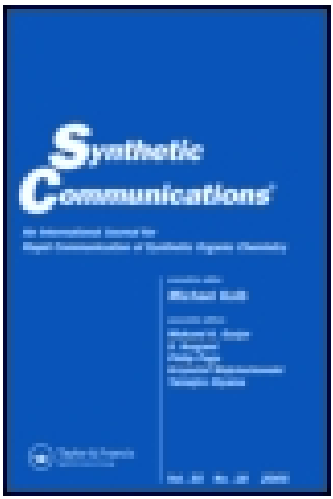


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Short Formal Synthesis of (-)-Serricornine

Ronaldo A. Pilli [a] & Carlos K. Z. De Andrade [a]
[a] Universidade Estadual de Campinas, Instituto de Química , 13081-970, Campinas, SP Brazil
Published online: 23 Sep 2006.

To cite this article: Ronaldo A. Pilli & Carlos K. Z. De Andrade (1994) A Short Formal Synthesis of (-)-Serricornine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:2, 233-241, DOI: 10.1080/00397919408013822

To link to this article: http://dx.doi.org/10.1080/00397919408013822

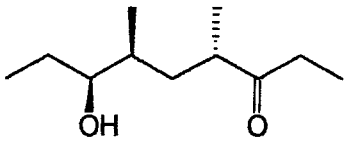
SYNTHETIC COMMUNICATIONS, 24(2), 233-241 (1994)

A SHORT FORMAL SYNTHESIS OF (-)-SERRICORNINE

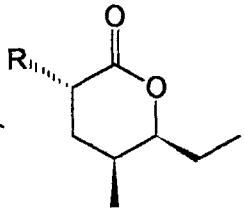
Ronaldo A. Pilli* and Carlos K.Z. de Andrade
Universidade Estadual de Campinas, Instituto de Química
13081-970 Campinas,SP Brazil

A short and efficient formal synthesis of serricornine (**1**), the sex pheromone of *Lasioderma serricorne F.*, is described. The homochiral aldol **5** is straightforwardly converted to tosylate **9** to give homochiral lactone **2a** (6 steps, 22% overall yield from oxazolidinone **4**), a known precursor of (-)-**1**.

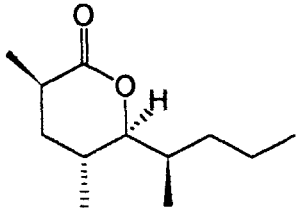
(-)-Serricornine (**1**) is the sex pheromone produced by the female cigarette beetle *Lasioderma serricorne F.* which is the major pest of cured tobacco leaves[1]. Due to the pheromonal activity both in its natural and racemic forms[2], several total syntheses of **1** have appeared in the literature[3] including two of its natural form [4,5] and two of its racemic form[6,7] which makes use of lactone **2b** as the ultimate precursor.



1



2a R=H
2b R=CH_3



3

Despite its popularity as a synthetic target few approaches to (-)-1 proved to be synthetically feasible from a practical point of view due either to the lack of stereocontrol during the construction of its asymmetric centers or to the excessive number of steps involved.

We have recently disclosed[8] an efficient and stereoselective total synthesis of (+/-)-invictolide (**3**) featuring an intramolecular alkylation step in the construction of the δ-lactone ring which coupled to enantioselective aldol methodologies should provide ready access to other natural products derived from the polyketide pathway.

