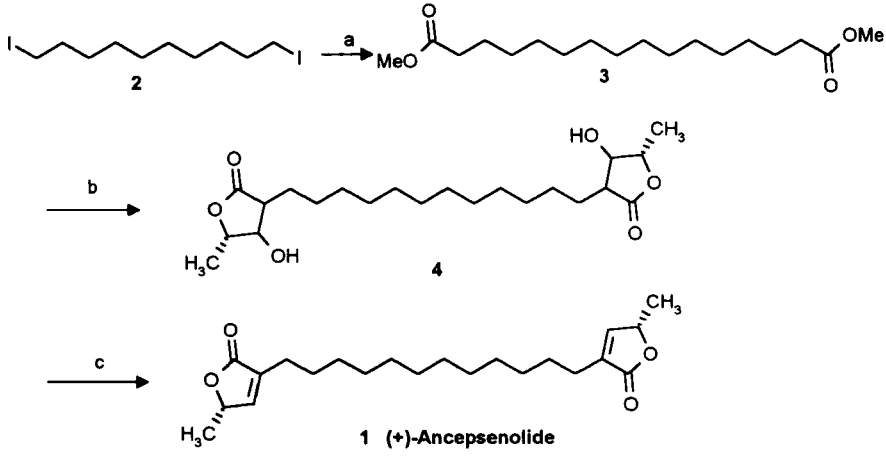


Annonacin



(+)-Ancepsenolide

(+)-Ancepsenolide represented a typical molecule with C_2 symmetry from which our two-directional synthetic strategy derives.



Reagents and conditions: a) $NiCl_2 6H_2O$ (2 eq.), Zn dust (10 eq.), methyl acrylate (9 eq.), py, rt, 53%. b) [1] LDA, THF-HMPA, -78°C; [2] (S)-*O-tert*-butyldimethylsilyl lactal, -78°C; [3] 5% (v/v) 49% HF, CH_3CN-THF (2:1), rt, 60% overall. c) [1] MsCl, Et_3N, DMAP, CH_2Cl_2, rt; [2] DBU, THF, rt, 96% overall.

At first, hexadecanyl dicarboxylic acid dimethyl ester **3** was prepared from a reductive Michael-type addition of methyl acrylate with 0.5 equivalent of 1,10-diiododecane **2** in the presence of zinc dust and $NiCl_2 \bullet 6H_2O$ in pyridine,[6] while 1,10-dibromodecane only gave a lower yield of mono-adduct with a catalytic amount of $Bu_4N^+I^-$ under the similar reaction condition. The lithium enolation of the diester was achieved by the treatment of **3** with LDA solution. The resulting solution was reacted with (S)-*O-tert*-butyldimethylsilyl lactal to give the aldol-type adducts as a mixture of diastereomers which was subsequently treated with 5% (v/v) 49% HF in THF-CH_3CN (1:2) at room temperature. A relatively simple

diastereomeric mixtures **4** were produced as white powder. Our initial attempt for its deprotection and lactonization with catalytic pyridinium p-toluenesulfonate in MeOH under reflux was failed. The final olifination was achieved by mesylation with MsCl and Et_3N and β-elimination with DBU at room temperature to give (+)-ancepsenolide (**1**) in high yield.

In conclusion, a two-directional strategy was developed for the synthesis of (+)-ancepsenolide. All physical data of the synthetic sample were coincident with those reported by Trost et al.[4]

Experimental Section

General The therometer was uncorrected. Opitical rotations were measured on a Perkin-Elmer 241 MC polarimeter. IR spectra were obtained on a Shimazu IR-440 spectrophotometer. ^1H NMR spectra were taken at an Bruker AMX-300 spectrometer. Mass spectra were obtained on a VG Quattro GC/MS/MS spectrometer. Column chromatography was performed on silica gel H (400 Mesh).

Hexadecanyl dicarboxylic acid dimethyl ester (3) To a 100 mL-flask was added powdered $NiCl_2{\cdot}2H_2O$ (2.38 g, 10 mmol), activated zinc dust (3.27 g, 50 mmol), pyridine (20 mL) and methyl acrylate (4 mL, 45 mmol) under nitrogen atmosphere. This mixture was well stirred at 60^0C for 30 min until a dark-red suspension was resulted. To this cooled mixture was then added the solution of diiododecane (1.97 g, 5 mmol) in pyridine (10 mL). The reaction mixture was then stirred overnight at room temperature. The mixture was diluted with EtOAc (40 mL) and filtered through a pad of Celite. The pad was washed with EtOAc (20 mL x 3). The combined organic layers were washed successively with 1.0 N HCl (50 mL x 4), 1 M EDTA (40 mL), and brine (40 mL x 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether-EtOAc = 50:1) to give a white solid (832 mg, 53%). IR(CCl_4): 1725 cm^{-1}. ^1H NMR (CCl_4, 60 MHz): 3.56 (6H, s), 2.21 (4H, t, J=6 Hz), 1.30 (24H, brm) ppm.

