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## Toward the Total Synthesis of Hygrolidin: Stereocontrolled Construction of the C1-C17 Seco-Acid Fragment and the C18-C25 Masked Hemiacetal Subunit

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Abstract: Toward the first total synthesis of 16-membered macrolide antibiotic hygrolidin, the C1-C17 seco-acid fragment and the C18-C25 masked hemiacetal subunit as potential precursors have been synthesized in enantiomerically homogeneous forms. Copyright © 1996 Elsevier Science Ltd

Hygrolidin (1),<sup>2</sup> isolated from the fermentation broth of *Streptomyces hygroscopicus* by Seto and coworkers in 1982, comprises the first member of the hygrolide class of macrolide antibiotics, which includes other hygrolidins<sup>3</sup> and the bafilomycins.<sup>4</sup> The hygrolides share a 16-membered tetraene macrocyclic nucleus, and represent variations in the substitution pattern at C2 and C18.<sup>5</sup> Apart from their antibacterial and antifungal activities, this family of macrolides together with the closely related 18-membered macrolides concanamycins<sup>6</sup> has been recently demonstrated to exhibit potent and relatively specific inhibitory activities on vacuolar ATPases.<sup>7</sup> Owing to the growing promise for probing the structure and function of the vacuolar ATPases coupled with their challenging molecular architecture, this unique class of macrolides has emerged as highly attractive and important targets for chemical synthesis.<sup>8</sup> While Evans and Calter<sup>9</sup> have developed an efficient aldol coupling method for the assembly of bafilomycin A<sub>1</sub> (2), Toshima and co-workers<sup>10</sup> have recently achieved the total synthesis of **2**.



In continuation of our efforts directed toward the synthesis of macrolides featuring an extremely efficient macrolactonization<sup>11</sup> by the modified Yamaguchi method<sup>12</sup> and some stereoselective transformations on the macrolactone ring<sup>13</sup> on the basis of conformational analyses by molecular mechanics calculations,<sup>14</sup> we have addressed the synthesis of hygrolidin (1) and analogues thereof.

Our synthetic strategy for hygrolidin (1) is outlined retrosynthetically in Scheme 1. Disconnection at the C17-C18 bond using aldol transform gives the C1-C17 macrocyclic fragment 3 and the C18-C25 ketone fragment 4 corresponding to the masked hemiacetal subunit. Retromacrolactonization disconnection provides the seco-acid fragment 5, which would be further disconnected at the C12-C13 bond to afford the C1-C12 fragment 6 and the C13-C17 fragment 7. Herein, we report the stereocontrolled syntheses of the C1-C17 seco-acid fragment 5 and the C18-C25 masked hemiacetal subunit 4, which lead to the first total synthesis of 1 via macrolactonization and fragment assembly aldol reaction as described in the following paper.<sup>15</sup>

The synthesis of the C1-C12 fragment 6 toward access to the C1-C17 seco-acid fragment 5 is detailed in Scheme 2. We chose the alcohol 8 with the desired C6-C8 stereotriad (C6, C7-*anti*-C7, C8-*anti*) as the starting material, which was readily prepared according to the procedure of Roush.<sup>16</sup> Coupling of the tosylate 9, obtained from 8 by a series of routine manipulations, with lithium acetylide afforded the alkyne 10 in 82% yield. The Zr-catalyzed carboalumination<sup>17</sup> of 10 with Me<sub>3</sub>Al-Cp<sub>2</sub>ZrCl<sub>2</sub> followed by treatment with ethyl chloroformate furnished the (*E*)- $\alpha$ , $\beta$ -unsaturated ester 11 as the sole product in 67% yield. Site-selective dihydroxylation of 11 with OsO<sub>4</sub>-NMO followed by reduction of the ester functionality gave the triol 12 in 59% yield. Oxidative cleavage of the *vic*-diol in 12 with NaIO4 and subsequent protection of the allylic alcohol with an ethoxyethyl group afforded the aldehyde 13 in 97% yield. Wittig olefination of 13 with ethyl 2-(triphenylphosphoranylidene)propionate was followed by adjustment of the oxidation state through a reductionoxidation sequence to give selectively the (*E*)- $\alpha$ , $\beta$ -unsaturated aldehyde 14 in 62% yield. Installation of the (*E*,*E*)- $\alpha$ , $\beta$ , $\gamma$ , $\delta$ -unsaturated ester functionality was completed by Horner-Wadsworth-Emmons olefination of 14 with ethyl 2-(diisopropylphosphono)propionate to give the ester 15 as a single geometrical isomer in 81% yield, which upon protecting group interchange<sup>18</sup> and subsequent oxidation furnished the fragment 6 in 66% yield.