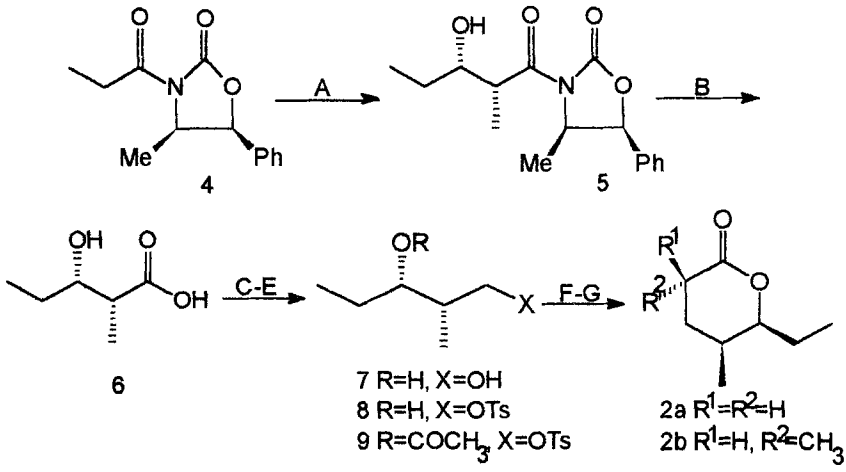
Results and Discussion

Among the conceivable methods to establish the absolute configuration of the three chiral centers present in **1**, aldol condensation stands as one of the most attractive due to the large number of reliable protocols available[9]. In our case, the chirality at C(6) and C(7) was efficiently established using Evans' methodology, the N-propionyl oxazolidinone **4** being prepared from readily available (2S,3R)-norephedrine[10]. The corresponding boron enolate was condensed with propionaldehyde to afford, after chromatographic purification , β–hydroxyimide **5** ($[\alpha]_D$=+20.69, c3.70, CH_2Cl_2) as a single diastereoisomer by ^{1}H- and ^{13}C-NMR spectroscopies.

Basic hydrolysis (LiOOH/THF/H_2O, rt) allowed the isolation of β–hydroxycarboxylic acid **6** (89 % yield, $[\alpha]_D$=–4.10, c4.80, CH_2Cl_2) and recovery of the corresponding oxazolidinone, in 90% yield ($[\alpha]_D$ =+161.6, c1.00, $CHCl_3$). Compound **6** was straightforwardly converted to its monotosylated derivative **8** ($[\alpha]_D$= -2.50, c3.00, CH_2Cl_2), in 90% overall yield, which was shown to be 91% enantiomerically pure through the ^{1}H-NMR analysis of its ester derivative with (R)-(+)-Mosher's acid[11] (a 21:1 ratio of the double triplets at δ5.07 and 5.01 ppm, assigned to H(3) of the major and minor isomers, respectively.

Ready access to lactone **2a** was secured through an intramolecular cyclization reaction involving the potassium enolate of

the acetyl derivative **9**. Although a conceivably simple approach to the construction of δ–lactones from aldol precursors, few successful examples of this reaction can be found in the literature[8,12].After considerable experimentation, we found out that the 6-exo-tet cyclization process could be carried out upon treatment of a THF solution of the acetyl derivative **9** and potassium **tert**-butoxide, at room temperature, and δ–lactone **2a**($[\alpha]_D$=-58.0, c0.90, CH_2Cl_2;lit.[13]: $[\alpha]_D$=-65.82., c1.024, $CHCl_3$) was isolated in 61% yield, after acidic work-up.



Scheme. A.i)($^nC_4H_9)_2BOTf$, CH_2Cl_2, O°C; ii)C_2H_5CHO,-78°C; iii) H_2O_2,H_2O,MeOH(80%);**B.**LiOH,H_2O_2,THF, H_2O (89%);**C.**$LiAlH_4$, THF(63%); **D.**p-TosCl,Et_3N,CH_2Cl_2,4-DMAP(cat.),(90%); **E.**Ac_2O, CH_2Cl_2,Et_3N,4-DMAP (cat.),(91%); **F.tert**-BuOK,THF,rt (61%); **G.** ref.4.

Due to the **cis** relationship of the two substituents in the six-membered ring, δ–lactone **2a** is known to be stereoselectively alkylated to afford **2b** ($[\alpha]_D$ =-42.0, c0.50, $CHCl_3$)[4a,13], in 75%

yield. Since **2b,** both in its racemic[6,7] and optically pure[4a,b] forms, has been previously converted to the sex pheromone, the results described herein constitute a short and efficient formal synthesis of (-)-serricornine (**1**) since it affords homochiral lactone **2a,** in 6 steps and 22% overall yield, from oxazolidinone **4**.

Experimental

Unless otherwise noted materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone immediately prior to use. Diisopropylethylamine, triethylamine and dichloromethane were distilled from calcium hydride. The reactions involving organometallic reagents were carried out under argon atmosphere.

Column chromatography was carried out in silica gel (70-230 Mesh) and the R_f values were measured in standard grade TLC silica gel and 30% ethyl acetate in hexanes (v/v) as eluent.

^{1}H-NMR spectra were determined in $CDCl_3$ or CCl_4 at 300 MHz and ^{13}C-NMR at 75.2 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane and ^{1}H-NMR spectra data are tabulated in order: multiplicity (s, singlet;d, doublet;t, triplet;dd, double doublet;dt, double triplet;q, quartet; dq, double quartet; qt, quintuplet; m, multiplet), number of protons, coupling constants in hertz. Infrared spectra were determined with a Perkin-Elmer 399B spectrophotometer. Elemental analyses were performed at Universidade Estadual de Campinas and specific rotations were measured at 25°C on a Polamat polarimeter (Carl Zeiss) at 546 nm (Hg lamp) and corrected to 589 nm (sodium D line).

