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A New, Ring Closing Metathesis-Based Synthesis of (−)-Fumagillol

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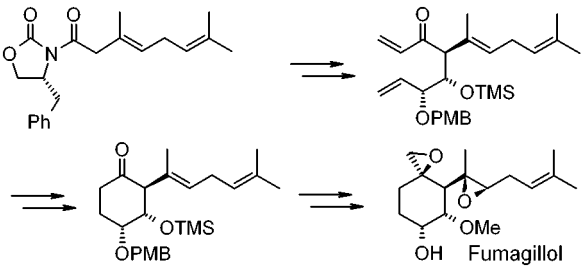
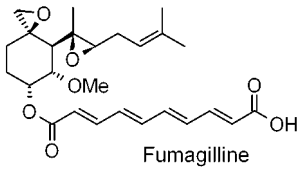
ABSTRACT



A new strategy to access the fumagillin/fumagillol skeleton is proposed. An Evans aldolization and a RCM involving an enone are used for the preparation of a key cyclohexanone intermediate, which was readily converted to fumagillol. The synthesis also features an efficient preparation of isogeraniol and isogeranic acid.

Inhibition of angiogenesis has emerged as a promising approach for the treatment of cancer. Among antiangiogenic agents, fumagillin and related naturally occurring or semisynthetic analogues have received close attention and some have reached the stage of clinical studies.



Methionine aminopeptidase 2 (Met-AP_2), a ubiquitous enzyme involved in protein post-translational processing, has been identified as the likely target for fumagillin. The X-ray structure of $MetAP_2$-fumagillin adducts is known,[1] and irreversible inhibition has been shown to arise from covalent modification of the enzyme via opening of a reactive epoxide by an active site histidine (His231).[1] The most extensively studied fumagillin analogues are esters of a highly substituted cyclohexanol called fumagillol. Preliminary structure−activity relationships (SAR) studies have shown that the nature of the acyl group is crucial for biological activity, some semisynthetic analogues being ca. 1000 times more active than the parent fumagillin.[2] The encouraging results obtained with currently available fumagillin analogues warrant further SAR studies, which are however hampered by the difficulty of obtaining fumagillol in appreciable quantity (until now, fumagillol has been obtained through degradation of the naturally occurring fumagillin). For this reason and because fumagillol represents an attractive synthetic challenge, several approaches to this molecule (and fumagillin) have been devised. Following the pioneering work of Corey in 1972,[3] this area of research remained dormant for several years, and it is only recently that two enantioselective syntheses of (−)-fumagillol/(−)-fumagillin,[4,5] two syntheses of racemic

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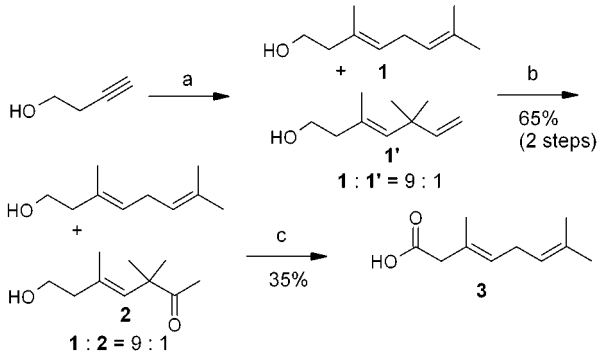
fumagillol/fumagillin,[6,22] and an approach to a fumagillin and ovalicin synthetic intermediate[7] have been reported. We disclose in this paper our own efforts in this research area and describe an alternative approach which may facilitate the availability of fumagillol.

Our strategy, based upon the retrosynthetic analysis outlined in Scheme 1, features two key steps: an Evans aldol

Scheme 1[a]



[a] (a) (i) Cp_2ZrCl_2 (0.4 equiv), $AlMe_3$ (3 equiv), CH_2Cl-CH_2Cl, 20 °C, 24 h (ii) 1-bromo-3-methyl-but-2-ene, $Pd(PPh_3)_4$ (1 mol %), 20 °C, 24 h; (b) CuCl (2 equiv), O_2 (1 atm), $PdCl_2(CH_3CN)_2$ (10 mol %), DMF/water (9:1), 30 °C, 48 h; (c) separation, CrO_3, H_2SO_4, H_2O/acetone, 0 °C, 10 min.

reaction to secure the relative relationship of the C5- and C6-linked hydroxyls and the side chain attached at C4 (see Figure 1 for numbering) and a ring closing metathesis (RCM) to form the six-membered ring.[8]

