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Enantioselective Approaches to Potential MetAP-2 Reversible Inhibitors

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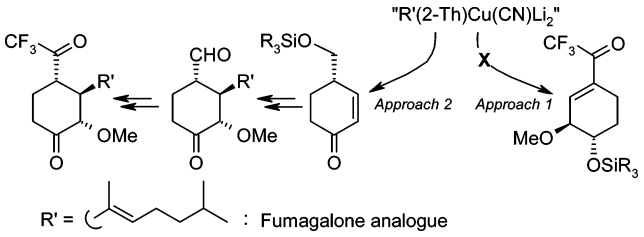

Enantioselective deprotonation of 4-substituted cyclohexanones and highly stereoselective conjugate addition of higher order mixed cuprates were the key steps in a concise synthesis of fumagalone-related molecules. The origin of the (low) biological activity of the new compounds as compared to fumagalone is briefly discussed.

Angiogenesis inhibitors based on the fumagillin structure, exemplified by TNP-470 (**1**, Figure 1), are generally believed to exert their biological effects through irreversible inhibition of methionine aminopeptidase 2 (MetAP-2).[1,2] Althought TNP-470 has shown therapeutic benefits in clinical studies, toxic side effects are a serious limiting factor. It has been suggested that these unwanted side effects may be partly linked to the irreversible character of the inhibition and the presence of reactive groups in the molecule. As a result, several types of MetAP-2 reversible inhibitors were recently prepared and shown to have antiproliferative properties on endothelial cells (EC).[3] In particular, fumagalone (**2**, Figure 1), derived from fumagillol by semi-synthesis, significantly inhibits MetAP-2 and shows a very good antiproliferative activity toward EC.[3a]

As part of an ongoing program aimed at discovering new MetAP-2 inhibitors, we have been working along

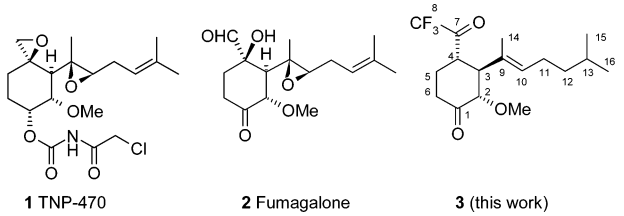

FIGURE 1. Some fumagillin analogues.

similar lines and would like to report our synthetic efforts in this area. In particular we wish to describe a short enantioselective synthesis of the trifluoromethyl ketone **3** (Figure 1) from simple prochiral precursors. The trifluoromethyl group in **3** was expected to increase the stability of the aminal assumed to be formed during the interaction with the enzyme, thus leading to stronger inhibition.[3a] Compound **3** also features a simplified side chain as compared to TNP-470 and fumagalone, lacking the double bond distal from the cyclohexyl ring, and the 9,10-epoxide (see Figure 1 for numbering). We have previously shown that these modifications did not significantly affect MetAP-2 inhibition in the case of irreversible fumagillin analogues.[4]

In our initial approach (Schemes 1−3), we had envisaged introducing the C9−C16 side chain by conjugate addition of an appropriate organometallic reagent to an intermediate α,β-unsaturated trifluoromethyl ketone. The latter, in turn, was to be prepared by a short sequence involving palladium-catalyzed methoxycarbonylation of a vinyltriflate and trifluoromethylation of the resulting α,β-unsaturated ester (or the corresponding α,β-unsaturated aldehyde). Little data is available regarding the addition of carbon nucleophiles to simple α,β-unsaturated trifluoromethyl ketones. Addition of methylmagnesium bromide on (*E*)-1,1,1-trifluoro-dodec-3-en-2-one was reported to proceed in a 1,2 fashion (apparently even in the presence of Cu(I) iodide).[5] On the other hand, addition of Grignard reagents to acyclic or alicyclic β-alkoxy-α,β-unsaturated trifluoromethyl ketones or to 1,1,1-trifluoro-4-phenyl-but-3-en-2-one yielded products of 1,4-addition.[6] In our case we reasoned that the increased bulk around the carbonyl group as compared to acyclic, α-nonsubstituted, α,β-unsaturated trifluoromethyl ketones should favor 1,4-attack.

