A Convergent, Enantioselective Total Synthesis of Streptogramin Antibiotic (−)-Madumycin II†

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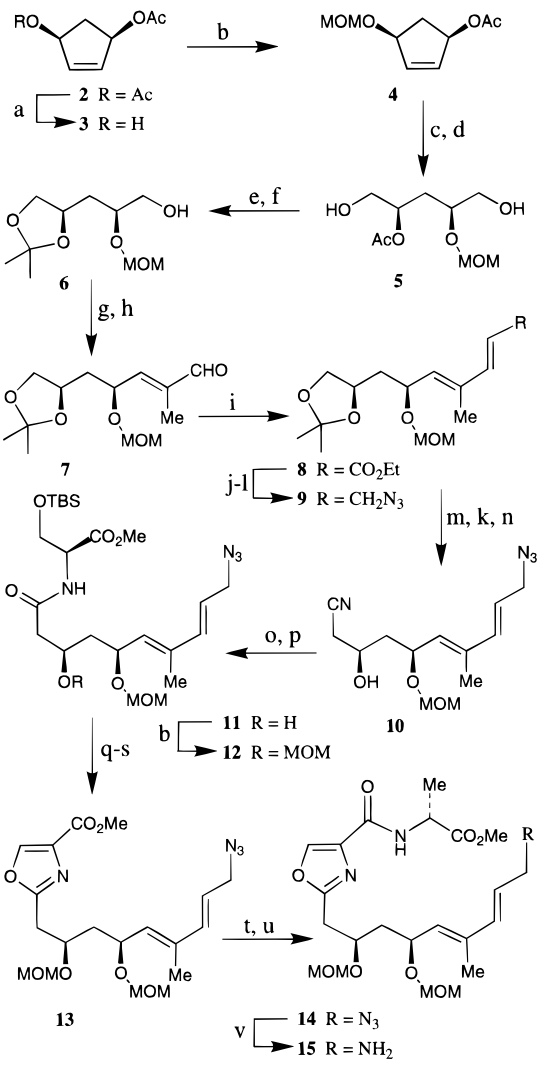
With the increasing threat of resistant microbes, the search for antibacterial agents effective against these pathogens is of contemporary interest in medicine.[2] The emergence of methicillin-resistant *S. aureus* or MRSA is particularly alarming since this strain of bacteria is resistant to all current antibiotics except vancomycin, which is burdened by its serious side effects.[3] The streptogramin antibiotics are comprised of two main groups; the group A antibiotics exhibit synergism with group B, and the possible mode of action includes the inhibition of protein synthesis by interfering with the bacterial ribosomal function.[4] Molecular modification and combination of both classes of streptogramins have been shown to be effective against MRSA and erythromycin-resistant *S. aureus* and *S. epidermidis*.[5] The significant therapeutic potential of streptogramins continues to foster immense synthetic interest.[6] Representative of group A streptogramins are madumycin II[7] and virginiamycin,[8] and their first enantioselective syntheses have been recently reported by Meyers[9] and Schlessinger,[10] respectively. We herein report a convergent and enantioselective total synthesis of (−)-madumycin II.

Our synthetic plan was to construct the oxazole-containing 1,3-diol synthon **15** and α,β-unsaturated acid unit **19** stereoselectively and assemble madumycin II by a macrolactonization strategy. To set both stereogenic centers of the 1,3-diol, an enzymatic asymmetrization of *meso*-diacetate **2** provided the monoacetate **3** in 95% enantiomeric excess (Scheme 1).[11] The hydroxyl group in **3** was protected as methoxymethyl (MOM) ether **4** in 95% yield.[12] Ozonolysis of **4** provided the corresponding dialdehyde, which was reduced with sodium borohydride to furnish the diol **5**. The removal of the acetate group in **5** afforded the triol, which was protected as the isopropylidene derivative **6** in 90% yield. Oxidation of the alcohol **6** with PCC followed by Wittig olefination furnished the α,β−unsaturated aldehyde **7** (*E*:*Z* ratio 10:1). Exposure of the aldehyde **7** to a Horner−Emmons olefination with triethyl phosphonoacetate afforded the *E*,*E*-diene ester **8** in 82% yield from **6**. Dibal-H reduction, followed by mesylation of the resulting alcohol, afforded

