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Studies directed towards the synthesis of antascomicin A: stereoselective synthesis of the C22–C34 fragment of the molecule☆

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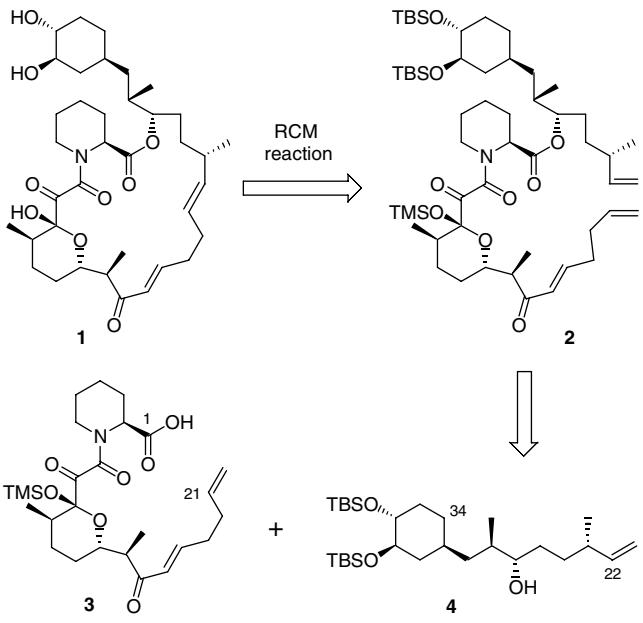
Abstract—A stereoselective synthesis of the C22–C34 fragment of the non-immunosuppressive immunophilin-binding natural product, antascomicin A was achieved using D-quinic acid as the starting material and highly stereoselective aldol reactions were employed, as key steps, to build the remaining stereocentres at C23, C26 and C27.

Although the binding affinities of antascomicins[1] to FKBP12 ($IC_{50} = 2$ nm, for antascomicin A, **1**) are very similar to that of FK506 or rapamycin (1.1 and 0.6 nm, respectively, in the same binding assay), they do not show any immunosuppressive activity. Such non-immunosuppressive immunophilin binding ligands as antascomicins, produced by fermenting a strain of the genus *Micromonospora* isolated from a soil sample collected in China,[1] hold much promise for the treatment of various neuro-degenerative disorders like Alzheimer's and Parkinson's diseases.[2] The biological activities of these molecules and their structural features have attracted the attention of synthetic organic chemists leading to the total syntheses of antascomicin B[3] and the C18–C34 fragment of antascomicin A.[4] As part of our studies directed towards the total synthesis of antascomicin A, we report here the stereoselective synthesis of the C22–C34 fragment of the molecule.[5]

Retrosynthetic analysis of antascomicin A (**1**) (Scheme 1) reveals that an acyclic precursor such as **2** was ideally suited to build the macrocyclic ring of the molecule using an RCM reaction.[6] Compound **2** could be easily assembled by coupling the C1–C21 unit **3** with the C22–C34 fragment **4** through an esterification reaction.



Scheme 1. Retrosynthetic analysis of antascomicin A (**1**).

For the synthesis of the C22–C34 fragment **4** of antascomicin A, D-quinic acid was chosen as the starting material. Scheme 2 outlines the details of the synthesis. D-(−)-Quinic acid **5** was transformed into the intermediate **6** in six steps and in 33% overall yield following the procedure reported earlier.[7] Silylation of **6** was followed by reduction to furnish the diol **7** in 76% yield. Selective

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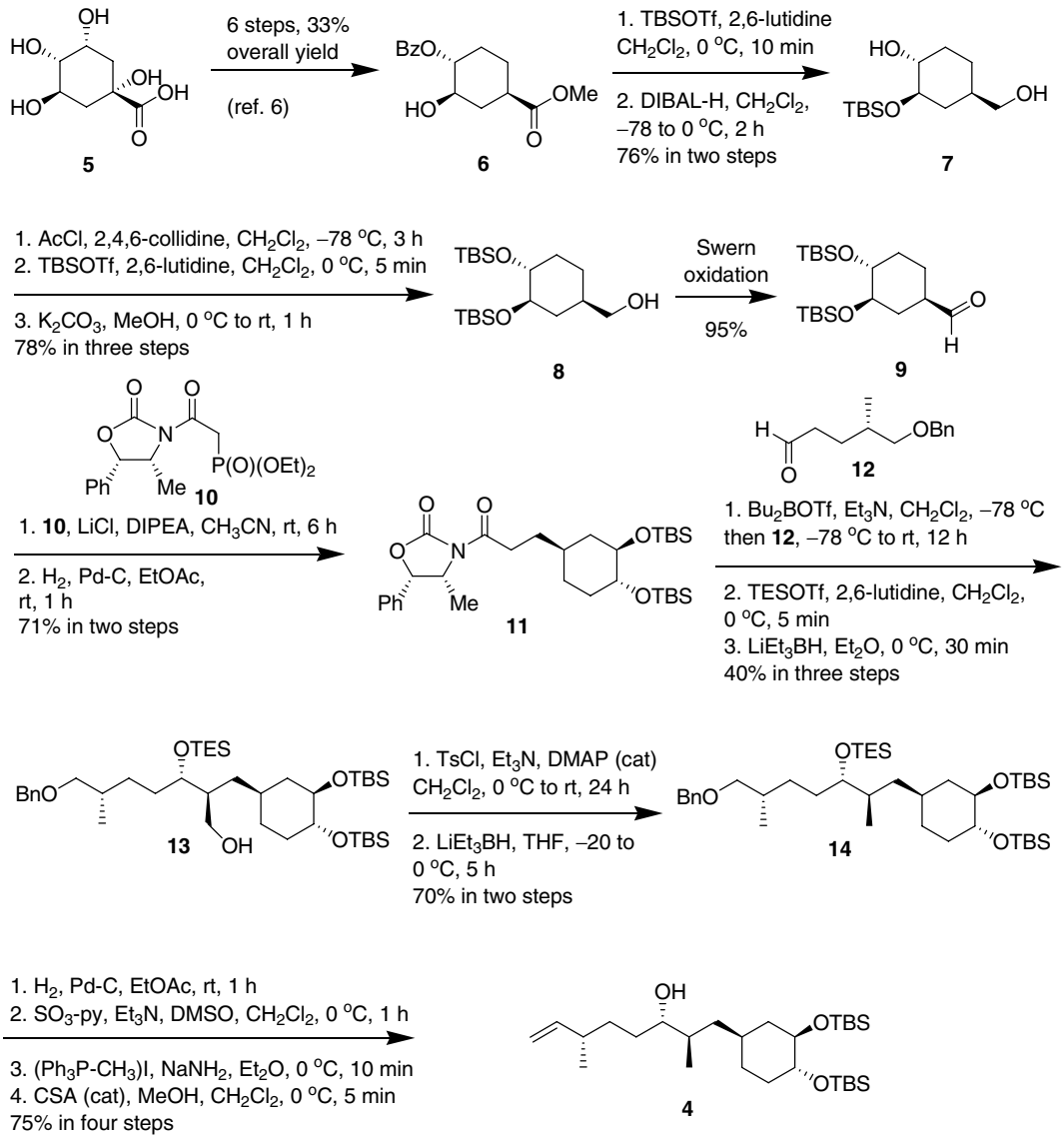