(4R,5S)-N-[(2'R,3'S)-3'-Hydroxy-2'-methyl-1'-oxopentyl]-4-methyl-5-phenyl-2-oxazolidinone (**5**).

To a 0.5M solution of oxazolidinone **4** (7.87 mmol, 1.82g) in CH_2Cl_2, under argon and at 0°C, was added di-n-butylboron triflate (9.84 mmol, 9.84 mL, 1.0M solution in CH_2Cl_2) followed by

diisopropylethylamine (10.62 mmol, 1.85 mL). After allowing 1.0 h for complete enolization, the reaction mixture was cooled to -78°C and freshly distilled propionaldehyde (15.74 mmol, 1.13 mL) was added. Stirring was continued for 45 min. at -78°C, followed by 2.0 h at room temperature. The reaction mixture was quenched with pH 7 phosphate buffer (10 mL) and the resulting mixture was extracted three times with CH_2Cl_2 and the organic solvent was rotary-evaporated. The residue was dissolved in methanol (10mL), 15 mL of a 3:1 (v/v) solution of methanol/hydrogen peroxide (30% v/v) was added at 0°C and the mixture allowed to stir for 1.0 h. The reactionmixture was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$. After filtration, the solvent was removed in a rotary evaporator and the pale yellow oil was chromatographed on silica gel (10% ethyl acetate in hexanes, v/v) to afford 1.83g (6.26 mmol, 80% yield, R_f=0.27) of aldol **5** as a pale yellow oil.

$[\alpha]_D$=+20.69 (c3.70, CH_2Cl_2)

IR(film., KBr): 3459, 1780 and 1699 cm^{-1}.

^{1}H-NMR($CDCl_3$):δ 0.89 (d,3H,J=6.6), 1.00 (t,3H,J=7.5), 1.24 (d,3H,J=7.0), 1.40-1.65 (m,2H), 3.00 (s,br,1H), 3.81(dq,1H,J=7.0 and 2.7), 3.86-3.91 (m,1H), 4.80 (qt,1H,J=7.3), 5.70 (d,1H,J=7.3), 7.29-7.43 (m,5H). ^{13}C-NMR ($CDCl_3$):δ10.20, 10.46, 14.41, 26,95, 41.97, 54.92, 73.29, 79.12, 125.90, 129.00, 129.10, 133.48, 152.92, 177.69.

(2S,3S)-3-Hydroxy-2-methyl pentanoic acid (**6**).

To a solution of aldol **5** (0.51 mmol, 0.150 g), THF (7.0 mL) and water (4.0 mL) at 0°C were added hydrogen peroxide (2.04 mmol, 0.2 mL, 30%v/v) and lithium hydroxide monohydrate (1.02 mmol, 24.5 mg). The reaction mixture was stirred for 1.0 h and then a solution of sodium thiosulfate (0.25 g in 1.0 mL of water) was added followed by a 5N solution of $NaHCO_3$ (4.0 mL). Extraction with CH_2Cl_2 gave the recovered chiral oxazolidinone (80.0 mg, 90% yield, $[\alpha]_D$=+161.6 (c1.00, $CHCl_3$)). The aqueous phase was acidified (pH 2.0) and then extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford hydroxyacid **6** (60.0 mg, 89% yield).

$[\alpha]_D$=-4.10 (c4.80,CH_2Cl_2).

IR(film, KBr): 3390 (br), 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$):δ0.99 (t,3H,J=7.5), 1.20 (d,3H,J=7.3), 1,45-158 (m,2H), 2.61 (dq,1H,J=7.2 and 3.5), 3.90 (m,1H), 6.3-6.5 (s,br,2H).^{13}C-NMR ($CDCl_3$):δ10.35, 10.45, 26.75, 43.97, 73.51, 181.29.

(2S,3S)-2-Methyl-1,3-pentanediol (**7**).

To a suspension of $LiAlH_4$ (4.16 mmol, 0.160g) in THF (4.0 mL) at 0°C was added hydroxyacid **6** (2.1 mmol, 0.275 g, 0.5M in THF). The reaction mixture was allowed to stir at room temperature overnight, diluted with ether (10 mL) and successively treated at 0°C with water (0.16 mL), 15% aqueous NaOH (0.16 mL) and water (0.48 mL). The inorganic solids were washed with ether (3x10 mL) and the organic extracts were dried over $MgSO_4$and evaporated under reduced pressure. The crude colorless oil was purified by chromatography on silica gel (20% ethyl acetate in hexanes, v/v) to give diol **7** (0.155g, 63% yield, R_f=0.24).

$[\alpha]_D$=+1.11 (c4.50, CH_2Cl_2).