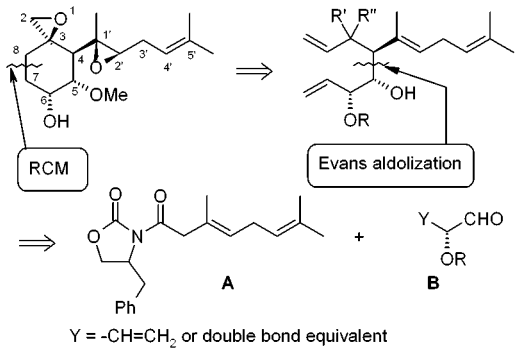


Figure 1. Fumagillol retrosynthesis.

Our first task was to prepare pure *E*-isogeranic acid. We were surprised to find that this compound had never been described in a pure form[9] and that isogeraniol, a potential precursor of isogeranic acid, had only been obtained by rather complicated or nonspecific methods.[10] This led us to develop the short, stereoselective synthesis shown in Scheme 1. Treatment of but-3-yn-1-ol with Cp_2ZrCl_2 and $AlMe_3$ according to Negishi,[11] followed by Pd^0-catalyzed coupling of the resulting alane with 1-bromo-3-methyl-but-2-ene afforded a 9:1 mixture of *E*-isogeraniol (**1**) and the positional isomer (**1′**). *E*-Isogeraniol and **1′** can neither be distinguished nor separated by chromatography or distillation, but the latter could easily be removed by Wacker oxidation of the crude reaction mixture. As expected, the terminal double bond in **1′** was quantitatively oxidized, while the more hindered trisubstituted olefine in isogeraniol was unaffected. Isogeraniol and the oxidation product **2** could be easily separated by chromatography on a short pad of SiO_2. Oxidation of *E*-isogeraniol to the desired *E*-isogeranic acid proved to be troublesome. The high sensitivity of the 1,4-dienic system toward oxidative conditions precluded the use of most methods commonly used for alcohol to aldehyde and carboxylic acid conversion. After much experimentation, we found that treatment with chromium trioxide in acidic medium[12] cleanly led to the desired *E*-isogeranic acid in 35% yield. Although the yield is modest, the desired acid was obtained in the pure *E*-form and easily separated from byproducts. Overall, the above short sequence constitutes a simple, very short stereoselective method for the synthesis of *E*-isogeraniol and *E*-isogeranic acid. With a convenient access to *E*-isogeranic acid in hand, we turned our attention to the crucial Evans aldolization.

In line with our retrosynthetic analysis, Evans aldolization using the dibutylboron enolate derived from **A** (*S* isomer)

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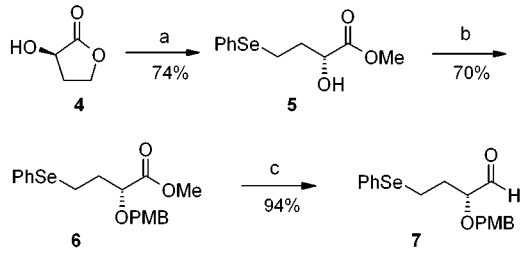
(22) A similar obervation has recently been made: Hutchings, M.; Moffat, D.; Simpkins, N. S. *Synlett* **2001**, 63−64.

and aldehyde **B** (R = PMB, Y = −CH=CH_2) was envisaged; a matter of concern was the ability of the β,γ-unsaturated aldehyde **B** to survive the aldolization conditions. In fact, in model studies, we found that, at low temperature and under a variety of conditions, no coupling could be obtained.[13] When raising the temperature, we found aldehyde **B** to be unstable and prone to base-induced reconjugation. Therefore, we prepared aldehyde **7** (Scheme 2), in which

Scheme 2[a]



[a] (a) (i) PhSe−SePh, $NaBH_4$, DMF, 90 °C, 2 h (ii) CH_2N_2, 20 °C; (b) PMBOC(CCl_3)=NH, camphorsulfonic acid (0.2 equiv), 20 °C, 20 h; (c) DIBAH, toluene, −78 °C, 20 min.

