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A Novel Stereoselective Route to a Fumagillin and Ovalicin Synthetic Intermediate

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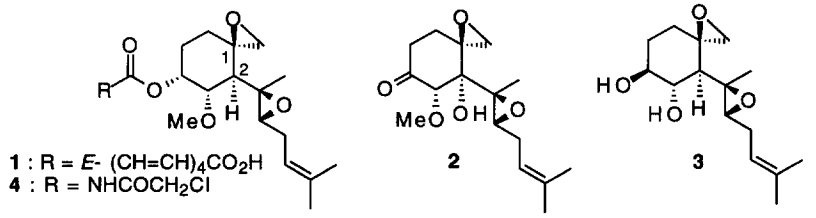
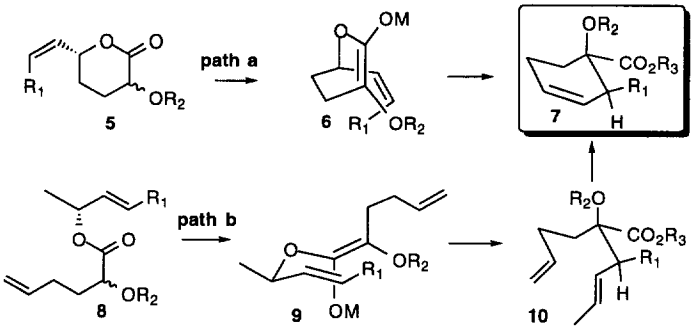
Abstract: A strategy using a highly stereoselective Claisen-Ireland rearrangement followed by a Grubbs metathesis afforded in a good overall yield after further functionalisation a potentially synthetic precursor of fumagillin and ovalicin.
Key words : rearrangement, metathesis, antitumour compounds.

Fumagillin **1**[1], ovalicin **2**[2] and FR65814 **3**[3] belong to a family of sesquiterpenes which display interesting biological activities such as inhibition of angiogenesis[4] for the two former compounds and immunosuppressive activity for the latter. The recent disclosure of AGM 1470 (or TNP-470) **4**[5] which showed a better therapeutic index than fumagillin **1** itself gave a new impulse to the synthesis of these compounds, which are promising candidates for the inhibition of tumour (Scheme 1). Thus, since the pioneering syntheses of fumagillin **1** and ovalicin **2** by Corey[6,7], several other total or formal syntheses of **1**[8], **2**[9] or **3**[10] and of modified compounds[11] have been described in the past recent years.



Scheme 1

Several strategies such as Diels-Alder cycloaddition[6], osmium tetroxide-mediated dihydroxylation[9a,9c], nucleophilic attack of dimethyloxosulfonium methylide on carbonyl[10] or Claisen type rearrangement[8] have been used for the stereoselective construction of the asymmetric centre at C 1. We have independently studied the possible use of the latter strategy in our laboratory with two possible cyclic or acyclic precursors : lactone **5** and ester **8** respectively.



Scheme 2

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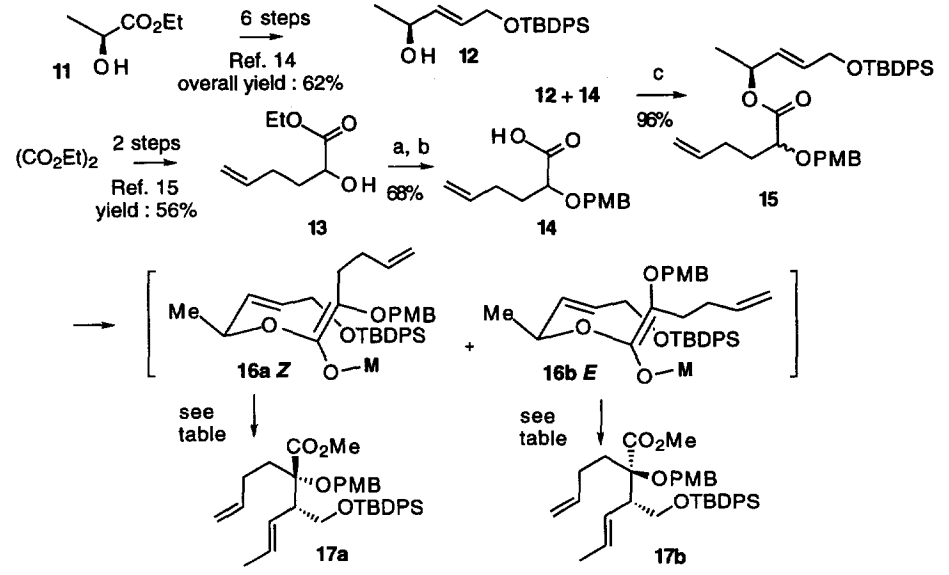
It appeared that the Claisen-Ireland rearrangement of compound **5**, following a strategy described earlier by Büchi[12] on a model system, was inoperative (Scheme 2, path a). In contrast, the less sterically demanding acyclic version of this reaction using ester **8** (Scheme 2, path b) was successfully developed and led to a stereoselective synthesis of a potential intermediate in the syntheses of both fumagillin **1** and ovalicin **2**, which is presented herein.

