Pergamon

Tetrahedron Letters, Vol. 36, No. 29, pp. 5251-5254, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00949-3

An Efficient Synthesis of the Antifungal Dilactone LL-Z1271α and of other Biologically Active Compounds

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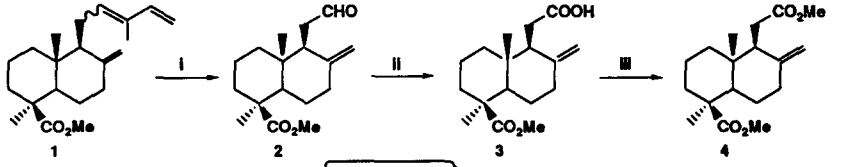
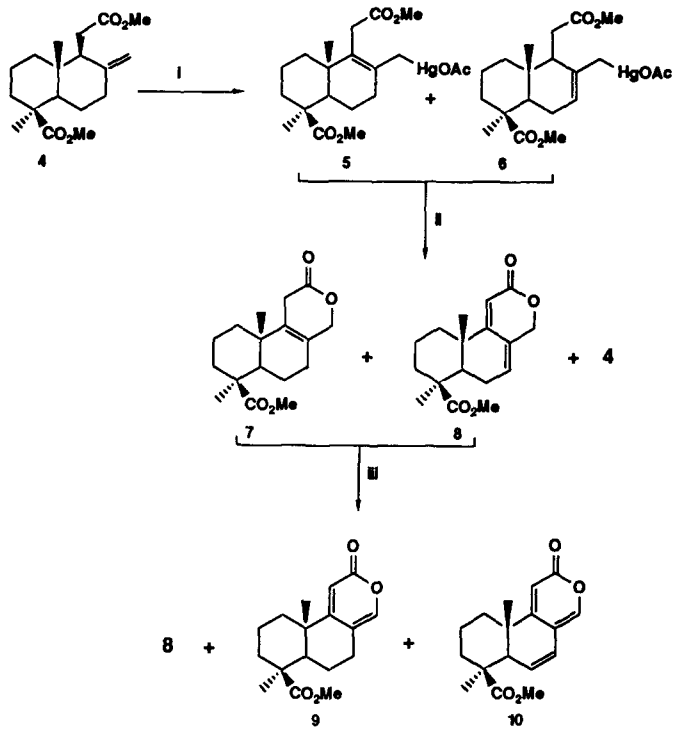
Abstract: The syntheses of the terpenoid antifungal LL-Z1271α and other related compounds were achieved starting from the communic acids. The synthetic approach includes a mercuriation-demercuriation reaction of a γ,δ-unsaturated methyl ester in the presence of O_2, giving rise to a lactone ring.

The mold metabolite LL-Z1271α (**14**), isolated from the fermentation broths of an *Acrostalagmus* species, shows antifungal activity *in vitro* against a number of fungi and *in vivo* against some experimental ringworm infections in guinea pigs.[1] Because of this, different procedures for its preparation have been described.[2] We wish to report herein an improved synthesis of **14** from the readily available carboxilic acid **3**,[3] using the methyl ester of communic acids **1** as starting material. The esterification of **3** with diazomethane leads to the methyl ester **4** in quantitative yield (scheme 1). In a previous work[4] we published that the mercuriation reaction in $\Delta^{8(17)}$ of communic acids takes place with the loss of the neighbouring 9-H hydrogen giving rise to the isomerization of the exocyclic double bond. With this in mind, **4** was refluxed for 45 minutes with two equivalents of mercuric acetate in dry toluene (scheme 2), affording a mixture of organomercurials **5** and **6** [5] which, after solvent evaporation, was reduced with $NaBH_4$/DMF in the presence of an excess of bubbling O_2, giving lactone **7** (75%), dienolide **8** (15%) and the starting product **4** (5%) .[6] The dehydrogenation of this mixture was achieved at a 75% yield using DDQ and p-toluenesulfonic acid to give **8**, **9** and **10** [7] in the ratio 8:3:1.



Scheme 1

i) O_3, CH_2Cl_2, -78°C; $S(CH_3)_2$, -78°C to rt, 66.3%; ii) $CrO_3/H_2SO_4/H_2O$, acetone, 90%; iii) CH_2N_2, Et_2O, 100%.



