Total Synthesis of Streptogramin Antibiotics. (−)-Madumycin II

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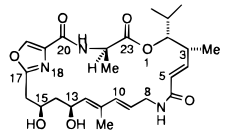
The presence of oxazoles and thiazoles as masked dehydropeptides in a number of important natural substances continues to attract considerable attention among organic chemists.[1] The streptogramin family of antibiotics, which arises from a number of microorganisms,[2] occurs as a mixture of two groups, A and B. Group A contains the oxazole moiety, whereas group B is mainly composed of peptide linkages. Their main mode of action involves inhibition of peptide biosynthesis in the bacterial ribosome.[3,4] Typical members of the structurally interesting group A are madumycin II (**1**) and virginiamycin M_2 (**2**). The former was isolated by Brazhnikova[5] and also by Chamberlin,[6] designating the same substance as A-2315A, whereas the latter was isolated by Lord Todd[7] and its structure confirmed by X-ray analysis.[8]

Synthetic efforts toward these and other members of the streptogramin group A compounds have been reported over the past 15 years and to date none have succeeded in reaching any of the targets.[9] We now report the first enantioselective total synthesis of madumycin II (A-2315A), (**1**) whereas the preceding paper by Schlessinger[10] reports the first enantioselective synthesis of virginiamycin M_2 (**2**).



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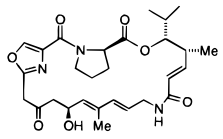

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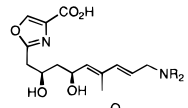
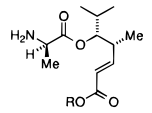


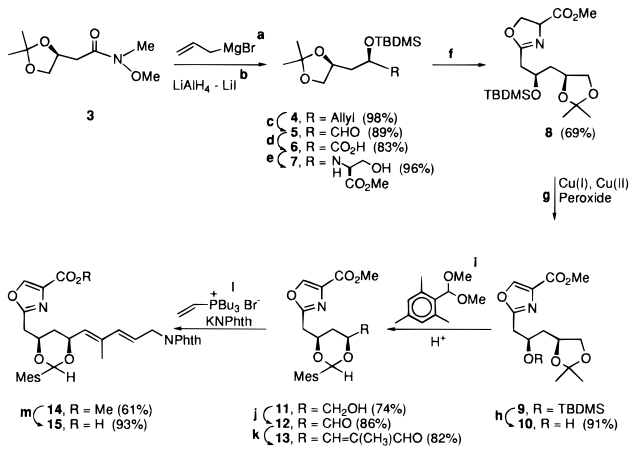
A, R_2 = H;



B, R = H; Me_3Si

Our route to **1** required two major components, **A** and **B**, obtained by disconnecting **1** at C-6 and C-20. Fragment A, representing the southern and western quadrants, was to be reconnected at these junctures with fragment B, representing the northern and eastern quadrants of madumycin.[11]

Scheme 1[a]



[a] Key: (a) −78 °C, 2.0 h, THF; (b) −100 °C, 45 min, 92%, Et_2O; workup; dry; TBDMSCI, imidazole, DMF; (c) O_3, DMS; (d) $NaClO_2$, NaH_2PO_4, H_2O_2 $CH_3CN{\cdot}H_2O$; (e) isobutylchloroformate, *N*-methylmorpholine, serine methylester·HCl; (f) $MeCO_2NS(O)_2NEt_3$ (ref 16); (g) *tert*-butylperbenzoate, CuBr, $Cu(OAc)_2$, benzene, reflux 7.5 h; (h) TBAF/THF, rt, 4 h; (i) camphorsulfonic acid, CH_2Cl_2, 0 °C, 48 h, 74%; (j) SO_3·pyridine, DMSO, Et_3N; (k) $PhP{=}C(CH_3)CHO$, benzene, reflux, 23 h; (l) $CH_2{=}CHPBu_3Br$, potassium phthalimide, THF, 65 °C, 48 h; (m) pyridine reflux, 11 h.

The route to fragment **A** began by treatment of the Weinreb amide **3**[12] with allylmagnesium bromide to furnish the β,γ-unsaturated ketone, which was reduced with high stereoselectivity (>99%) to the single diastereomeric alcohol, under chelation control (LiI, $LiAlH_4$), possessing the *syn* 1,3-configuration[13] (Scheme 1). The allylic alcohol was masked as the *tert*-butyldimethylsilyl ether (TBS) **4** and was then subjected to ozonolysis, affording the aldehyde **5**. Oxidation[14] of the aldehyde **5** with sodium chlorite−H_2O_2 gave the carboxylic acid **6** which was immediately transformed with (*S*)-serine ethyl ester into the hydroxyamide **7** *via* the mixed anhydride. Cyclization[15]

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(11) There existed some doubt regarding the stereochemistry at C-13, C-15 by the original workers[5,6] who established the structure of **1**. However, this was resolved during our synthesis of **4** by independent means and shown to be correct as previously proposed (*syn* C-13, C-15); see text and ref 26 below.