The requisite chiral vinyltriflate was prepared as shown in Scheme 1. Asymmetric deprotonation of 4-*tert*-

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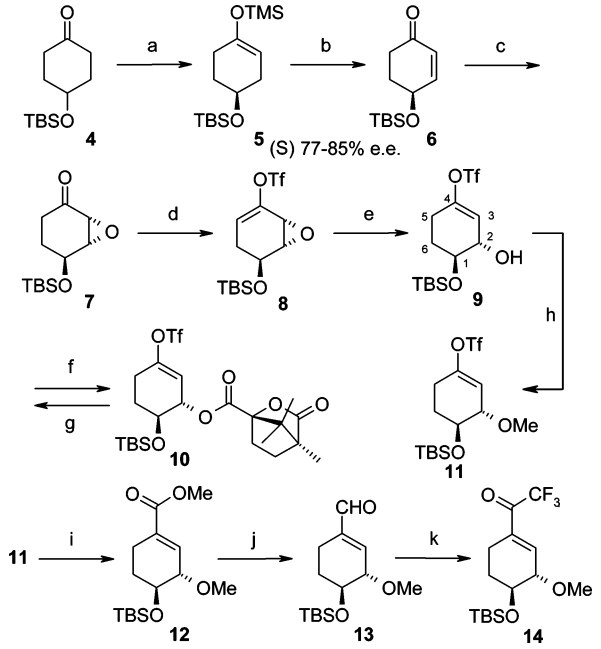
SCHEME 1[a]

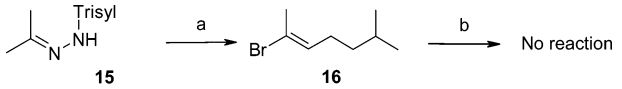


[a] Reagents and conditions: (a) lithium (+)-bis(α-methylbenzylamide), TMSCl, THF, −100 °C, 3 h; (b) $Pd(OAc)_2$, O_2, DMSO, 20 °C, 16 h, 72% (two steps); (c) TBHP, Triton B, toluene, 0 °C, 3 h, 78%; (d) (i) LiHMDS, THF, −15 °C, 15 min; (ii) $PhN(Tf)_2$, 0 °C, 16 h, 75%; (e) BH_3·THF, 0 °C, 4 h, 80%; (f) (i) camphanyl chloride, DMAP, Et_3N, CH_2Cl_2, rt, 16 h; (ii) chromatography, 78%; (g) DIBAL, THF, −78 → −40 °C, 16 h, 68%; (h) MeI, Ag_2O, MS 4 Å, Et_2O, 40 °C, 16 h; (i) CO (1 atm), $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF, 20 °C, 16 h, 83% (two steps); (j) (i) DIBAL, THF, −78 °C, 2 h; (ii) Dess−Martin periodinane, CH_2Cl_2, 2 h, 20 °C, 83% (two steps); (k) (i) CF_3TMS, TBAF (0.05 equiv), THF, 0 °C; (ii) Dess−Martin periodinane, CH_2Cl_2, 20 °C, 16 h, 55%.

butyl-dimethylsilyloxy-cyclohexanone (**4**) using the lithium amide derived from (+)-bis(α-methylbenzylamine)[7] and silylation of the resulting lithium enolate afforded the (*S*)-silyl enolether **5**. Treatment with $Pd(OAc)_2/O_2$[8] yielded cyclohexenone **6** in 77−85% enantiomeric excess (ee), which was converted to a single *anti*-epoxide **7**. Regioselective proton abstraction in **7** and treatment of the enolate with *N*-phenyltrifluoromethanesulfonimide gave the vinyl triflate **8**.[9]