Scheme 2. Stereoselective synthesis of C22–C34 fragment **4**.

acylation of the primary hydroxyl group, silylation of the secondary hydroxyl and deprotection of the acetate gave the disilylated intermediate **8** in 78% yield in three steps. Finally Swern oxidation[8] of **8** furnished the aldehyde **9** in 95% yield.

Horner–Wadsworth–Emmons olefination of **9** with the (1*S*,2*R*)-(+)-norephedrine-derived keto-phosphonate **10**[9] using LiCl–DIPEA[10] provided an α,β-unsaturated amide intermediate, which was hydrogenated to furnish the *N*-acylated chiral auxiliary **11**.[11] The enolate of **11** was reacted with the aldehyde **12**[12] to furnish the aldol product as a single isomer. The stereochemistries of the newly generated chiral centres were assigned on the basis of an earlier reported work.[11] The aldol adduct was then silylated and the chiral auxiliary was removed by reduction with lithium triethylborohydride to furnish **13** in 40% yield in three steps. A two-step protocol was followed to convert the hydroxymethyl group of **13** to a methyl group—tosylation followed by nucleophilic substitution of the tosylate group with hydride—to furnish **14** in 70% yield.[11] Debenzylation of **14** by catalytic hydrogenation, oxidation of the resulting primary hydroxyl group, one-carbon Wittig olefination and finally an acid-catalyzed desilylation step furnished the target fragment **4** in 75% yield.[13] Further work is now in progress to couple **4** with the C1–C21 fragment **3** and complete the total synthesis of the molecule.

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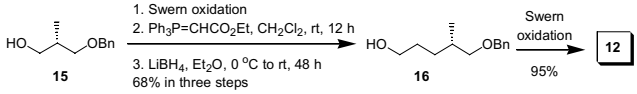
12. Aldehyde **12** was synthesized from the mono-benzylated chiral 2-methyl-propane-1,3-diol **15**, which was prepared from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate in two steps—benzylation with *O*-benzyl trichloroacetimidate under acidic conditions followed by reduction of the ester with lithium aluminium hydride. Compound **15** was then transformed into **12** in four steps, as shown below, and in 65% overall yield.



13. Data of **4**. $R_f = 0.5$ (SiO_2, 10% EtOAc in petroleum ether); $[\alpha]_D^{27}$ −23.1 (*c* 0.016, $CHCl_3$); IR (KBr): ν_{max} 3422, 2929, 2857, 1465, 1253, 835 and 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.69 (ddd, $J = 16.0$, 10.0, 7.3 Hz, 1H, olefinic proton), 4.97 (dd, $J = 16.0$, 1.7 Hz, 1H, olefinic proton), 4.92 (dd, $J = 10.0$, 1.7 Hz, 1H, olefinic proton), 3.42–3.32 (m, 3H, C*H*–O–), 2.11 (m, 1H, allylic C*H*), 1.89–1.82 (m, 2H, C*H*), 1.63–1.04 (m, 12H, CH_2), 1.00 (d, $J = 6.7$ Hz, 3H, CH_3), 0.893 (s, 9H, *t*-butyl), 0.888 (s, 9H, *t*-butyl) 0.87 (d, $J = 6.8$ Hz, 3H, CH_3), 0.068 (s, 12H, $2Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.55, 112.71, 76.47, 75.92, 40.49, 38.16, 37.90, 35.95, 34.04, 33.50, 33.19, 32.15, 31.09, 26.11, 20.19, 18.19, 15.57, −3.79, −4.63, −4.67; mass (ESIMS): *m*/*z* 521 $[M+Na]^+$, 522 $[M+Na+H]^+$; HRMS (ESIMS): calcd for $C_{28}H_{59}O_3Si_2$ $[M+H]^+$: 499.4002, found: 499.4004.