Alcohol **12** was prepared in six steps from ethyl (*S*)-(-)- lactate **11**[13] according to a known sequence of reactions in an improved 62% overall yield[14]. Protection of the known hydroxyester **13**[15] followed by saponification gave rise to the acid derivative **14** (Scheme 3). Dicyclohexylcarbodiimide mediated esterification between alcohol **12** and acid **14** afforded the ester **15** in 58% overall yield from ethyl lactate **11** (Scheme 3).

With ester derivative **15** in hand, the corner stone Claisen-Ireland rearrangement[16] was studied. Reaction conditions and results are summarised in the table. In all cases, the Claisen-Ireland reaction was followed by a diazomethane esterification of the resulting crude mixture of carboxylic acids. Isomeric methyl ester derivatives **17a** and **17b** were then isolated.



Scheme 3 : a) $Cl_3CC(OPMB)NH$, 4 equiv., TfOH, cat., CH_2Cl_2, 0°C to RT, 20 h. b) KOH, 5 equiv., MeOH, H_2O, R.T., 20 h. c) DCC, 1. 2 equiv., DMAP, 0. 1 equiv., CH_2Cl_2, R.T., 1 h.

Four parameters were successively submitted to variation. The time between deprotonation and TMSCl quenching did not show any influence on the diastereoselectivity of the reaction (entries 1-3). However, when the deprotonation was performed at lower temperature, -90°C *versus* -78°C, the stereoselectivity was significantly lower (entries 1 and 4). For the same base, lithium di*iso*propylamide, the diastereoselectivity is modified by the nature of the solvent, better results and reversal of the diastereoselectivity to give **17a** as the major isomer, being obtained in less polar solvents like ether or toluene (entries 5 and 6). Curiously, the same reversal of selectivity was observed using the polar solvent

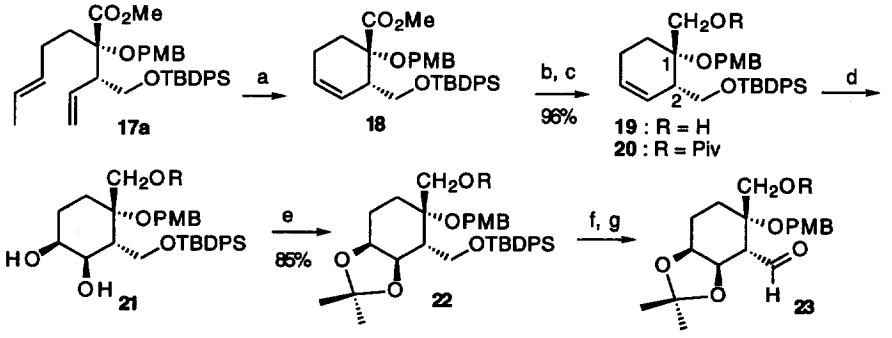
mixture, THF-HMPA (entry 7). At this point, this finding is difficult to rationalise. Finally, a dramatic improvement in diastereoselectivity was observed with potassium bis(trimethylsilyl)amide in toluene (entry 8). Under these conditions the ester derivative **17a** was obtained in 90% yield with recovery of the starting material **15**[17] in 10% yield. Configurations in ester **17a** were established after further transformations. If chair like transition states are assumed in this acyclic Claisen rearrangement with a *pseudo* equatorial position for the methyl on the stereogenic carbon, two enolates **16a** *Z* or **16b** *E* can be formed after deprotonation. The use of less polar solvents should favour **16a** in which the cation is internally chelated. With the bulkier potassium cation, an additional chelation with the oxygen of silyl ether can reinforce the stability of the transition state **16a** over **16b** and explain the total selectivity observed in that case.