IR (film, KBr): 3356 cm^{-1}.

^{1}H-NMR($CDCl_3$):δ 0.89 (d,3H,J=7.1), 0.93 (t,3H,J=7.5), 1.40-1.60 (m,2H), 1.75-1.85 (m,1H), 3.10 (s,br,1H), 3.35 (s,br,1H), 3.68 (d,2H,J=5.6), 3.70-3.75 (m,1H). ^{13}C-NMR ($CDCl_3$):δ9.75, 10.43,26.69, 38.52, 66.82, 75.76.

(2S,3S)-2-Methyl-1-O-p-toluenesulfonyl-1,3-pentanediol (**8**).

To a 0.5M solution of diol **7** (1.06 mmol, 0.125 g) in CH_2Cl_2 at 0°C was added p-toluenesulfonyl chloride (1.16 mmol, 0.222 g), triethylamine (1.16 mmol, 0.16 mL) and a catalytic amount (ca. 1 mol %) of N,N-dimethyl-4-aminopyridine (4-DMAP). The mixture was allowed to stand in the freezer overnight and it was then diluted with CH_2Cl_2. The phases were separated and the organic one was washed with water, 10% HCl, satd. aq. $NaHCO_3$, brine and dried over $MgSO_4$.Filtration, removal of the organic solvent under reduced pressure and silica gel chromatography (10% ethyl acetate in hexanes, v/v) of the crude product, afforded tosylate **8** (0.260g, 90% yield, R_f=0.59) as a colorless oil.

$[\alpha]_D$=-2.50 (c3.0, CH_2Cl_2).

IR(film, KBr): 3550, 1598, 1460 and 1356 cm^{-1}.

^{1}H-NMR ($CDCl_3$):δ 0.84 (d,3H,J=7.0), 0.91 (t,3H,J=7.0), 1.35-1.55 (m,2H), 1.85-1.95 (m,2H), 2.45 (s,3H), 3.57-3.63 (m,1H), 3.89 (dd,1H,J=10.0 and 6.0), 4.08 (dd,1H,J=9.7 and 7.7), 7.56 (d, 2H,J=8.4), 7.79 (d,2H,J=8.4). ^{13}C-NMR ($CDCl_3$):δ 9.21, 10.26, 21.43, 27.04, 37.21, 71.88, 72.80, 127.86, 129.88, 132.93, 144.87.

Elemental analysis calcd. for $C_{13}H_{20}SO_4$:C, 57.35%; H, 7.35%. Found: C, 57.20%; H, 7.50%.

(2S,3S)-3-O-Acetyl-2-methyl-1-O-p-toluenesulfonyl-1,3-pentanediol (**9**).

To a 0.5M solution of **8** (0.23 mmol, 0.063 g) in CH_2Cl_2 were added acetic anhydride (0.27 mmol, 0.03 mL), triethylamine (0.25 mmol, 0.04 mL) and a catalytic amount of N,N-dimethyl-4-aminopyridine (ca. 1 mol%). The reaction mixture was stirred at room temperature for 0.5 h and then poured into water. The phases were separated and the organic phase was washed with water, 10% HCl, satd. aq. $NaHCO_3$, brine and dried over $MgSO_4$. Filtration, removal of the organic solvent under reduced pressure and silica gel chromatography (10% ethyl acetate in hexanes, v/v) of the crude residue afforded **9** (0.066 g, 91% yield, R_f=0.67)as a colorless oil.

$[\alpha]_D$=-1.06 (c2.70, CH_2Cl_2).

IR(film, KBr): 1735, 1598 and 1460 cm^{-1}.

^{1}H-NMR ($CDCl_3$):δ 0.83 (t,3H,J=7.5), 0.92 (d,3H,J=7.0), 1.45-1.60 (m,2H), 1.97 (s,3H), 2.05-2.11 (m,1H), 2.45 (s,3H), 3.90 (dq, 2H, J=9.0 and 6.4), 4.78-4.84 (m,1H), 7.35(d,2H,J=8.2), 7.79 (d,2H,J=8.2). ^{13}C-NMR ($CDCl_3$):δ9.93, 11.05, 20.95, 21.68, 24.22, 35.75, 71.91, 74.83, 128.18, 130.08, 135.11, 145.06, 170.86.

Elemental analysis calcd. for $C_{15}H_{22}SO_5$:C, 57.32%; H,7.00%. Found: C, 57.27%; H, 7.09%.

(5S,6S)-6-Ethyl-tetrahydro-5-methyl-2H-pyran-2-one (**2a**).

