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Stereocontrolled Synthesis of Lissoclinolide by Sequential Transition Metal-Catalyzed Lactonization / Cross-Coupling Reactions

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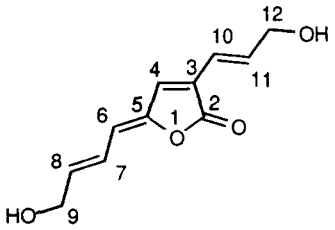
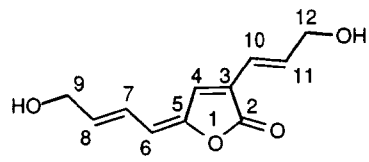
Abstract: Lissoclinolide, **1**, which is an antibiotic butenolide isolated from a Tunicate, has been synthesized stereoselectively by a reaction sequence in which the Ag(I)-catalyzed lactonization of (2*E*,6*E*)-2-bromo-8-hydroxy-2,6-octadien-4-ynoic acid, (*E*,*E*)-**13**, and the Pd/Cu-catalyzed cross-coupling reaction of so obtained (*Z*)-2-bromo-5-[(*E*)-4-hydroxy-2-butenylidene]-5*H*-furan-2-one, (*Z*,*E*)-**14**, with (*E*)-3-hydroxy-1-propenyltributylstannane, **15**, have been used as the key steps.

Lissoclinolide, **1**, is a (*Z*)-5-ylidene-5*H*-furan-2-one isolated from *Lissoclinum patella*, which exhibits activity against the Gram negative bacterium *Escherichia coli*.[1] Compound **1** has been reported as having the same general structure as a metabolic product named tetrenolin, which has been isolated from cultures of *Micropolispora venezualensis* and is bioactive against Gram positive bacteria.[2] In particular, it has been suggested that the structure of tetrenolin, **2**, differs from that of **1** in the configuration of the $\Delta^{5,6}$ double bond.[1]



1



2

To the best of our knowledge no synthesis of compounds **1** and **2** has been reported in the literature. We now wish to describe the first stereocontrolled synthesis of **1** which is based on our recently developed general procedure for the preparation of 3-substituted and 3,4-disubstituted (*Z*)-5-ylidene-5*H*-furan-2-ones, **5**.[3] This procedure involves a Pd(II)- or Ag(I)-mediated cyclization of easily available (*E*)-3-(1-alkynyl)-2-bromopropenoic acids, **3**, followed by a Pd-catalyzed cross-coupling reaction of the resultant (Z)-3-bromo-5-

