Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 1011-1014, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02363-1

A Short Chemoenzymatic Synthesis of (+)-Multifidene and (+)-Viridiene

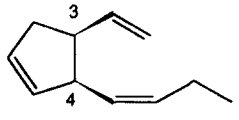
Jacques Lebreton, Véronique Alphand and Roland Furstoss*

Groupe de Chimie Organique et Bioorganique, associé au CNRS, Faculté des Sciences de Luminy, Case 901, 163, av. de Luminy, F - 13288 Marseille Cedex 9, France.

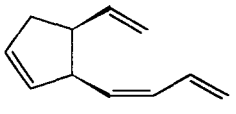
Abstract : (+)-Multifidene **1** and (+)-Viridiene **2**, the major constituents of some brown algae pheromones, were synthesized in five steps from racemic bicycloheptenone **3** *via* a novel microbiological Baeyer-Villiger oxidation.performed using the fungi *Cunninghamella echinulata.*

The combined use of chemical synthesis and of enzymatic (or microbiologically) mediated transformations is a new very promising strategy for the synthesis of enantiopure bioactive compounds and a variety of such molecules have been synthesized recently following these combined methodologies.[1] We have been interested in using this type of approach for the synthesis of some bioactive molecules,[2] and have recently focused our attention on some algae pheromones.[3] In many species of marine brown algae, female gametes secrete a complex bouquet of olefinic C_{11} hydrocarbons as chemical signals to stimulate and attract male gametes and thus initiate the sexual fusion. The threshold concentration for biological activity of these simple and highly volatile pheromones is quite impressive, usually in the range of 10^{-12} to 10^{-9} mol/l sea water.[4]

(+)-Multifidene-**1** is the major and most active pheromone of the algae *Cutleria multifida* and *Chorda tomentosa*[4] and (+)-Viridiene **2** was isolated as a major component in *Desmarestia aculeata* and *viridis*.[5]



(+)-(3*S*,4*S*)-Multifidene **1**



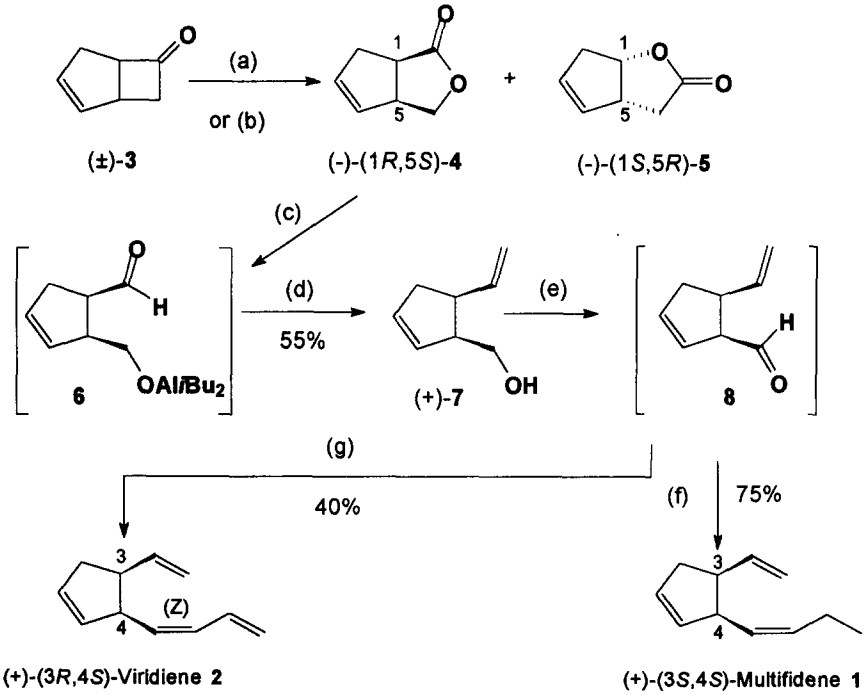
(+)-(3*R*,4*S*)-Viridiene **2**

In this paper we describe a very short and efficient enantioselective synthesis of (+)-Multifidene **1**[6] and (+)-Viridiene **2**[7] *via* a chemoenzymatic strategy, starting from the enantiopure bicyclic lactone **4** prepared using a new microbiologically mediated Baeyer-Villiger oxidation of the bicyclic ketone **3**.