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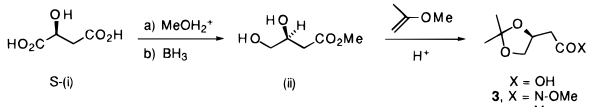

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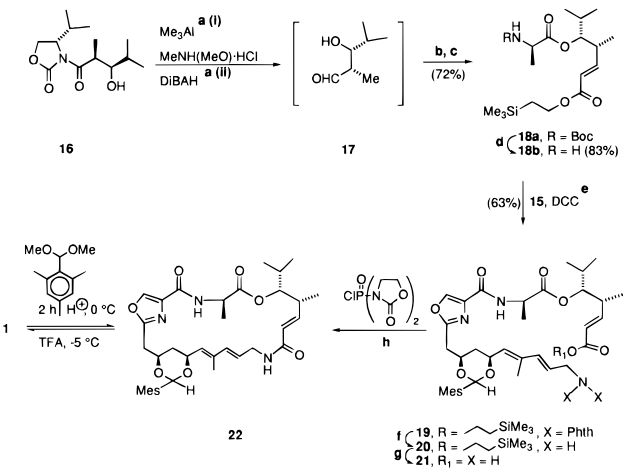
to the oxazoline **8** was accomplished in 65−70% overall yield from the acid **6** using the Burgess reagent.[16] Oxidation, using our previously described Cu(I)−Cu(II) peroxide reagent,[17] transformed the oxazoline **8** to the oxazole **9** in 81% yield.

It was now necessary to release the hydroxy group in **9** to the hydroxydioxolane **10** in order to transform it to the isomeric 1,3-dioxane **11**. This was accomplished by initially treating the silyl ether **9** with fluoride ion and then subjecting the resulting alcohol **10** to equilibrating exchange conditions[9a] using the dimethylacetal of 1,3,5-mesitylformaldehyde (Mes). In this fashion **10** was transformed, in good yield, with catalytic camphorsulfonic acid, to the stereochemically pure[18] 1,3-dioxane **11**. Oxidation gave the aldehyde **12** and Wittig olefination, using α-formylethylidinetriphenylphosphorane,[19] smoothly produced the pure (*E*)-α,*β*-unsaturated aldehyde **13**. Chain extension of the aldehyde was implemented by treating **13** with vinyl triphenylphosphonium bromide in the presence of potassium phthalimide[9a] to afford the (*E*,*E*)-diene imide **14**. Removal of the methyl from the methyl ester with LiI in pyridine[20] then furnished the key fragment **A** as the free carboxylic acid **15**.

The northeastern portion (**B**) was accessed by initially preparing the *syn* adduct **16**, *via* an Evans' chiral enolate as earlier described,[21] in 76% yield with greater than 99:1 diastereoselectivity. Removal of the chiral auxiliary *via* the Weinreb amide[12b] followed by DiBAH reduction[22] produced the unstable aldehyde **17**, which was immediately subjected to Horner−Emmons−Wadsworth olefination[23] (Scheme 2). The resulting unsaturated silyl ester (pure (*E*)-isomer, 72% yield) was esterified with *N*-Boc-D-alanine to afford the depsipeptide **18a** in quantitative yield. Removal of the Boc group with toluenesulfonic acid gave the primary amino ester **18b**, which was now set to undergo amide coupling to fragment **A** (**15**).

The amide connection of **15** to **18b** was performed using DCC and produced **19** in 63% yield. Treatment of the latter with methylamine in ethanol−benzene[24] gave the free primary amine **20** in 78% yield. After cooling in THF, the *β*-silylethyl ester **20** was smoothly fragmented using Bu_4NF. The resulting crude amino acid **21** was dried by azeotropic water removal using benzene and cyclized (1.5 mM in CH_2Cl_2) with Bop−Cl[25] in the presence of Hünig's base to afford **22** (32% from **20**). Hydrolysis of the dioxane moiety in **22** gave madumycin II in

Scheme 2[a]



[a] Key: (a) (i) 0 °C, 3 h, CH_2Cl_2, (ii) 68%, toluene −78 °C, 30 min; (b) $(EtO)_2$ $P(O)CH_2CO_2CH_2CH_2SiMe_3$, LiCl, CH_3CN, *i*-$PrEt_2N$; (c) DCC, D-Boc-alanine, CH_2Cl_2, 0 °C → rt, 11 h; (d) TsOH·H_2O, 23 °C, 16 h; (e) DMAP, CH_2Cl_2, 0 → 25 °C, 9 h; (f) CH_3NH_2, ethanol·benzene 50 °C, 48 h; (g) Bu_4NF, THF, 0 → 25 °C, 4 h; (h) *i*-Pr_2EtN, BopCl, CH_2Cl_2, −10 to 23 °C, 18 h.

86% yield, which contained 8−10% of a double bond isomer (NMR). This impurity was unexpected, and it was important to determine whether it was carried forward from **15** or had arisen during the hydrolysis of the dioxane **22**. An authentic sample of **1** (Eli Lilly) was, therefore, transformed into the mesityldioxane **22** which was identical in every respect (NMR, *M*/*e*) with **22** obtained in the current synthetic route. When **22**, derived from authentic **1**, was subjected to hydrolysis (TFA, −5 °C) under conditions described above, the same quantity of olefinic impurity (8−10%) in **1** appeared. Thus, the olefinic isomer was simply a consequence of the hydrolysis conditions to remove the mesitylene acetal (i.e. **22** to **1**).

Finally, the earlier question[11] of stereochemistry at C-13, C-15 can now be confirmed as *syn*, since complete identity between synthetic and natural madumycin was observed. The C-13, C-15 *syn* stereochemistry in the synthetic sample was supported by synthesis of **4** and further by an independent analysis[26] as described by Fenical and Rychnovsky.[27]

In summary, we have performed the first synthesis of madumycin II (A-2315A) in 29 steps with an overall yield of 1.8% from malic acid. Furthermore, the stereochemistry appears to be on firm ground on the basis of the synthetic intermediates utilized.

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Supporting Information Available: Experimental procedures for **3**−**9**, **19**−**22**, and **1**; NMR spectra for all key intermediates (87 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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