entry	1	2	3	4	5	6	7	8
solvent	THF	THF	THF	THF	ether	toluene	THF-HMPA	toluene
base	LDA	LDA	LDA	LDA	LDA	LDA	LDA	KHMDS
temperature °C (a)	-78	-78	-78	-90	-78	-78	-78	-78
time (min.) (b)	30	10	90	30	30	30	30	30
d.s. 17a/17b	25/75	27/73	27/73	50/50	61/39	83/17	70/30	<95/5
yield %	50	52	46	35	53	42	60	90

(a) temperature for deprotonation. (b) time of deprotonation before introducing TMSCl. (c) yields are not optimised except for entry 8. Distillation of TMSCl over quinoline improved the yield from 71 to 90% in that case.

Ring closing metathesis was examined next. Metathesis with the Grubbs catalyst[18] afforded in nearly quantitative yield the anticipated cyclohexene derivative **18**. Di*iso*butyl aluminium hydride reduction of the ester group in **18** gave rise to the alcohol derivative **19** which, after esterification, furnished the ester **20** in 96% overall yield from **17a** (Scheme 4). NOESY experiments on **20** allowed the determination of configurations at C1 and C2. In particular, a nOe between CH_2OPiv and C2-H is characteristic of a *cis* relationship between these hydrogens.

Osmium tetroxide-mediated dihydroxylation of compound **20** afforded stereoselectively diol **21** which was converted to the acetonide derivative **22** in 85% overall yield (Scheme 4). Selective deprotection of silylether in **22** followed by tetrapropylammonium perruthenate (TPAP) oxidation afforded in 74% yield aldehyde **23**, a synthetic intermediate for further side chain elaboration.



Scheme 4 : a) Grubbs catalyst, 0. 1 equiv., CH_2Cl_2, Rfx, 30 min. b) DIBAH, CH_2Cl_2, -78°C to 0°C, 2 h. c) PivCl, DMAP, C_5H_5N, 80°C, 20h. d) OsO_4, 0.1 equiv., NMO, 3 equiv., $MeSO_2NH_2$, 1. 1 equiv., *t*-BuOH, H_2O, 90 min. , R.T. e) $(MeO)_2CMe_2$, CSA, 0. 2 equiv., R.T., 30 min. f) NH_4F, MeOH, Rfx., 48 h. g) TPAP, 0. 1 equiv., NMO, 1. 5 equiv., CH_2Cl_2, R.T., 60 min.

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17) Typical experiment : To a stirred solution of KHMDS (523mg, 1.5 equiv.) in anhydrous toluene (6 mL) at -78°C under argon, was added dropwise, a solution of ester **15** (1g, 1. 74 mmol) in toluene (6 mL). After 30 minutes, chlorotrimethylsilane (443 µL, 2 equiv.) was added slowly. After additional 5 minutes at - 78°C, the reaction mixture was warmed up to room temperature and stirred for 90 minutes and quenched with an saturated aqueous solution of NH_4Cl. Extraction with ether was followed by the usual work up procedure. The crude acid derivative was treated with an excess of diazomethane in ether for 30 minutes at room temperature. After evaporation, the resulting mixture was purified by column chromatography (SiO_2, heptane-ether 20/1 to 12/1) and afforded **17a** (920mg, 90%) as a pale yellow oil and **15** (10%).
18) For a recent example of preparation of functionalised cyclohexene by ring closure metathesis, see : Sellier, O.; Van de Weghe, P.; Le Nouen, D.; Strehler, C.; Eustache, J. *Tetrahedron Letters*, **1999**, *40*, 853-856 and references therein.