We have previously described that some *Acinetobacter* bacteria are able to oxidize ketone **3** in an enantiodivergent fashion, thus allowing the concomitant synthesis of both enantiopure (-)-(1*R*,5*S*)-**4** (ee > 98 %) and (-)-(1*S*,5*R*) **5** (ee > 95 %).[8] However, this approach necessitates the separation of the two lactones, which may be cumbersome when used on large scale quantities. We recently have discovered that this problem can be overcome by performing this Baeyer-Villiger oxidation using the fungus *Cunninghamella echinulata* (NRRL 3655) which leads to the single enantiopure (ee > 98%) (-)-(1*R*,5*S*) enantiomer of **4** in 30% yield.

As described in scheme 1, reduction of this lactone **4** with diisobutylaluminium hydride (DIBAL-H) at low temperature in toluene, followed by *in situ* condensation of the intermediate aldehyde **6** with triphenyl(methylidene)phosphorane (formed from the phosphonium bromide with BuLi as base) afforded the hydroxyolefin **7** in acceptable yield (50 to 55 %).[9] Attempts to improve the yield of this transformation by changing either the base used to form the ylide [tBuOK, sodium bis(trimethylsilyl)amide (NaHMDS)] and/or the solvent for the reduction step (THF instead of toluene) were unsuccessful. Nevertheless, no by-product was formed in this step (or even detected by analysis of the ^{1}H NMR spectrum of the crude mixture), indicating that this moderate yield is probably due to the high volatility of the hydroxyolefin **7**. To reach our targets, the most

Scheme 1 : Synthetic way to (+)-(3*S*,4*S*)-Multifidene 1 and (+)-(3*R*,4*S*)-Viridiene 2.



Conditions : (a) Culture of *Acinetobacter*. (b) Culture of *C. echinulata*. (c) 1.4 eq. DIBAL-H, tol., -78°C, 1h. (d) 2.2 eq. $Ph_3P{=}CH_2$, THF, -78°C to rt, 12h. (e) 1.3 eq. $(ClCO)_2$, 2.6 eq. DMSO, THF, -78°C, 3h, then 5.2 eq. Et_3N, -78° to 0°C, 1h. (f) ~10 eq. $Ph_3P{=}CH$-Et, -78°C to rt, 12h. (g) ~10 eq. $Ph_3P{=}CH{-}CH{=}CH_2$, -100°C to rt, 12h, then 4-phenyl-2,3,4-triazoline-3,5-dione, THF, rt, 5 min.

obvious and direct route was the oxidation of **7** to the corresponding aldehyde **8**, followed by Wittig olefination. However, two different reports from the literature mentioned the failure to use the aldehyde **8** for construction of the C-4 side chain with either stabilized or non-stabilized phosphonium ylides.[6e,10] In order to avoid either isomerisation of **8** to its conjugated isomer or epimerisation, we decided to prepare and trap this unstable aldehyde *in situ* using Wittig reagents. However, although the one pot (two-steps) Swern-Wittig condensation is largely used with stabilized ylides,[11] only one example has been reported to our knowledge with such non-stabilized intermediates.[12] Thus, **7** was oxidized in THF using a typical Swern oxidation procedure[11b] and the resulting solution of aldehyde **8** was treated at -78°C by slow addition of a triphenyl(propylidene)phosphorane solution (formed from the phosphonium bromide using NaHMDS as a base). After purification, we were gratified to isolate (+)-Multifidene **1** as a single isomer in 75% yield (2 mmol. scale). No epimerization and /or isomerisation of **8** were observed during this transformation The obtained (+)-Multifidene **1** was shown by GC analysis to be more than 98% pure, indicating that very high (Z) side-chain selectivity did occur.[13] The spectral ^{1}H and ^{13}C NMR data for (+)-**1** were identical with those previously reported.[6a] The enantiomeric purity of (+)-**1** was checked by chiral GC analysis which indicated an ee value of 98%.[15] The (3*S*,4*S*) absolute configuration of our product, which results from the absolute configuration of the starting lactone chiron, was ascertained by the positive sign of its optical rotation ($[\alpha]_{578}^{18}$ = +259 (c = 1, CCl_4) (literature[6b] $[\alpha]_{578}^{20}$ = + 261 (c = 0.83, CCl_4)). as previously described by Jaenicke and coll.[16]