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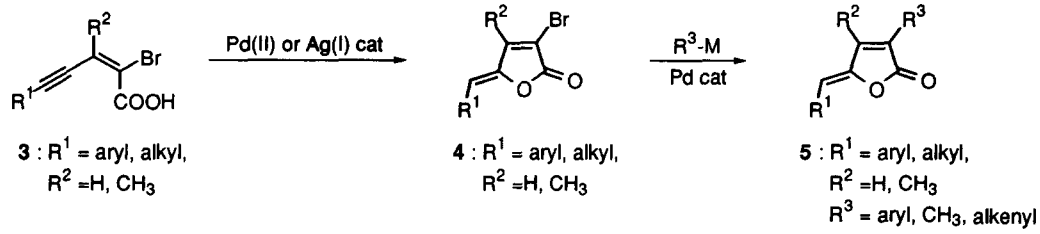
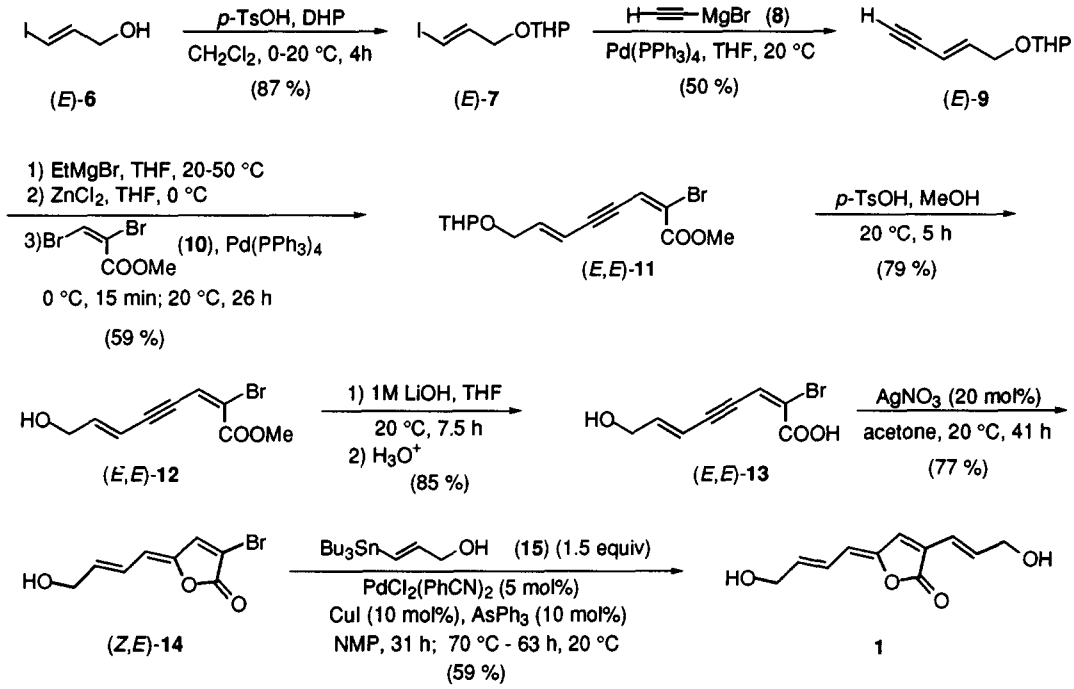
ylidene-5H-furan-2-ones, **4**, with an organozinc or an organotin compound (Scheme 1).[3]



Scheme 1

Scheme 2 illustrates the reaction sequence used to prepare a key intermediate of the synthesis of **1**, *i.e.* (2*E*,6*E*)-2-bromo-8-hydroxy-2,6-octadien-4-ynoic acid, (*E*,*E*)-**13**, as well as the two steps used to convert this carboxylic acid into lissoclinolide, **1**. These last steps were very similar to those summarized in Scheme 1.



Scheme 2

In particular, (*E*)-3-iodo-2-propen-1-ol, (*E*)-**6**, which was available in 50 % yield by treatment of ethyl (*E*)-3-iodopropenoate with $LiAlH_4$ in Et_2O at 0 °C,[4] was converted in 87 % yield into the corresponding tetrahydropyranyloxy derivative, (*E*)-**7**. According to a general procedure for the direct synthesis of terminal acetylenes,[5] the cross-coupling reaction of this iodo derivative with 1.5 equiv of commercially available ethynylmagnesium bromide in THF in the presence of 5 mol % $Pd(PPh_3)_4$ provided compound (*E*)-**9**[6] in 50 % yield. This (*E*)-3-en-1-yne was converted into the corresponding (*E*)-3-en-1-ynylzinc chloride by reaction with ethylmagnesium bromide in THF followed by transmetalation with anhydrous $ZnCl_2$ in THF. According to a general procedure which we previously developed for the regioselective and stereospecific monoalkynylation, monoarylation and monoalkylation of stereodefined alkyl 2,3-dibromo-2-enoates,[7] this organozinc derivative

