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Enantioselective synthesis of the farnesyltransferase inhibitor, A-345665.0

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Abstract—The stereoselective synthesis of A-345665.0 **1**, a novel farnesyl transferase inhibitor, is described. The key step involves a stereoselective addition of an imidazolyl Grignard reagent to aldehyde **8** in the presence of an external chiral auxiliary. Crystallization of the product as the dimeric zinc complex **12** facilitates the isolation of product in >98:2 er. The biaryl linkage is formed by the use of a Suzuki coupling, employing boronic acid **4** prepared by the directed ortho-lithiation of benzonitrile **6**. The overall yield for the six step sequence is 21%.

Mutation of the *ras*-oncogene regulating cell growth and proliferation is implicated in up to 25% of human cancers.[1] After transcription of the protein and further activation by normal *ras*-protein activation processes (cysteine–farnesylation, cleavage of a tripeptide and C-terminal methylation), the mutated *ras*-protein derives an uncontrolled cell growth and proliferation.[2] One strategy for the interruption of this process is by the inhibition of the farnesylation process, which is mediated by farnesyl transferase (FT). A-345665.0 (**1**)[3] has been identified as a FT inhibitor possessing excellent potency, bioavailability and pharmacokinetics.[4] Herein, we disclose research into the preparation of A-345665.0.

Among the synthetic challenges presented by A-345665.0 (**1**) are the biaryl formation and generation of the stereogenic center. Choosing to construct the biaryl through a Suzuki protocol and hoping to find a method for the stereoselective addition of the imidazole moiety to the aldehyde, retrosynthetic analysis (Fig. 1) led us to iodoimidazole **2**, benzylbromide **3**, aldehyde/boronic acid **4**, and quinoline triflate **5** as the starting materials.

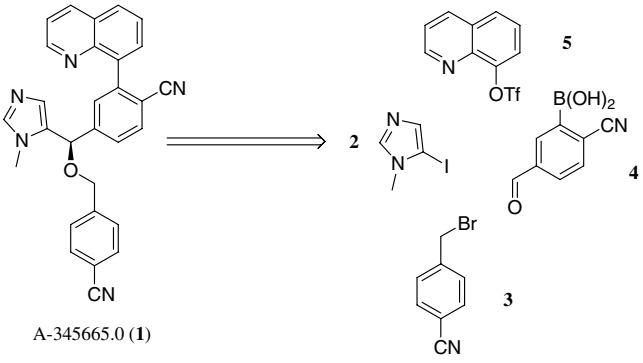

Figure 1. Retrosynthetic analysis of A-345665.0.

Directed ortho metalation of arenes[5] followed by trapping the anion with a trialkyl boronate is a powerful method for the generation of boronic acids. Recently, Vedsø and co-workers[6] found that by using a modification of the method described by Martin and Krizan,[7] arenes bearing sensitive electron-withdrawing groups could be ortho metalated with LiTMP and trapped in situ with triisopropylborate ($B(OiPr)_3$) to produce, after work-up, the corresponding boronic acid. We found that by protecting commercially available 4-cyanobenzaldehyde **6a** as its diethyl acetal (Scheme 1), the desired boronic acid **4** could be obtained by the reaction of **6b** with LiTMP in the presence of $B(OiPr)_3$ at −70 °C, followed by the acidic work-up. Suzuki

Keywords: Farnesyl-transferase inhibitor; FTI; Asymmetric addition; Suzuki coupling; Palladium coupling.
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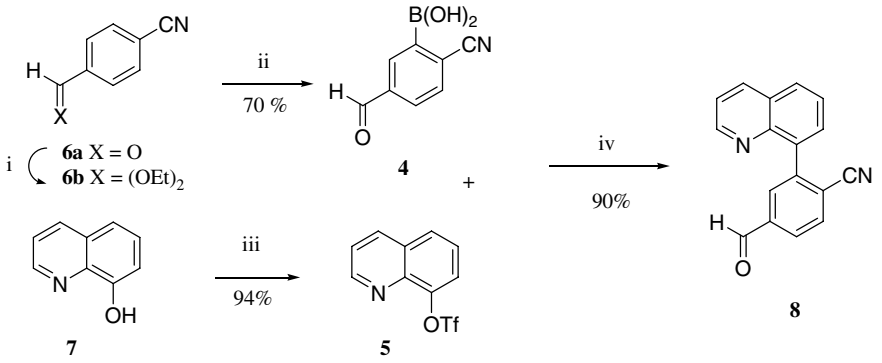
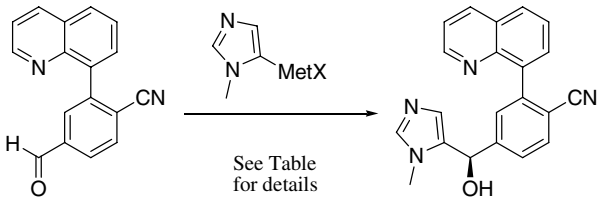


Scheme 1. Reagents and conditions: (i) triethyl orthoformate, ethanol, reflux; (ii) LiTMP, B(O-*i*Pr)$_3$, THF, −60 °C; (iii) Tf_2O, pyr, −5 °C and (iv) KF, toluence/methanol, cat. $Pd(OAc)_2$, cat. biphenyl-2-dicyclohexyl-phosphane, 68 °C.