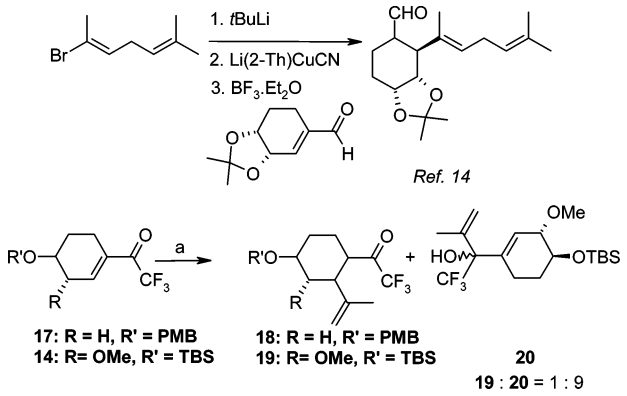
The synthesis of the key intermediate **14** was then completed as depicted in Scheme 1. Treatment of **8** with BH_3 afforded the allyl alcohol **9**, resulting from 1,5-reduction[10] of the vinyl epoxide moiety. O-Acylation with camphanyl chloride and chromatographic separation of the resulting diastereoisomeric esters afforded **10**, which was saponified to yield enantiomerically pure (1*S*,2*S*)-**9** (ee > 99%). After methylation of the hydroxyl group, methoxycarbonylation furnished the α,β-unsaturated ester **12** in excellent yield. Finally, the required trifluoromethyl ketone **14** was obtained from **12** in four steps

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) BuLi (2 equiv), DME, −78 °C, 10 min, then $ICH_2CH_2CH(CH_3)CH_3$, −40 °C, 14 h; (ii) BuLi (1 equiv), TMEDA, −78 → 0 °C; (iii) $BrCH_2CH_2Br$, −78 °C, 1 h, 57%; (b) (i) *t*BuLi (1.8 equiv), Li(2-Th)CuCN, BF_3·Et_2O, THF, −78 °C; (ii) **12**, **13**, or **14**.

SCHEME 3[a]



[a] Reagents and conditions: (a) $BrMgC(CH_3)=CH_2$, THF, 0 °C, ca. 40% (**18**) or ca. 30% (**19** + **20**).

(DIBAL reduction of **12** to the corresponding allylic alcohol, Dess−Martin oxidation of the latter to the corresponding α,β-unsaturated aldehyde **13**, formation of the trifluoromethyl alcohol, and again Dess−Martin oxidation). The overall yield over these four steps was 46%.

For the C9−C16 side chain introduction, (*E*)-2-bromo-6-methyl-hept-2-ene **16** was prepared using Corey's variation[11] of the Shapiro reaction[12] and converted to the corresponding high-order mixed cuprate by reaction with 2-thienylcyanocuprate.[13] Unfortunately, no 1,4-addition was observed with trifluoromethyl ketone **14** or the two alternative Michael acceptors **12** and **13** (Scheme 2).

This disappointing result was unexpected in view of the good results reported by Sorensen using a similar sequence in his synthesis of fumagillol[14] (Scheme 3).

To better understand this discrepancy, model studies were then performed. As can be seen in Scheme 3, addition of 2-propenylmagnesium bromide to the simple conjugated trifluoromethyl ketone **17**[15] afforded the expected addition product **18** in fair yield. Switching to **14** as an acceptor, however, resulted in a sluggish reaction leading predominantly to the 1,2-addition product **20** (Scheme 3). In the Sorensen case, the protected

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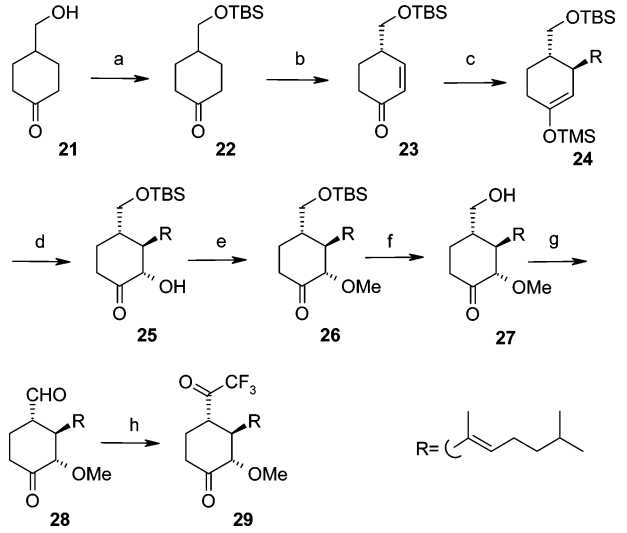
(15) Compound **17** was prepared in a few steps from the known 4-(4-methoxy-benzyloxy)-cyclohexanone (Spino, C.; Hill, B.; Dube, P.; Gingras, S. *Can. J. Chem.* **2003**, *81*, 81−108); the ketone was converted to the corresponding enol triflate and the latter was converted to **17** as described in the preparation of **14** (see Supporting Information for details).