was then reacted with 0.83 equiv of methyl (*E*)-2,3-dibromopropenoate, **10**,[7b] in THF solution in the presence of 5 mol % $Pd(PPh_3)_4$. Stereoisomerically pure compound (*E,E*)-**11** was so obtained in 59 % isolated yield. Removal of the tetrahydropyranyloxy group from this compound by treatment with catalytic amounts of *p*-TsOH in methanol provided in 79 % yield compound (*E,E*)-**12**,[8] which was saponified by reaction with an aqueous 1M solution of LiOH at 20 °C followed by acidification. Lactonization of the so obtained crude carboxylic acid, (*E,E*)-**13**, by reaction with 20 mol % $AgNO_3$ in acetone at 20 °C afforded crude (*Z,E*)-**14**, which was purified by MPLC on silica gel using a mixture of CH_2Cl_2 and THF (95 : 5) as eluant. Chemically and stereoisomerically pure (*Z*)-2-bromo-5-[(*E*)-4-hydroxy-2-butenylidene]-5*H*-furan-2-one, (*Z,E*)-**14**,[9] was so obtained in 65 % yield based on (*E,E*)-**12**. Finally, reaction of (*Z,E*)-**14** with 1.5 equiv of (*E*)-3-hydroxy-1-propenyltributylstannane, **15**,[10] in NMP solution at 70 °C for 31 h and then at 20 °C for 63 h, in the presence of 5 mol % $PdCl_2(PhCN)_2$, 10 mol % CuI and 10 mol % $AsPh_3$, provided in 59 % isolated yield stereoisomerically pure lissoclinolide, **1**, as well as a very small amount of a stereoisomer which was shown to be tetrenolin, **2**.[11,12]

The structure and stereochemistry of compounds **1** and **2** were established on the basis of their ^1H and ^{13}C NMR spectra at 600 and 150 MHz, respectively, and by a combination of NMR techniques which included homonuclear shift correlation (^1H-^1H COSY), nuclear Overhauser experiments (NOESY), ^1H-^{13}C heteronuclear shift correlation experiments and ^1H-^{13}C long-range heteronuclear shift correlation experiments. The NMR data of compound **1** were in satisfactory agreement with those reported for the natural product.[1] Nevertheless, whereas this last compound was described as a pale yellow glass, our synthetic substance was a pale yellow crystalline solid having m.p. 124-126 °C.

Acknowledgements. We gratefully acknowledge the financial support from the the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) and the Progetto Finalizzato *Beni Culturali* (CNR, Roma). We wish also to thank Prof. Annalaura Segre for the use of NMR facilities of the Servizio NMR dell'Area della Ricerca di Roma (CNR, Roma).

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8. All new products in this study gave satisfactory spectral and microanalytical data.
9. Compound (*Z,E*)-**14** had: m.p. 110 °C. EIMS, *m/z* (%) 232 (31), 230 (52), 203 (92), 201 (100), 200 (64), 174 (40), 123 (23), 95 (44). IR (KBr): 3279, 3123, 1757, 1642, 1100, 1010, 983, 933, 926, 896, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.49 (1H, s, H-4), 6.78 (1H, ddt, J = 15.6, 11.4 and 1.6 Hz, H-7), 6.25

(1H, dt, J = 15.6 and 5.1 Hz, H-8), 5.92 (1H, d, J = 11.4 Hz, H-6), 4.32 (2H, br d, J = 5.1 Hz, H-9), 1.70 ppm (1H, br s, OH).