Scheme 1[a]



[a] Key: (a) acetyl cholinesterase, pH = 7 buffer, 12 h, 85%; (b) MOMCl, *i*-Pr_2NEt, DMAP, 95%; (c) O_3, MeOH−CH_2Cl_2 (1:1), −78 °C, then Me_2S, −78 to +23 °C; (d) $NaBH_4$, EtOH, 0 °C, 2 h, 95%; (e) aqueous MeOH, Et_3N, 23 °C, 12 h; (f) $Me_2C(OMe)_2$, *p*-TsOH (cat.), CH_2Cl_2, 23 °C, 1 h, 90%; (g) PCC, 4A-sieves, CH_2Cl_2, 6 h; (h) $Ph_3P{=}C(Me)CHO$, PhMe, 114 °C, 12 h; (i) NaH, $(EtO)_2P(O)$-CH_2CO_2Et, 82%; (j) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 95%; (k) MsCl, Et_3N, CH_2Cl_2; (l) NaN_3, DMF, 23 °C, 8 h, 67%; (m) *p*-TsOH, MeOH, 23 °C, 12 h; (n) LiCN, THF−EtOH (1:1), 80 °C, 2 h, 75%; (o) aqueous 4N NaOH, MeOH, 60 °C, 8 h then H_3O^+; (p) BOP, *i*-Pr_2NEt, *O*-TBS-L-serine methyl ester, MeCN, 23 °C, 5 h, 72%; (q) TBAF, THF, 0 °C, 1 h; (r) Burgess salt, THF, 23 °C, 6 h; (s) $CuBr_2$, DBU, HMTA, CH_2Cl_2, 42 °C, 5 h, 45% from **12**; (t) aqueous LiOH, THF, 23 °C, 4 h then H_3O^+; (u) D-alanine-OMe, BOP, *i*-Pr_2NEt, MeCN, 99%; (v) $HS(CH_2)_3SH$, Et_3N, MeOH, 65%.

† This manuscript is dedicated to Professor A. I. Meyers on the occasion of his 65th birthday.

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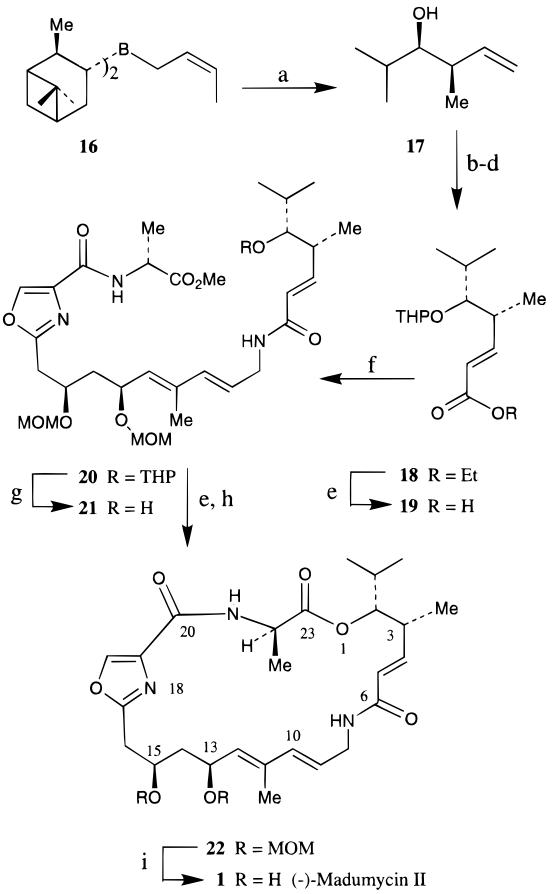
the mesylate. Treatment of the mesylate with sodium azide in DMF furnished the azide **9**. Selective removal of the isopropylidene group in **9** resulted in diol which was converted to the cyanide **10**.