SCHEME 4[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, THF, 20 °C, 2 h, 75%; (b) (i) lithium (+)-bis(α-methylbenzylamide), TMSCl, THF, −95 °C, 3 h; (ii) $Pd(OAc)_2$, O_2, DMSO, 20 °C, 16 h, 69% (two steps); (c) $LiC(CH_3)=CHCH_2CH_2CH(CH_3)CH_3$, Li(2-Th)CuCN, THF, −78 °C, 30 min, then TMSCl, 30 min.; (d) mCPBA (1 equiv) CH_2Cl_2, 0 °C, 1 h, then CF_3COOH, MeOH, 0 °C, 30 min, 52% (two steps); (e) MeI, Ag_2O, MS 4 Å, Et_2O, 40 °C, 16 h, 96%; (f) TBAF, THF, 20 °C, 4 h, 84%; (g) Dess−Martin periodinane, CH_2Cl_2, 20 °C, 2 h, 83%; (h) (i) CF_3TMS, TBAF (0.05 equiv), THF, 0 °C then TBAF (1 equiv); (ii) Dess−Martin periodinane, CH_2Cl_2, 20 °C, 16 h, 40% (two steps).

hydroxyls are located on the same face of the cyclohexene ring. It can be tentatively proposed that the isopropylidene protecting group both locks the conformation of the acceptor and maintains the isopropyl group away from the acceptor. In our case, these two beneficial factors are absent and the methoxy group may be able to hinder approach of the incoming nucleophile to the 4-position. We cannot exclude that the replacement of the PMB in **14** by a TBS group in **17** also contributes to rendering conjugate addition of the Grignard reagent more difficult. Overall, however, even in the simpler case, the yields were low and clearly not acceptable for the synthesis of more elaborated molecules. These studies, although imperfect, served their purpose and indicated that our strategy needed to be reexamined.

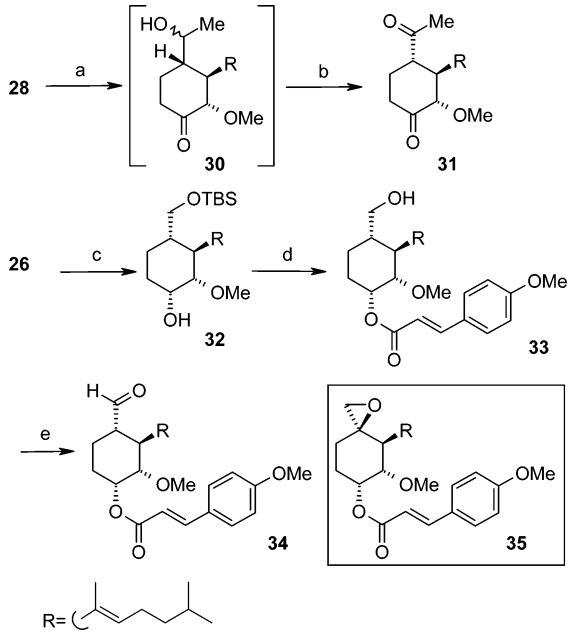
At this point we had two possibilities: either repeat the approach shown in Scheme 2 but using (3*S*,4*R*)-3,4-dihydroxy-1-cyclohexene-carboxaldehyde (Sorensen's intermediate), which required the enantioselective synthesis of the latter[16] (or the conversion of aldehyde **13** to the Sorensen intermediate), or modify our synthesis.