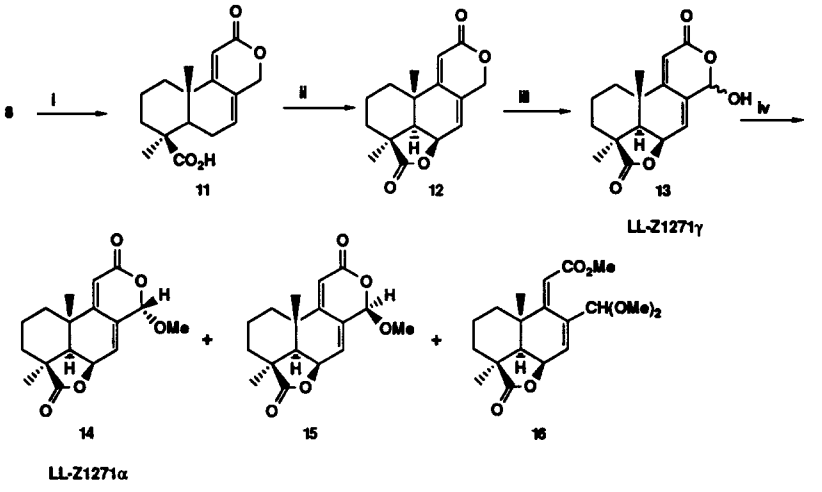
Scheme 2

i) $Hg(OAc)_2$, toluene, reflux, 45min, 100%; ii) $NaBH_4$, O_2, DMF, rt, 90%; iii) DDQ, PTSA, dioxane, reflux, 75%.

The methylester **8** (scheme 3) was transformed by treatment with concentrated sulphuric acid into the free acid **11**, and this substance was treated with lead tetraacetate with the aim of closing ring D. The known product **12** [8] was obtained at a 50% yield. The reaction of **12** with three moles of selenium dioxide in refluxing dry dioxane for 1h gave an 85% yield of the lactol **13**, identical in properties to LL-Z1271γ (isolated together with **14** from an *Acrostalagmus* species [2b]), and a 15% recovery of **12**.

Finally, lactol **13** was treated with methanol/sulphuric acid giving as the main product LL-Z1271α (**14**, 50%). In addition, the C-14 epimer **15** (35%) and the dimethyl acetal **16** [9] (15%) were isolated from the reaction mixture (PLC).

As outlined in table 1, compounds **12**, **13**, **14**, **15** and **16** were tested against several fungi, **14** and **15** showing a good fungicidal activity. Furthermore, with **14** and **15** protein synthesis blocking assays were performed in an *in vitro* system derived from *S. cerevisiae*, proving that both compounds are good inhibitors of the synthesis of proteins in this assayed system, showing an ED_{50} 2-6 μM.



Scheme 3

i) H_2SO_4, rt, 100%; ii) $Pb(OAc)_4$, benzene, hv, 60 h, 50%; iii) SeO_2, 3 eq., dioxane, reflux, 1h; iv) CH_3OH, H_2SO_4, rt.

Table 1. Antifungal Activity; MIC (μg/ml):

	A	B	C
12	<12.5	<6.25	<3.12
13	>25	>25	>25
14	<3.12	<3.12	<3.12
15	<6.25	<6.25	<3.12
16	<6.25	>25	<25

A : *Saccharomyces cerevisiae*

B : *Candida albicans*

C : *Cryptococcum neoformans*

Acknowledgements: Financial support of this work by DGICYT (PB 92-0942) is gratefully acknowledged. We are specially thankfull to Dr. Juan P. Garcia Ballesta (Instituto de Biologia Molecular, Madrid) who carried out the protein synthesis assays. J. Elmerabet thanks to the Instituto de Cooperación con el Mundo Arabe for a predoctoral studentship.