The natural enantiomer (+)-(3*R*,4*S*) Viridiene **2** was similarly synthesized from the olefinic alcohol **7** (2 mmol scale). Thus, a triphenyl(propenylidene)phosphorane solution was slowly added to the aldehyde solution at 100°C.[17] After work-up, this afforded a 75/25 mixture[18] of the Z and E-isomers of (+)-**2** in 70-80% crude yield. (+)-Viridiene **2** was obtained stereochemicaly pure in 40% yield after removal of the E isomer using 4-phenyl-2,3,4-triazoline-3,5-dione as selective dienophile.[19] The spectral ^{1}H NMR data of (+)-**2** were in good agreement with those previously reported[7,20] and its enantiomeric purity was shown by chiral GC analysis to be higher than 98%[21] ($[\alpha]_{578}^{18}$ = + 239 (c = 2.1, pentane); literature[7a] $[\alpha]_{578}^{20}$ = + 228 (c = 0.224, pentane)).

In conclusion, very short five-step synthese of the enantiopure (+)-Multifidene **1** and (+)-Viridiene **2** have been achieved, respectively in 18% and 10% overall yields. These syntheses implie a novel enantioselective Baeyer-Villiger oxidation of commercial racemic bicycloheptenone **3** which was performed using the fungus *Cunninghamella echinulata* (NRRL 3655). Our strategy compares very favourably with the ones previously described[6,7] which required 9 to 11 steps to synthesize the same compounds in less than 5% overall yield. Work is currently in progress in our laboratory in order to explore further possibilities offered by combining a biotransformation methodology with chemical synthesis.

Acknowledgements. This work has been achieved in the context of an European Community "Human Capital and Mobility" Program.

References and Notes.

(1) Theil F. *Tetrahedron: Asymmetry* **1995**, 6, 1693-1698; Johnson C. R., Nerurkar B. M., Golebiowski A., Sundram H., Esker J. L. *J. Chem. Soc., Chem. Commun* **1995**, 1139-1140; For an excellent review see : Azerad R. *Bull. Soc. Chim. Fr.*, **1995**, *132*, 17-51 and literature cited.

(2) Archelas A., Furstoss R. *Tetrahedron Lett.*, **1992**, *33*, 5241-5242; Alphand V, Archelas A., Furstoss R. *J. Org. Chem.* **1990**, 55, 347-350.

(3) Wirth W., Fischer-Lui I., Boland W., Icheln D., Runge T., König W. A., Phillips J., Clayton M. *Helv. Chim. Acta.*, **1992**, *75*, 734-744 and literature cited.

(4) Maier I., Müller D. G., Gassmann G., Boland W., Marner F.-J., Jaenicke L. *Naturwissenschaften*, **1984**, *71*, 48-49.

(5) Müller D. G., Peters A., Gassmann G., Boland W., Marner F.-J., Jaenicke L. *Naturwissenschaften*, **1982**, *69*, 290-291.

(6) For synthesis of (+)-**1** see a) Hemamalini S., Scheffold R. *Helv. Chim. Acta.*, **1995**, *78*, 447-451. For (+)-**1** and (-)-**1** see b) Boland W., Jaenicke L., Müller D. G. *Liebiegs Ann. Chem.*, **1981**, 2266-2271. For (-)-**1** see c) Kramp P., Helmchen G., Holmes, A. B. *J. Chem. Soc., Chem. Commun.*, **1993**, 551-552. For racemic **1** see d) Randall M. L., Tallario J. A., Snapper M. L. *J. Am. Chem. Soc.*, **1995**, *117*, 9610-9611. e) Burks J. E., Crandall J. K. *J. Org. Chem.*, **1984**, *49*, 4663-4670. f) Crouse G. D., Paquette L. A. *J. Org. Chem.*, **1981**, *46*, 4272-4274. g) Boland W., Jaenicke L. *J. Org. Chem.*, **1979**, *44*, 4819-4824. h) Boland W., Jaenicke L. *Chem. Ber.*, **1978**, *111*, 3262-3275.

(7) For synthesis of (+)-**2** see a) Boland W., Jaenicke L., Niedermeyer U., Jaenicke L., Görish H. *Helv. Chim. Acta.*, **1985**, *68*, 2062-2073. For racemic **2** see b) ref 5d. c) Boland W., Jakoby K., Jaenicke L. *Helv. Chim. Acta.*, **1982**, *65*, 2355-2362.

(8) Alphand V., Archelas A., Furstoss R. *Tetrahedron Lett.*, **1989**, *30*, 3663-3664. Alphand V., Furstoss R. *J. Org. Chem.*, **1992**, *57*, 1306-1309.