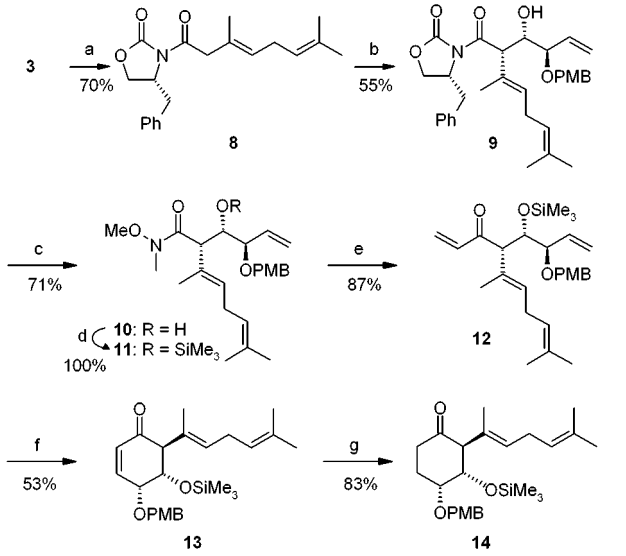
the β,γ-olefinic double bond is now masked, but here again, we could not obtain useful yields of aldol. An additional problem in this case arises from the sensitivity of the phenylselenyl moiety toward the oxidative conditions used for the workup.

Faced with the above problems, we decided to modify our original plans. Although the Evans aldolization is most often performed using boron enolates, which generally provide excellent diastereo- and enantioselectivities, other types of enolates have also been employed. In particular, lithium enolates have been successfully used in aldolization reactions with high degrees of selectivity. The reaction thus performed does not require an oxidative workup. In comparison to their boron counterpart, lithium enolates also afford *syn* aldols predominantly, but the enantioselectivity is opposite,[14,15] which required that we started from *R* (instead of *S* as originally planned) benzyloxazolidinone. A further point of concern was the possible influence of the asymmetric center in aldehyde **7** on the enantioselectivity of the reaction; this effect is known to be important in the case of Evans aldolizations involving α-alkoxyaldehydes, especially when using lithium enolates.[14] Inspection of the literature suggested that, in our case, high degrees of enantioselectivity could be expected as the asymmetric induction of the chiral auxiliary and that of the aldehyde asymmetric center were "matched".[15]

The first part of our synthesis, leading to an advanced intermediate toward fumagillol is shown in Scheme 3.

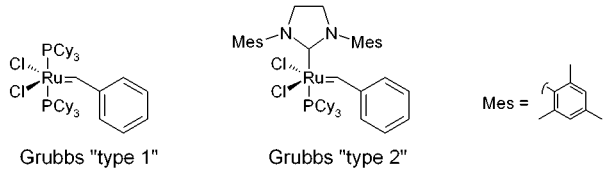
The *N*-acyl oxazolidinone **8** (Scheme 3) was deprotonated at low temperature and treated with aldehyde **7**. The raw aldol thus obtained was subjected to periodate oxidation. Concomitant spontaneous elimination of selenenic acid furnished a single product to which the expected structure **9** was tentatively attributed.

Scheme 3[a]



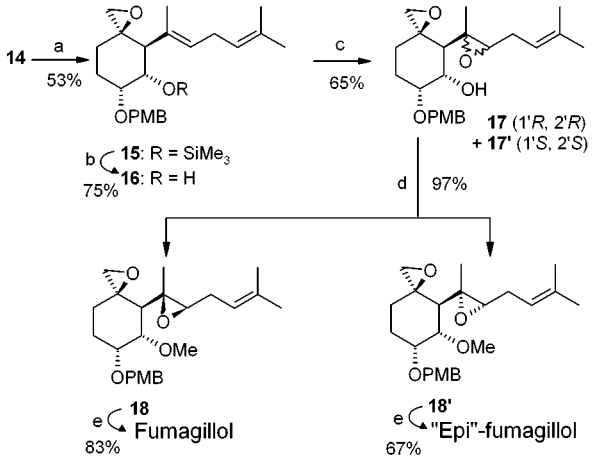
[a] (a) (i) $(CH_3)_3C-C(=O)Cl$, NEt_3, −78 °C, 15 min, then 0 °C, 15 min (ii) (*R*)-4-benzyl-2-oxazolidinone lithium salt, −78 °C, 20 min; (b) (i) LDA, −78 °C, 30 min (ii) **7**, −78 °C, 90 min then workup (iii) NBu_4IO_4, $CHCl_3$, reflux, 2 h; (c) (i) *N*,*O*-dimethylhydroxylamine (3.5 equiv), $AlMe_3$ (2 M in toluene, 3.5 equiv), THF, 20 °C, 30 min, then **9**, 0 → 20 °C, 16 h; (d) $(CH_3)_3SiCl$, NEt_3, DMAP (1 equiv) THF, 20 °C, 2 h; (e) vinylmagnesium bromide, THF, 20 °C, 12 h; (f) $Ti(OiPr)_4$, Grubbs's "type I" catalyst (20 mol %), CH_2Cl_2, 55 °C, 24 h; (g) RaNi, THF, 0 °C, 20 min.