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5. **5** : ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.70 (s, CH_3-C_{10}), 0.97 (ddd, J = 13.5, 13.5, 4.3 Hz, $H_{3\alpha}$), 1.03 (ddd, J = 13.3, 13.5, 4.1 Hz, $H_{1\alpha}$), 1.18 (s, CH_3-C_4), 1.34 (dd, J = 12.5, 1.5 Hz, H_5), 1.48 (1H, dm, J = 15 Hz), 1.65 (1H, dm, J = 12.5 Hz), 1.7- 1.8 (2H, m), 1.95- 2.2 (4H, m), 2.03 (s, OAc), 2.32 (d, J = 10.8 Hz, H_{11a}), 2.69 (d, J = 10.8 Hz, H_{11b}), 3.06 (d, J = 16.9 Hz, H_{14a}), 3.17 (d, J = 16.9 Hz, H_{11b}), 3.59 (s, OCH_3-C_{12}), 3.66 (s, OCH_3-C_4). H_7 for **6** can be seen at δ 5.22.

6. **7** : ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.78 (s, CH_3-C_{10}), 1.00 (ddd, J = 13.5, 13.5, 4.3 Hz, $H_{3\alpha}$), 1.10 (ddd, J = 13, 12.8, 4.2 Hz, $H_{1\alpha}$), 1.19 (s, CH_3-C_4), 1.33 (dd, J = 12.3, 1.8 Hz, H_5), 1.53 (dm, J = 14.2 Hz, $H_{2\alpha}$), 1.69 (1H, dm, J = 12.8 Hz), 1.74-1.85 (2H, m), 1.94-1.99 (2H, m), 2.06 (1H, dm, J = 11 Hz), 2.21 (1H, dm, J = 13.5 Hz), 2.87 (dq, J = 20, 2.3 Hz, H_{11a}), 2.95 (dq, J = 20, 2.3 Hz, H_{11b}), 3.61 (s, OCH_3), 4.56 (dm, J = 15 Hz, $H_{14\alpha}$), 4.63 (dm, J = 15 Hz, $H_{14\beta}$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 17.07 (C_{20}), 19.20 (C_2), 20.00 (C_6), 27.75 (C_7), 28.31 (C_{18}), 29.08 (C_1), 35.98 (C_3), 37.49 (C_{11}), 37.60 (C_{10}), 43.72 (C_4), 51.30 (OCH_3), 52.76 (C_5), 71.17 (C_{14}), 124.00 (C_8), 133.72 (C_9), 170.94 (C_{12}), 177.46 (C_{19}).

8 : ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (s, CH_3-C_{10}), 1.08 (ddd, J = 13.5, 13.5, 4 Hz, $H_{3\alpha}$), 1.22 (s, CH_3-C_4), 1.46 (ddd, J = 13.7, 14.3, 4.2 Hz, $H_{1\alpha}$), 1.63 (dd, J = 11.7, 4.7 Hz, H_5), 1.65 (dm, J = 13.5 Hz, $H_{2\alpha}$), 1.92 (ddddd, J = 14.3, 13.5, 13.5, 3.4, 3.4 Hz, $H_{2\beta}$), 1.93 (dddd, J = 13.7, 3.5, 1.7, 1 Hz, $H_{1\beta}$), 2.24 (dddd, J = 13.5, 3.4, 3.2, 1.7 Hz, $H_{3\beta}$), 2.56 (ddd, J = 19.7, 5.7, 5 Hz, $H_{6\alpha}$), 2.91 (ddm, J = 19.7, 11.7 Hz, $H_{6\beta}$), 3.69 (s, OCH_3), 4.78 (dddd, J = 13.2, 2.2, 1.1, 1.1 Hz, $H_{14\alpha}$), 4.86 (dddd, J = 13.2, 3.7, 2, 2 Hz, $H_{14\beta}$), 5.72 (brs, H_{11}), 6.12 (m, H_7); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.35 (C_{20}), 19.45 (C_2), 24.88 (C_6), 28.27 (C_{18}), 36.01 (C_1), 37.53 (C_{10}), 37.72 (C_3), 44.22 (C_4), 49.16 (C_5), 51.70 (OCH_3), 69.73 (C_{14}), 109.96 (C_{11}), 125.21 (C_8), 131.11 (C_7), 162.98 (C_9), 165.63 (C_{12}), 177.12 (C_{19}).