(9) Boland W., Ney P., Jaenicke L. *Synthesis*, **1980**, 1015-1017.

(10) Wirth D., Boland W., Jaenicke L. *Helv. Chim. Acta.*, **1992**, *75*, 751-758.

(11) For a recent ref. see : a) Ahman J., Somfai P. *Tetrahedron Lett.*, **1995**, *36*, 303-306. For a review on Swern oxidation see b) Tidwell T. T. *Synthesis*, **1990**, 857-870.

(12) Ireland R.E., Norbeck D. W. *J. Org. Chem.*, **1985**, 50, 2198-2202.

(13) Attempts to perform the same transformation in similar conditions using the Dess-Martin[14] reagent as oxidant led to a 7:3 mixture of **1** and its C-4 epimer in 50-60% yield : chemical shifts of the protons at 3.31 ppm (C-4, m (*t*-like)) and at 2.92 ppm (C-3, *qi.*, J = 8.2 Hz) on the ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of the crude mixture are in agreement with the previous data reported in the literature (see ref. 6h) for the C-4 epimer of Multifidene **1**.

(14) Meyer S. D., Schreiber S. L. *J. Org. Chem.*, **1994**, *59*, 7549-7552.

(15) Enantiomeric excesses were determined by chiral GC analysis using a 25 m capillary column (6-*O*-methyl-2,3-di-*O*-pentyl)-β-cyclodextrine and a racemic sample as reference (the retention time order was determined by coinjection racemic/chiral material). For **1** : oven at 40°C (+)-(3*S*,4*S*)-Multifidene **1** t_R = 27.6 min. and (-)-(3*R*,4*R*)-Multifidene **1** t_R = 27.9 min..

(16) Boland W., Mertes K., Jaenicke L., Müller D. G., Fölster E. *Helv. Chim. Acta.*, **1983**, *66*, 1905-1913.

(17) The addition of a triphenyl(propenylidene)phosphorane solution to the reaction mixture at -78°C gave rise to a nearly 1/1 mixture of (+)-Viridiene **2** (Z isomer) and of its E isomer in low yield.

(18) The Z/E ratio was determined by integration of the C-4 proton signal in the ^{1}H NMR spectrum of the crude mixture (see ref. 19) and by GC analysis (see ref. 15) : oven at 40°C (+)-(3*R*,4*S*)-Viridiene **2** t_R = 26.5 min. and E-Viridiene **2** t_R = 26.0 min..

(19) Cookson R.C., Gilani S.S.H., Stevens I.D.R. *J.Chem. Soc.(C)* **1967**,1906-1909.

(20) (+)-Viridiene **2** : ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) : 2.22-2.58 (*m*, 2H); 3.03 (*qi*, J = 8.0 Hz, 1H (C-3)); 3.80 (*t*, J = 9.3 Hz, 1H (C-4)); 4.90-5.30 (*m*, 6H); 5.60 (*m*, 1H); 5.75-5.95 (*m*, 2H); 6.01 (*t*, J = 17.8 Hz, 1H); 6.68 (*ddd*, J = 11.0, 11.0, 17.8 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$) δ (ppm) : 36.9 (t), 46.8 (d), 47.1 (d), 114.4 (t), 117.4 (t), 129.2 (d), 130.4 (d), 131.7 (d), 132.2 (d), 133.5 (d), 139.6 (d).
E-Viridiene **2** : on the ^{1}H NMR (250 MHz, $CDCl_3$) spectrum of the crude mixture the E-Viridiene **2** could be only distinguished from Viridiene **2** by these two chemical schifts : δ (ppm) 3.30 (br *t*, J = 8.1 Hz, 1H (C-4)); 6.25 (*ddd*, J = 10.5, 10.5, 17.0 Hz, 1H). ^{13}C NMR (250 MHz, $CDCl_3$) δ (ppm) : 37.1 (t), 47.2 (d), 51.7 (d), 114.3 (t), 115.2 (t), 130.7 (d), 130.9 (d), 133.1 (d), 134.6 (d), 137.0 (d), 139.9 (d).

(21) GC analysis (see ref. 15) : oven at 35°C (+)-(3*S*,4*S*)-Viridiene **2** t_R = 37.1 min. and (-)-(3*R*,4*R*)- Viridiene **2** t_R = 38.2 min..

(*Received in France* 10 *November* 1995; *accepted* 11 *December* 1995)