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11. Synthesis of lissoclinolide, **1**. A dried flask flushed with argon was charged with $PdCl_2(PhCN)_2$ (0.096 g, 0.251 mmol), CuI (0.095 g, 0.502 mmol) $AsPh_3$ (0.153 g, 0.502 mmol), compound (*Z,E*)-**14** (1.16 g, 5.02 mmol) and deareated NMP (30 ml). A deareated solution of (*E*)-3-hydroxy-1-propenyltributylstannane, **15**, (2.61 g, 7.53 mmol) in dry NMP (10 ml) was then added and the mixture was stirred for 31 h at 70 °C and for 63 h at 20 °C. After this period a TLC analysis showed that compound (*Z,E*)-**14** had been completely consumed. Thus the reaction mixture was poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with $CHCl_3$. The collected organic extracts were dried, filtered and concentrated at 50 °C at 20 Torr and then at 50 °C at 0.02 Torr. The residue was diluted with a cold mixture (20 ml) of $CHCl_3$ and methanol (9 : 1) and the resulting mixture was filtered. The pale yellow solid so obtained was sequentially washed with cold $CHCl_3$, benzene and hexane and dried *in vacuo* to give chemically and stereoisomerically pure compound **1** (0.53 g). The filtrates obtained from this purification were collected and concentrated *in vacuo* and the residue so obtained was purified by MPLC on silica gel using a mixture of $CHCl_3$ and methanol (92.5 : 7.5) as eluant. Concentration of the first eluted chromatographic fractions allowed to obtain an additional amount of pure **1** (0.08 g). On the other hand, concentration of the last eluted chromatographic fractions allowed to obtain 0.06 g of a solid which on the basis of NMR data resulted to be constituted of a mixture of lissoclinolide, **1**, and a substance having the structure suggested for tetrenolin, **2**,[1] in a *ca.* 1 : 5 ratio, respectively. The overall yield of compound **1** was 59 % based on (*Z,E*)-**14**. Compound **1** had: m.p. 124-126 °C. ESI-MS: 209 ($M+H^+$); ESI-MS-MS, *m/z* (%): 209 (6), 173 (6), 145 (61), 121 (100), 107 (31), 93 (48), 65 (33). IR (KBr): 3246, 1746, 1090, 1061, 1008, 966, 945 cm^{-1}. ^1H NMR (CD_3OD, 600 MHz): δ 7.440 (1H, s, H-4), 6.984 (1H, dt, J = 16.0 and 5.0 Hz, H-11), 6.832 (1H, ddt, J = 15.4, 11.4 and 1.6 Hz, H-7), 6.529 (1H, dt, J = 16.0 and 1.8 Hz, H-10), 6.241 (1H, dt, J = 15.4 and 5.3 Hz, H-8), 6.067 (1H, d, J = 11.4 Hz, H-6), 4.291 (2H, dd, J = 5.0 and 1.8 Hz, H-12), 4.273 ppm (2H, dd, J = 5.3 and 1.6 Hz, H-9). ^{13}C NMR (CD_3OD, 150 MHz): δ 170.16 (C-2), 149.43 (C-5), 140.80 (C-8), 138.99 (C-11), 136.68 (C-4), 129.03 (C-3), 124.16 (C-7), 119.54 (C-10), 114.96 (C-5), 63.46 (C-9), 63.42 ppm (C-12). Compound **2** had: ^1H NMR (CD_3OD, 600 MHz): δ 7.890 (1H, s, H-4), 7.033 (1H, dt, J = 16.0 and 4.9 Hz, H-11), 6.778 (1H, dtd, J = 15.0, 12.0 and 1.8 Hz, H-7), 6.566 (1H, dt, J = 16.0 and 1.8 Hz, H-10), 6.410 (1H, d, J = 12.0 Hz, H-6), 6.223 (1H, dtd, J = 15.0, 5.3 and 0.9 Hz, H-8), 4.303 (2H, dt, J = 4.9 and 1.5 Hz, H-12), 4.276 ppm (2H, dd, J = 5.3 and 1.1 Hz, H-9). ^{13}C NMR (CD_3OD, 150 MHz): δ 170.34 (C-2), 151.34 (C-5), 140.80 (C-8), 139.67 (C-11), 132.36 (C-4), 124.33 (C-3), 124.30 (C-7), 119.51 (C-10), 115.93 (C-6), 63.46 (C-9), 63.42 ppm (C-12). The *Z* configuration of the $\Delta^{5,6}$ double bond of compound **1** (lissoclinolide) was determined by a NOESY experiment. In fact, the NOESY 2D map clearly showed a cross-peak between the signals assigned to H-4 and H-6. On the contrary, for compound **2** a NOESY experiment showed a cross-peak between the signals assigned to H-4 and H-7 and thus confirmed the *E* configuration of the $\Delta^{5,6}$ double bond of this compound.
12. For the synthesis of other natural or unnatural 5*H*-furan-2-one derivatives in which a key step was a palladium-catalyzed cross-coupling reaction between an organotin compound and an organic halide or triflate, see: *(a)* Görth, F. C.; Umland, A.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1055-1062; *(b)* Hollingworth, G. J.; Richecoeur, A. M. E.; Sweeney, J. *J. Chem. Soc., Perkin Trans. I* 1996, 2833-2836.