Bis-hydoxylated lactone (4) To a well-stirred solution of diisopropylamine (448 mg, 4.43 mmol) in anhydrous THF (18 mL) was added n-BuLi solution in hexanes (1.8 M, 2.2 mL, 4 mmol) at -78^0C under N_2 atmosphere. After 30 min, HMPA (0.8 mL, 4.60 mmol) was added and the mixture was stirred for an additional 0.5 h. Dimethyl ester **3** (560 mg, 1.78 mmol) in THF (5 mL) was then

added via syringe and the whole solution was stirred for 30 min at -78^{0}C. The freshly prepared (S)-*O-tert*-butyldimethylsilyl lactal (735 mg, 3.91 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 2 h until the aqueous sat. NH_4Cl (5 mL) was added to quench it. After usual workup, the crude product (720 mg) was obtained as a clear oil which was used for next step without further purification.

The resulting residue in CH_3CN (10 mL) and THF (5 mL) was treated with 49% aqueous HF (0.8 mL) at room temperature for 2 days. The reaction mixture was slowly poured into 5% $NaHCO_3$ solution (10 mL) under stirring and extracted with ether (10 mL x 3). The combined organic layers were washed with brine (10 mL x 2) and dried over Na_2SO_4. The solvent was removed and a white solid was produced. Recrystallization of the crude product from ether (5 mL) and petrolum ether (10 mL) gave a white powdered solid (423 mg, 60% from **3**). IR(KBr): 3450, 1750 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 4.51 (1H, m), 4.20 (1H, m), 3.83 (1H, dd, J=8.2, 8.4 Hz), 3.69 (1H, d, J=15.1 Hz), 2.59 (2H, m), 2.13 (2H, brs), 1.45 (6H, d, J=6.3 Hz), 1.26 ~ 1.95 (24H, m) ppm. FABMS(m/z): 399 [MH^+], 381[MH^+-H_2O), 362 [M^+-H_2Ox2].

(+)-Ancepsenolide (1) The bis-hydroxylated lactone **4** (230 mg, 0.578 mmol) was treated with MsCl (145 mg, 1.27 mmol), triethylamine (257 mg, 2.54 mmol) and a catalytic amount of 4-N,N-dimethylaminopyridine in dry dichrolomethane (5 mL) at room temperature for 12 h. The mixture was diluted with ether (10 mL) and washed with water (10 mL), 1 N HCl (10 mL), water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solvent was removed and the crude product was dried *in vacuum* prior to use for next step.

The resulting oil (310 mg) was dissolved in dry THF (3 mL) and then treated with DBU (190 mg, 1.17 mmol) at room temperature for 5 h until a single spot was detected on TLC. The solvent was removed and the residue was purified on a silica gel column (petroleum ether-EtOAc(v/v) = 4:1). (+)-Ancepsenolide was obtained as a white solid (201 mg, 96% from **4**). mp. 96-98^{0}C. lit[4]: mp. 95.5-97.5^{0}C. $[\alpha]_D^{20}$ 39.2 (0.76, $CHCl_3$). lit[4]: $[\alpha]_D^{20}$ 39.6 (0.4, $CHCl_3$). IR (KBr): 1740, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.98 (2H, d, J=1.4 Hz), 4.98 (2H, dq, J=1.5 Hz, 6.7 Hz), 2.26 (4H, J=1.1, 7.3 Hz), 1.55 (4H, m), 1.40 (6H, d, J=6.8 Hz), 1.27 (16H, brm) ppm. EIMS (m/z, %): 363 [MH^+, 23.31].

Acknowledgment: We are grateful to the National Science Foundation of China for financial support (1995-1997).

References:

1. a) Rupprecht, J. K., Hui, Y.-H., McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. b) Fang, X.-P., Rieser, M. J., Gu, Z.-M., McLaughlin, J. L. *Phytochemical Analysis* **1993**, *4*, 27. c) Yao, Z.-J., Wu, Y.-L. *Youji Huaxue*, **1995**, *15*, 120.
2. McCloud, T. G., Smith, D L., Chang, C.-J., Cassady, J. M. *Experientia*, **1987**, *43*, 947.
3. Schmitz, F. J., Lorance, E. D. *J. Org. Chem.* **1971**, *36*, 719.
4. Trost, B. M., Muller, T. J. J., Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888. for a synthesis of the racemate, see: Podraza, K. F., Sneden, A. T. *J. Nat. Prod.* **1985**, *48*, 792.
5. a) Yao, Z.-J., Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157. b) Yao, Z.-J., Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 1170.
6. Manchand, P. S., Yiannikouros, G. P., Belica, P. S., Madan, P. *J. Org. Chem.* **1995**, *60*, 6574.

(Received in Japan 13 February 1996)