We rapidly came to the conclusion that the second option was more promising and less time-consuming, and this led us to the synthesis shown in Scheme 4, a variant of our initial approach influenced by Taber's synthesis of fumagillin.[17]

Here again, the synthesis commences by the enantioselective deprotonation of a cyclohexanone precursor **22** (obtained by silylation of 4-hydroxymethyl-cyclohexanone (**21**)).[18] Silylation of the resulting enolate afforded the corresponding silyl enolether, which was converted in good yield to the α,*β*-unsaturated ketone **23** by treatment with palladium acetate, under oxygen atmosphere as described earlier. Conjugate addition of the high-order mixed cuprate formed from 6-methyl-hept-2-enyllithium and lithium 2-thienylcyanocuprate and quenching of the resulting enolate with trimethylsilyl chloride gave the silyl enol **24**. Selective oxidation of the latter with mCPBA[19] took place as expected on the least hindered C1-*re* face of the C1−C2 olefinic double bond (see Figure 1 for numbering), to afford the α-hydroxyketone **25**. The trisubstituted side chain double bond was not affected. The overall yield for the sequence **23** → **25** was a satisfactory 52%. At this point chiral HPLC showed that **25** was a 92:8 mixture of 2(*S*),3(*S*),4(*S*) and 2(*R*),3(*R*),4(*R*) enantiomers. Methylation of the free hydroxyl group, removal of the TBS group, and oxidation of the primary alcohol using Dess−Martin periodinane afforded the crucial synthetic intermediate, the aldehyde **28**. Trifluoromethylation followed by oxidation completed our synthesis of the target trifluoromethyl ketone **29**.

For comparison purposes, besides aldehyde **28**, available from the synthesis, the methyl ketone **31** and cinnamyl ester **34**, the latter being a direct analogue of the strongly biologically active fumagillin analogue **35**,[4] were prepared using standard methodology (Scheme 5).

SCHEME 5[a]



[a] Reagents and conditions: (a) MeLi (1 equiv), THF, −78 °C, 1 h; (b) Dess−Martin periodinane, CH_2Cl_2, 20 °C, 14 h, 76% (two steps); (c) L-Selectride, THF, −78 °C, 1 h, 70% (dr >9:1); (d) (i) *p*-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 20 °C, 48 h; (ii) TBAF, THF, 20 °C, 16 h, 80% (e) Dess−Martin periodinane, CH_2Cl_2, 20 °C, 16 h, 87%

(16) At the time this work was in progress, the enantioselective synthesis of the required Sorensen's intermediate had not been disclosed (ref 14a).

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TABLE 1. MetAP-2 Inhibition by Compounds 28, 29, 31, and 34

	28	**29**	**31**	**34**	**2**[3a]
IC_{50} (μM)	281	>500	>500	>500	8
K_i (μM)	70				

The inhibitory activity of compounds **28**, **29**, **31**, and **34** against MetAP-2 was measured as described earlier (Table 1) (see also full description of the assay in Supporting Information). Except for the aldehyde **28**, which shows weak biological activity, none of the other analogues, in particular the trifluoromethyl ketone **29**, significantly inhibited MetAP-2.

In conclusion, we have examined two enantioselective approaches to potential fumagillin-like reversible inhibitors, using cheap, readily available starting materials. The first approach, although unsuccessful, provided useful information regarding the limitations of vinyl cuprates or vinyl Grignards conjugate additions to 3,4-substituted-1-cyclohexene carbaldehydes. The second approach was successfully applied to the synthesis of several structurally simple, fumagalone-related molecules, one of which was a weak, reversible MetAP-2 inhibitor. The poor biological activity of the new analogues is surprising. The most important difference between our compounds and fumagalone is the lack of a hydroxyl group linked to C4 in the former. It is quite possible that this group creates interactions crucial for binding to residues within the active site of MetAP-2, and this would explain the results of the biological assays in our case. Work to clarify this point is underway in our laboratory.

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Supporting Information Available: Detailed experimental procedures including biological assay and ^{13}C data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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