To a suspension of **tert**-BuOK (1.20 mmol, 0.136g) in THF (6.0 mL) at 0°C was added **9** (0.30 mmol, 0.095 g, 0.5M in THF) dropwise. The cooling bath was removed and the reaction was let to stir at room temperature for 30 min. The solvent was removed under

reduced pressure and the mixture was diluted with ether (20 mL), acidified with conc. HCl (0.25 mL) and let to stir overnight at room temperature. Extraction with ether (3x10 mL), drying over $MgSO_4$, evaporation of the solvent under reduced pressure and column chromatography on Florisil (10% ethyl acetate in hexanes, v/v) afforded lactone **2a** (0.026g, 61% yield, R_f=0.60) as a colorless oil.

$[\alpha]_D$=-58.0 (c0.90, CH_2Cl_2).

IR (film, KBr):1740 cm^{-1}.

^{1}H-NMR (CCl_4):δ 0.96 (d,3H,J=7.1), 1.01 (t,3H,J=7.4), 1.50-1.78 (m,4H), 2.04-2.12 (m,1H), 2.54 (dd,2H,J=7.9 and 6.5), 4.18-4.24 (m,1H). ^{13}C-NMR (CCl_4):δ10.19, 12.57, 25.09, 26.44, 29.14, 82.78, 168.37.

Elemental analysis calcd. for $C_8H_{14}O_2$: C, 67.57%; H, 9.92%.Found : C-67.21%; H-10.24%

Acknowledgments

The authors gratefully acknowledge financial support for this work from Fundação de Amparo à Pesquisa do Estado de São Paulo (Fapesp), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and International Foundation for Science (IFS,Sweden).

Bibliography

1.a) Burkholder,W.E. **in** "Control of Insect Behavior by Natural Products", Wood,D., Silverstein, R. and Nakajima, M., Eds., Academic Press, New York, 1970;b)Chuman, T., Kohno,M., Kato, K. and Noguchi, M. Tetrahedron Lett. **1979**, 2361;c) Mori, K., Nomi, H., Chuman, T., Kato, K. and Noguchi, M. Tetrahedron **1982**,*38*,3705.

2.a) Chuman,T., Kato, K. and Noguchi, M., Agric.Biol.Chem. **1979**,*43*,2005;b) Ono, M., Onishi,I., Chuman, T., Kohno, M. and Kato, K., Agric.Biol.Chem. **1980**,*44*,2259; c) Chuman, T.,

Mochizuki, K., Mori, M., Kohno, M., Kato, K. and Noguchi, M., J.Chem.Ecol. **1985**,*11*,417. and references therein.

3.a) Shimizu, I., Hayashi, K., Ide, N. and Oshima, M., Tetrahedron **1991**,*47*,2991;b) Redlich, H., Samm, K., Lenfers, J.B. and Bruns, W., Carbohydrate Res. **1988**,*174*,341; c) Mori, K. and Watanabe, H. Tetrahedron **1985**,*41*,3423;f) Mori, M., Chuman, T., Kato, K. and Mori, K., Tetrahedron Lett. **1982**,*23*,4593.

4. Kobayashi, Y., Kitano, Y., Takeda, Y. and Sato, F., Tetrahedron **1986**,*42*,2937;

5. Katsuki,T. and Yamaguchi,M., Tetrahedron Lett. **1987**,*28*,651.

6. Bartlett, P.A., Richardson, D.P. and Myerson, J., Tetrahedron **1984**,*40*,3217.

7. Pilli, R. A. and Murta, M.M., Synth. Commun. **1988**,*18*,981.

8. Pilli, R. A. and Murta, M.M., J.Org.Chem. **1993**,*58,338.*

9. Heathcock, C.H. in "Asymmetric Synthesis", vol.3, part B, Academic Press, 1984, pp.111-212.

10.Evans, D.A., Bartroli,J. and Shih,T.L., J.Am.Chem.Soc. **1981**,*101*,2127.

11.a)Mosher,H.S., Dale,J.A. and Dull,D.L., J.Org.Chem. **1969**,*34*,2543;b)Rieser,M.J., Hui,Y., Rupprecht,J.K., Kozlowski,J.F., Wood,K.V., McLabughlin,J.L., Hanson,P.R., Zhuang,Z. and Hoye,T.R., J.Am.Chem.Soc. **1992**,*114*,10203.

12.Nakai,E., Kitahara,E., Sayo,N., Ueno,Y. and Nakai,T., Chem.Lett. **1985**,1725.

13. Takano,S., Sekiguchi,Y. and Ogasawara,K., Heterocycles **1989**,*29*,445

(Received in the USA 06 April 1993)