7. **9** : ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.02 (s, CH_3-C_{10}), 1.08 (ddd, J = 13.5, 13.5, 4.2 Hz, $H_{3\alpha}$), 1.27 (s, CH_3-C_4), 1.42 (dd, J = 12, 2 Hz, H_5), 1.45 (ddd, J = 13, 13, 4.4 Hz, $H_{1\alpha}$), 1.66 (dm, J = 14.3 Hz, $H_{6\alpha}$), 1.80- 2.00 (m, $H_{2\alpha}$, $H_{6\beta}$), 2.07 (dm, J = 13 Hz, $H_{1\beta}$), 2.16 (dddd, J = 14.1, 6, 2.3, 2.3 Hz, $H_{2\beta}$), 2.28 (dddd, J = 13.5, 3.3, 3.3, 1.5 Hz, $H_{3\beta}$), 2.40 (dddd, J = 16, 12.9, 6.1, 2.1 Hz, $H_{7\alpha}$), 2.70 (ddm, J = 16, 5.3 Hz, $H_{7\beta}$), 3.67 (s, OCH_3), 6.20 (s, H_{11}), 7.23 (brs, H_{14}); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 19.62 (C_6), 20.39 (C_2), 22.57 (C_{20}), 25.26 (C_7), 28.53 (C_{18}), 37.32 (C_3), 37.99 (C_1), 39.29 (C_{10}), 44.10 (C_4), 51.32 (C_5), 51.55 (OCH_3), 110.75 (C_{11}), 114.86 (C_8), 147.42 (C_{14}), 163.55 (C_{12}), 167.70 (C_9), 177.20 (C_{19}).

10 : ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89 (s, CH_3-C_{10}), 1.10 (ddd, J ~ 13.5, 13.5, 4.2 Hz, $H_{3\alpha}$), 1.30 (s, CH_3-C_4), 1.50 (ddd, J ~ 14, 13.7, 4.2 Hz, $H_{1\alpha}$), 1.72 (dm, J ~ 13.5 Hz, $H_{2\alpha}$), 1.90 (ddddd, J ~ 14.3, 13.5, 13.5, 3.4, 3.4 Hz, $H_{2\beta}$), 2.03 (dddd, J ~ 13.7, 3.5, 1.7, 1 Hz, $H_{1\beta}$), 2.21 (dd, J = 3.1, 2.35 Hz, H_5), 2.31 (dddd, J ~ 13.5, 3.4, 3.2, 1.7 Hz, $H_{3\beta}$), 3.67 (s, OCH_3), 6.15 (s, H_{11}), 6.21 (dd, J = 10.0, 3.1 Hz, H_6), 6.44 (dd, J = 10.0, 2.35 Hz, H_7), 7.28 (s, H_{14}).

8. This cyclization was assayed by treatment of **11** with the iodosobenzene diacetate-iodine system in cyclohexane, yielding a complex mixture, the major products being those resulting from the decarboxylation of **11** in C-4.

9. **16** : ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.13 (s, CH_3-C_{10}), 1.26 (s, CH_3-C_4), 1.86 (d, J = 4.7 Hz, H_5), 2.29 (ddd, J = 14.9, 6.1, 4.1 Hz, $H_{3\beta}$), 3.17 (s, OCH_3), 3.34 (s, OCH_3), 3.73 (s, $COOCH_3$), 4.99 (ddd, J = 4.7, 4, 1.9 Hz, H_6), 5.34 (dd, J = 2, 1.9 Hz, H_{14}), 5.70 (s, H_{11}), 6.50 (dd, J = 4, 2 Hz, H_7); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 18.24 (C_2), 21.75 (C_{20}), 25.26 (C_{18}), 28.40 (C_3), 32.13 (C_1), 38.59 (C_{10}), 43.02 (C_4), 50.92 (C_5), 51.69 (OCH_3), 52.71 (OCH_3), 53.24 (OCH_3), 72.34 (C_6), 100.56 (C_{14}), 114.65 (C_{11}), 125.86 (C_7), 139.92 (C_8), 153.98 (C_9), 167.81 (C_{12}), 180.59 (C_{19}).

(*Received in UK* 12 *April* 1995; *revised* 22 *May* 1995; *accepted* 26 *May* 1995)