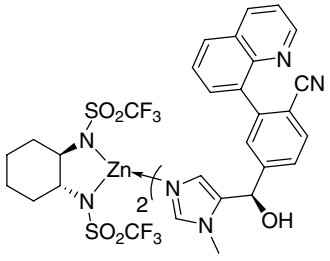
coupling of boronic acid **4** with quinoline triflate **5** (prepared from commercially available hydroxyquinoline **7**) was accomplished with catalytic $Pd(OAc)_2$ using biphenyl-2-yl-dicyclohexyl-phosphane[8] as the ligand and afforded aldehyde **8**. With the aldehyde in hand, the stereoselective addition of an imidazolyl moiety was investigated.

The enantioselective additions of alkyl[9] and to a lesser extent arylzinc[10] reagents to carbonyl compounds constitute a powerful method for the construction of chiral secondary alcohols. We felt, however, that the presence of heteroatoms would disrupt the highly ordered coordination complex needed to effect high levels of stereoselection. Guided by the work of chemists from Merck and Dupont on the stereoselective synthesis of Efavirnez,[11] we explored the external chiral auxiliary approach for the addition of organometallic reagents to aldehyde **8** (Eq. 1). Starting with 5-iodo-1-methyl-1*H*-imidazole, the corresponding Grignard[12] or organozinc[13] reagent could be prepared. The additions of chiral auxiliaries to the imidazolyl metallic reagent, with and without various additives, were explored to effect the stereoselective addition to aldehyde **8** (Table 1). The use of 1-phenyl-2-pyrrolidin-1-yl-propan-1-ol (**10**) under a variety of conditions afforded alcohol **9** in moderate enantiomeric excesses (34–60%) and in variable yields (41–80%). Aldehyde **8**, was prone to undergo a Cannizzaro[14] disproportionation to the corresponding primary alcohol and acid, and these products were seen in the crude reaction mixtures.



8 **9** (1)

Bis-sulfonamide **11**[15] has also proven to be an effective ligand for the stereoselective addition of organozinc reagents to carbonyl compounds. We found that the treatment of **11** with dimethylzinc in CH_2Cl_2 followed by the addition of 3-methyl-3*H*-imidazol-4-yl magnesium chloride,[12] produced a reagent that delivered the imidazolyl moiety to aldehyde **8** in an 85% HPLC yield, 80% ee and without Cannizzaro side products. The selectivity was not greatly affected by temperature (84% ee at −40 °C, 70% ee at 0 °C). The chiral purity[16] of the product was further enhanced through its isolation as a 2:1:1 complex of alcohol **9**:zinc:sulfonamide (**12**).[17,18] The isolation of complex **12** (69% yield from **8**) from ethanol afforded alcohol **9** in a 98% ee after decomplexation by partitioning **12** between CH_2Cl_2 and aqueous NaOH.

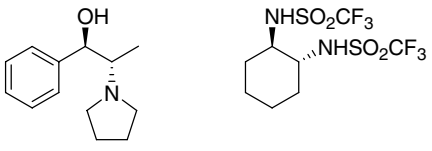


12

The exact nature of the imidazolyl Grignard reagent was not determined, however, its use for the addition of the imidazolyl moiety could be extended to other aldehydes,

Table 1. Enantioselective additions to **8**

Entry	MetX	Ligand	Additive	HPLC yield (%)	Ee (%)
1	ZnI	**10**	BuLi	40	60
2	ZnI	**10**	None	62	55
3	ZnI	**10**	Me_2Zn, trifluoroethanol	81	34
4	MgCl	**10**	Me_2Zn, trifluoroethanol	41	56
5	MgCl	**11**	Me_2Zn	85	80



