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

Renzo Rossi,*[a] Fabio Bellina,*[a] Matteo Biagetti[a] and Luisa Mannina[b]

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56126 Pisa, Italy,[a] and Corso di Laurea in Scienze Ambientali, Università del Molise, Via Mazzini 8, I-86170 Isernia, Italy[b]

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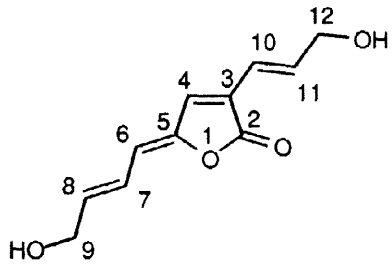
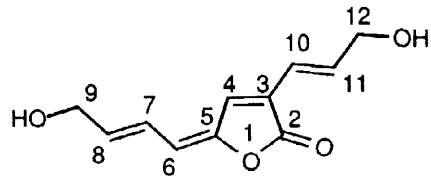
Abstract: Lissoclinolide, **1**, which is an antibiotic butenolide isolated from a Tunicate, has been synthesized stereoselectively by a reaction sequence in which the Ag(I)-catalyzed lactonization of (2*E*,6*E*)-2-bromo-8-hydroxy-2,6-octadien-4-ynoic acid, (*E*,*E*)-**13**, and the Pd/Cu-catalyzed cross-coupling 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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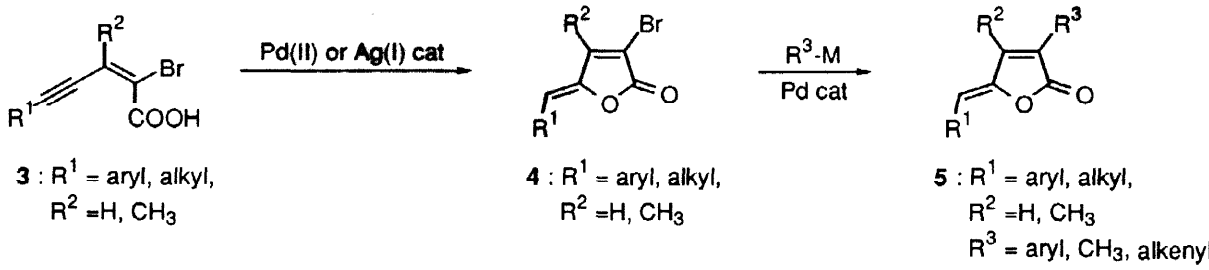
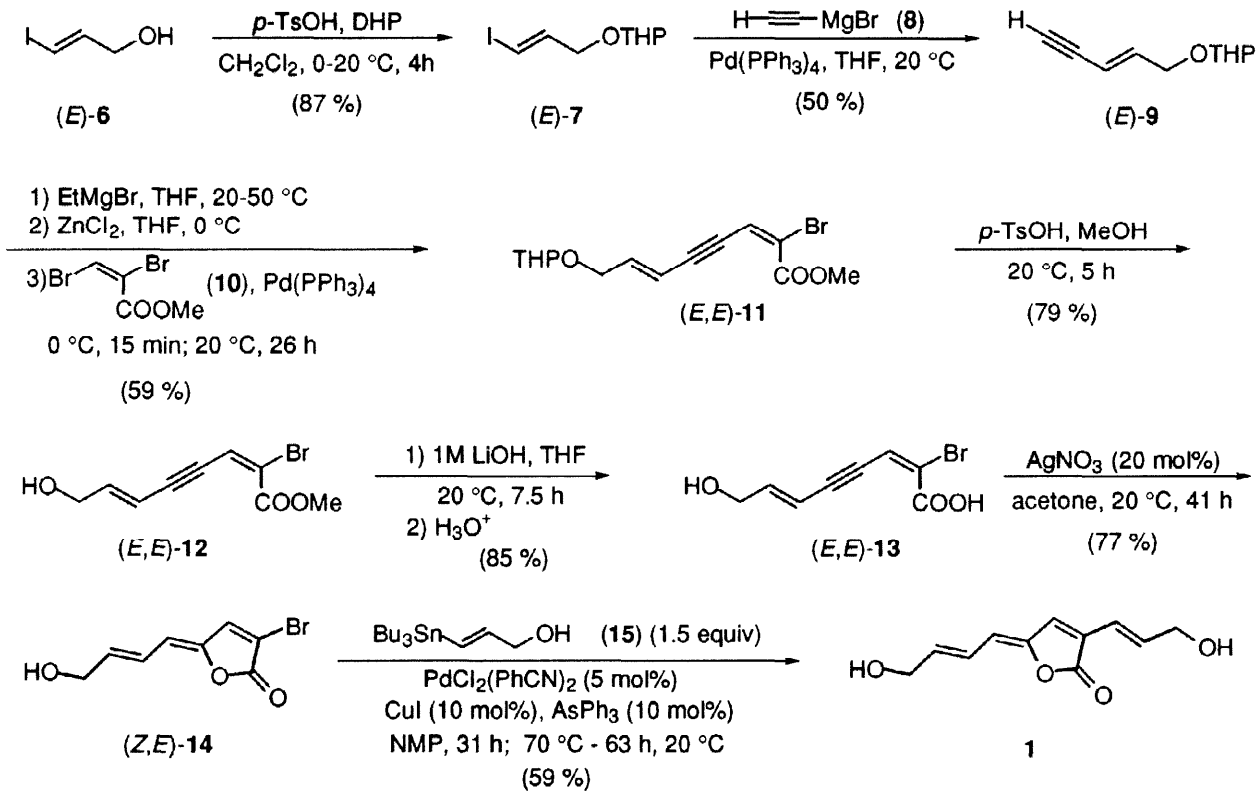
ylidene-5H-furan-2-ones, **4**, with an organozinc or an organotin compound (Scheme 1).[3]