To elaborate the oxazole functionality, the cyanide **10** was hydrolyzed, and the resulting acid was treated with 1.5 equiv of BOP reagent[13] and 4 equiv of *i*-Pr_2NEt in acetonitrile in the presence of 2 equiv of silyl-protected L-serine methyl ester to furnish the amide **11** in 72% yield. Protection of the hydroxyl group of **11** afforded the bis-MOM derivative **12** in 78% yield. The bis-MOM **12** was transformed into oxazole **13** by the following reaction sequence: (1) deprotection of the silyl group by exposure to *n*-$Bu_4N^+F^-$ in THF at 0 °C for 1 h; (2) conversion of the resulting alcohol to oxazoline with Burgess salt[14] in THF at 23 °C for 6 h, and (3) oxidation[15] of the corresponding oxazoline to oxazole **13**. Methyl ester hydrolysis of **13** followed by coupling of the resulting acid with D-alanine methyl ester furnished the depsiptide **14**. Selective reduction[16] of azide **14** with an excess of propanedithiol and Et_3N in methanol afforded amine **15** in 65% yield.

The synthesis of α,β−unsaturated acid **19** is outlined in Scheme 2. Reaction of **16** with isobutyraldehyde afforded *syn*-homoallyl alcohol **17** in 75% yield and high optical purity (>95% ee).[17] Olefin **17** was subjected to ozonolytic cleavage, and the resulting aldehyde was exposed to a Horner−Emmons olefination protocol to provide the corresponding α,β-unsaturated ester. The hydroxyl group was subsequently protected as THP ether **18** in 75% yield. Saponification of **18** with aqueous LiOH provided the acid **19** in quantitative yield.

After construction of amine **15** and acid **19** with the appropriate stereochemistry, our plan was to form an amide bond between these fragments and then effect macrolactonization between the C-2 hydroxyl group and C-23 carboxylic acid. Thus, coupling of amine **15** and acid **19** was carried out in the presence of BOP reagent[13] to furnish the amide **20** in 78% yield. The removal of THP ether was carried out by treatment of **20** with a catalytic amount of *p*-TsOH in methanol. Saponification of **21** with aqueous LiOH at 0 °C for 3 h furnished the corresponding hydroxy acid, which was subjected to Yamaguchi macrolactonization[18] conditions with 2,4,6-trichlorobenzoyl chloride, Et_3N, and DMAP at 23 °C for 12 h to provide the macrolactone **22** (α^{23}_D −144, *c* 0.15, $CHCl_3$) in 63% yield. Removal of the bis-MOM by exposure to *n*-$Bu_4N^+Br^-$ (2 equiv) and an excess of dichlorodimethylsilane in CH_2Cl_2 at 0 °C for 6 h provided synthetic (−)-madumycin II (47% yield) and both mono-MOM derivatives of madumycin II (10−12%).[19] Spectral data (IR and 400 MHz NMR) and TLC characteristics of synthetic madumycin II (α^{23}_D −115, *c* 0.03, $CHCl_3$) are identical with a sample of natural madumycin II (α^{23}_D −127, *c* 0.11, $CHCl_3$) provided by Eli Lilly.[20]

Scheme 2[a]



[a] Key: (a) Me_2CHCHO, −78 °C, 3 h, then 3 N NaOH and H_2O_2, 75%; (b) O_3, MeOH−CH_2Cl_2 (1:1), −78 °C, then Me_2S, −78 °C to 23 °C; (c) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, 23 °C; (d) dihydropyran, PPTS, CH_2Cl_2, 23 °C, 1 h, 75% from **17**; (e) aqueous LiOH, THF; (f) amine **15**, BOP, *i*-Pr_2NEt, MeCN, 23 °C, 6 h, 78%; (g) *p*-TsOH (cat.), MeOH, 23 °C, 4 h, 95%; (h) $Cl_3C_6H_2COCl$, Et_3N, PhMe, 23 °C, 4 h then DMAP, 23 °C, 12 h, 63% from **21**; (i) Me_2SiCl_2, *n*-$Bu_4N^+Br^-$, 4A sieves, CH_2Cl_2, 0 °C, 6 h, 47%.

In conclusion, an enantioselective, convergent synthesis of (−)-madumycin II has been accomplished. The current synthesis of madumycin II may find useful application for the preparation of structural variants of madumycin and other members in this family of antibiotics.

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Supporting Information Available: Experimental procedures and spectral data for synthetic intermediates **2**−**22** and NMR spectra for natural and synthetic madumycin II (22 pages).

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