10 **11**

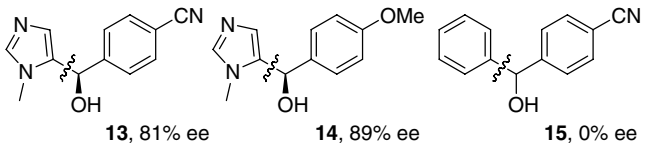
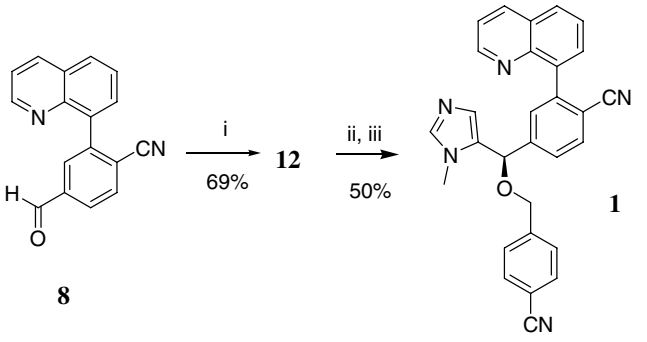


Figure 2.

such as 4-cyanobenzaldehyde and *p*-anisaldehyde to produce secondary alcohols **13** and **14**, respectively. Unfortunately, other Grignard reagents (PhMgBr) when used under these conditions gave racemic product **15** (Fig. 2).

With the chiral alcohol in hand, the ether was constructed (equation 2) by the alkylation of **9** with benzylbromide **12** to afford the farnesyltransferase inhibitor A-345665.0 (**1**).



Reagents and conditions: (i) see Ref. 18; (ii) aq NaOH, CH_2Cl_2; (iii) LiHMDS, 4-cyanobenzyl bromide, Bu_4NI (10 mol %), DMF, 0 °C.

(2)

In summary, we have developed a short and selective synthesis of A-345665.0. It is highlighted by the formation of a chiral secondary alcohol through the enantioselective addition of a imidazolyl Grigand reagent to an aldehyde using an external chiral auxiliary.

Acknowledgments

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18. *General procedure for* **12**: A solution of PhMgBr (1.0 M in THF, 37.0 mL, 37.0 mmol) was added at −10 °C to a solution of 5-iodo-1-methyl-1*H*-imidazole (8.3 g, 40.0 mmol) in CH_2Cl_2 (100 mL) and the resulting mixture stirred at −10 °C for an additional 45 min. In a separate reaction vessel, a solution of dimethylzinc (2 M in toluene, 20.0 mL, 40.0 mmol) was added to a solution of *N*,*N*′-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(1,1,1-trifluoromethanesulfonamide) (**11**) (15.0 g, 39.7 mmol) in CH_2Cl_2 (50 mL) at an ambient temperature. After an additional 45 min, THF (50 mL) was added. The resulting solution of zinc sulfonamide was added to the imidazolyl Grignard reagent, and after stirring the resulting mixture at −10 °C for 1 h, aldehyde **8** (5.2 g, 20.1 mmol) was added

and the reaction allowed to proceed for 1 h. After an aqueous work-up (5% aqueous NH_4OAc, 10% MeOH in CH_2Cl_2), the organic layer was concentrated in vacuo. The resulting residue was suspended in EtOH (50 mL), warmed to 50 °C, and the suspension stirred for 8 h. After cooling to ambient temperature, the solid was collected, washed with EtOH (10 mL), and dried in a vacuum oven at 50 °C to yield 8.25 g (4.67 g of alcohol **9** by HPLC analysis versus a standard (69% yield)) of complex **12**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08–1.26 (m, 4H) 1.55–1.66 (m, 2H) 2.28–2.41 (m, 2H) 2.90–3.00 (m, 2H) 3.73 (s, 6H) 6.05 (d, $J = 5.15$ Hz, 2H) 6.44 (d, $J = 5.52$ Hz, 2H) 6.72 (s, 2H) 7.56–7.81 (m, 10H) 7.98 (s, 2H) 8.13 (dd, $J = 8.09$, 1.47 Hz, 2H) 8.48 (dd, $J = 8.46$, 1.84 Hz, 2H) 8.86 (dd, $J = 4.04$, 1.84 Hz, 2H) ppm. ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.3, 31.1, 32.7, 38.7, 38.9, 39.2, 39.5, 39.8, 40.1, 40.3, 62.1, 64.8, 112.3, 118.1, 118.4, 121.8, 122.4, 125.6, 125.9, 126.1, 128.0, 129.4, 130.4, 132.6, 135.0, 136.4, 136.9, 140.3, 143.2, 145.2, 146.4, 150.52 ppm. Anal. Calcd. for $C_{50}H_{42}F_6N_{10}O_6S_2Zn$–$H_2O$, C, 52.66; H, 3.89; F, 10.00; N, 12.2; S, 5.62; found C, 52.39; H, 3.80; F, 10.08; N,12.24; S, 6.13.