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).

References and Notes

1. Davidson, S. D.; Ireland, C. M. *J. Nat. Prod.* **1990**, *53*, 1036-1038.
2. *(a)* Gallo, G. G.; Coronelli, C.; Vigevani, A.; Lancini, G. C. *Tetrahedron* **1969**, *25*, 5677-5680; *(b)* Pagani, H.; Lancini, G.; Tamoni, G.; Coronelli, C. *J. Antibiot.* **1973**, *26*, 1-6.
3. Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 3017-3020.
4. Carpita, A.; Neri, D.; Rossi, R. *Gazz. Chim. Ital.* **1987**, *117*, 481-489.
5. *(a)* Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957-8960; *(b)* Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591-8594.
6. *(a)* Aksela, R.; Oehlschlager, A. C. *Tetrahedron* **1991**, *47*, 1163-1176; *(b)* Cowie, J. S.; Landor, P. D.; Landor, S. R.; Punjia, N. *J. Chem. Soc. Perkin Trans I* **1972**, 2197-2201.
7. *(a)* Bellina, F.; Carpita, A.; De Santis, M; Rossi, R. *Tetrahedron Lett.* **1994**, *35*, 6913-6916; *(b)* Rossi, R.; Bellina, F.; Carpita, A.; Gori, R. *Gazz. Chim. Ital.* **1995**, *125*, 381-392; *(c)* Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095-4110; *(d)* Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135-156; *(e)* Rossi, R.; Bellina, F.; Carpita, A. in *Recent Developments in Synthetic Organic Chemistry,* Pandalai, S. G. Ed., Transworld Research Network, Trivandrum, **1998**, in press.
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).

10. *(a)* Lai, M-T.; Li, D.; Oh, E.; Liu, H-W. *J. Am. Chem. Soc.* **1993**, *115*, 1619-1628; *(b)* Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851-3854.

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. 1* 1996, 2833-2836.