Cleavage of the chiral auxiliary by *N*,*O*-dimethylhydroxylamine in the presence of trimethylaluminum and treatment of the resulting amide with vinylmagnesium bromide afforded enone **12**, ready for metathesis. We are aware of only two examples of RCM involving an olefine and an α,β-unsaturated ketone.[16] Electron-deficient dienic systems (containing α,β-unsaturated esters or amides) are known to be relatively poorly reactive in RCM reactions and generally require Lewis acid catalysis.[17] In addition, systems containing an olefine and an α,β-unsaturated ketone would be expected to be sensitive to Lewis acids. Therefore, the feasibility of this particular metathesis was unclear. We found that the only reaction conditions leading to an acceptable (53%) yield of the desired cyclohexenone **13** required the Grubbs catalyst type 1[18] in the presence of $Ti(OiPr)_4$, using dichloromethane as a solvent. Switching to benzene or using Grubbs type 2 catalyst[19] led to no reaction or formation of polymeric material, respectively.



Reduction of the α,β-unsaturated ketone in **13** with Raney nickel[20] cleanly afforded the substituted cyclohexanone **14**.

Scheme 4[a]



[a] (a) (i) $Me_3S^+OI^-$, NaH, LiI, DMSO/THF, 20 °C, 30 min; (b) *p*-toluenesulfonic acid, H_2O/THF, 0.5 h; (c) Ti(O*i*Pr)$_4$ (2 equiv), *t*-BuOOH, CH_2Cl_2, −25 °C, 12 h; (d) MeI (30 equiv), NaH, THF/DMF (1:1), 20 °C, 8 h; (e) DDQ, CH_2Cl_2/H_2O, 20 °C, 90 min.

The final steps of our synthesis are shown in Scheme 4.

In a case related to ours, in which the trimethylsilyl group in **14** was replaced by a PMB group and the absolute configuration at C4 was opposite to that in **14**, the ylide derived from trimethylsulfoxonium iodide had been shown to afford exclusively the epoxide resulting from attack on the *si* face of the ketone.[21] In our case, the same observation was made but the desired epoxide was only formed in low (14%) yield, the main product of the reaction being a cyclopropanone resulting from base-induced β-elimination followed by cyclopropanation of the resulting enone.[22] The situation was greatly improved by adding anhydrous LiI to the reaction mixture. In this case a good (53%) yield of **15** was obtained. After removal of the silyl protecting group, hydroxyl-directed epoxidation of the C1′−C2′ double bond was examined. This operation was best conducted using the Sharpless system Ti(O*i*Pr)$_4$/*t*-BuOOH (and not VO(acac)$_2$/*t*-BuOOH)[23] and afforded a mixture of the two, nonseparable epoxides **17** and **17′** in a 1:1 ratio.[24] Thus, although regioselectivity was complete, as expected, no stereoselectivity was observed under a variety of conditions. This was surprising in view of the good facial selectivity favoring the desired isomer reported for the same reaction performed on a close analogue of **16**.[6] It may be speculated that the observed different selectivities result from a "fine-tuning" of the preferred cyclohexane conformation(s) depending on the nature of the substituants (e.g., OPMB for **16** vs OH in the reported example). Any difference at this level may reasonably be expected to influence the conformationnal distribution of the C4-linked side chain and the accessibility of one or the other face of the C1′−C2′ olefinic bond.

Finally, methylation worked extremely well by using MeI/NaH to afford **18** and **18′**, which could be readily separated by chromatography. DDQ removal of the PMB protecting group in **18** proceeded smoothly to afford (−)-fumagillol, whose data was identical in all respects with that already reported,[5,6] thereby confirming our proposed structural assignment for compound **9**. In the same way, **18′** was converted to "epi"-fumagillol.

Acknowledgment. We thank Drs. Didier Le Nouen and Stéphane Bourg for help with NMR recording and interpretation. We thank the CNRS and Galderma R&D for a fellowship to J-G.B. Financial support of this project by Galderma R&D is gratefully aknowledged.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016343Z

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