(a) TBAF, THF, 2 h, 93%; (b) TsCl, pyridine,  $CH_2Cl_2$ , 19 h, 93%; (c) TBSOTf, 2,6-lutidine,  $CH_2Cl_2$ , 1.5 h, 99%; (d) LiC=CH, DMSO, THF, 1.5 h, 82%; (e)  $Cl_2ZrCp_2$ , Me<sub>3</sub>Al,  $ClCH_2CH_2Cl$ ,  $ClCO_2Et$ , 20 h, 67%; (f) OsO<sub>4</sub>, NMO, THF, H<sub>2</sub>O, 48 h, 64%; (g) DIBAH,  $CH_2Cl_2$ , -78 °C, 1.5 h, 92%; (h) NalO<sub>4</sub>, phosphate buffer (pH 6.86), MeOH, 1 h; (i) EVE, PPTS,  $CH_2Cl_2$ , 8 h, 97% (2 steps); (j) Ph<sub>3</sub>P=C(CH<sub>3</sub>)CO<sub>2</sub>Et, benzene, reflux, 24 h, 85%; (k) DIBAH,  $CH_2Cl_2$ , -78 °C, 1.5 h, 92%; (l) MnO<sub>2</sub>,  $CH_2Cl_2$ , 3 h, 79%; (m) (<sup>1</sup>PrO)<sub>2</sub>P(O)CH(CH<sub>3</sub>)CO<sub>2</sub>Et, <sup>1</sup>BuOK, THF, -78 °C to rt, 15 h, 81%; (n) TBAF, THF, 15 h, 78%; (o) TESCl, imidazole, DMAP,  $CH_2Cl_2$ , 18 h, quant.; (p) PPTS, <sup>1</sup>PrOH, 8 h, 88%; (q) MnO<sub>2</sub>,  $CH_2Cl_2$ , 3 h, 96%.

The expeditious synthesis of the C13-C17 fragment 7 was implemented by employing Evans' aldol methodology<sup>19</sup> as shown in Scheme 3. Condensation of the boron enolate derived from the N-propionyl-2-oxazolidinone 16 with methacrolein led to the diastereomerically pure aldol adduct 17 in 71% yield. Protection

of the C15 hydroxyl group as an ethoxyethyl ether followed by removal of the oxazolidinone auxiliary by reduction with lithium borohydride<sup>20</sup> afforded the enantiomerically pure alcohol **18** in 92% yield. Protection of **18** as a *tert*-butyldiphenylsilyl ether and subsequent oxidative cleavage of the double bond to unmask the carbonyl group provided the fragment **7** in 70% yield.



(a) Bu<sub>2</sub>BOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 to -50 °C, 10 h, 71%; (b) EVE, PPTS, CH<sub>2</sub>Cl<sub>2</sub>, 2 h; (c) LiBH<sub>4</sub>, H<sub>2</sub>O, Et<sub>2</sub>O, 2 h, 92% (2 steps); (d) TBDPSCl, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, 15 h, 85%; (e) OsO<sub>4</sub>, NMO, acetone, H<sub>2</sub>O, 18 h, 91%; (f) NaIO<sub>4</sub>, phosphate buffer (pH 6.86), THF, 1 h, 91%. Scheme 3

With the C1-C12 fragment 6 and the C13-C17 fragment 7 in hand, the stage was now set for elaboration of the C1-C17 seco-acid 5 as depicted in Scheme 4. Aldol fragment coupling of 6 and 7 using LiHMDS-ZnCl<sub>2</sub> followed by successive acetylation and elimination provided the (E,E)-dienone 19 as a single geometrical isomer in 70% yield. Chelation-controlled reduction<sup>21</sup> of the ketone carbonyl group in 19 with zinc borohydride led to the exclusive formation of the desired alcohol 20 in 65% yield. Methylation of the resulting hydroxyl group in 20 and saponification of the ethyl ester were followed by concurrent deprotection of the C15 ethoxyethyl and C7 triethylsilyl ethers under carefully defined acidic conditions to give the seco-acid 5 for macrolactonization in 33% yield.



(a) 7, LiHMDS, ZnCl<sub>2</sub>, THF, -78 to -50 °C, 45 min, 87%; (b) Ac<sub>2</sub>O, pyridine, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, -78 to 0 °C, 4 h; (c) DBU, benzene, 10 °C, 2 h, 80% (2 steps); (d) Zn(BH<sub>4</sub>)<sub>2</sub>, Et<sub>2</sub>O, -78 to -25 °C, 48 h, 65%; (e) KHMDS, MeI, THF, -78 to 0 °C, 6 h, 80%; (f) 0.5 N NaOH, MeOH, THF, 48 h, 40 °C, 70%; (g) 0.3 N H<sub>2</sub>SO<sub>4</sub>, THF, 8 h, 59%. Scheme 4

The synthesis of the C18-C25 masked hemiacetal subunit 4 was here again initiated with the chiral auxiliary-based aldol reaction developed by  $Evans^{19}$  (Scheme 5). Removal of the oxazolidinone auxiliary from the diastereometrically pure aldol adduct 22 by transamination<sup>22</sup> with trimethylaluminum and N,O-dimethyl-



(a)  $Bu_2BOTf$ ,  $Et_3N$ ,  $CH_2Cl_2$ , 7 h, -78 to 0 °C, 71%; (b)  $Me_3Al$ , MeONMeH-HCl, THF, -20 °C to rt, 5 h; (c) TESCl, imidazole,  $CH_2Cl_2$ , 8 h, 73% (2 steps); (d)  $BrMgCH_2C(CH_2)CH_2CH_3$ ,  $Et_2O$ , 0 °C, 1.5 h, 82%; (e) 0.3 N H<sub>2</sub>SO<sub>4</sub>, THF, 2 h, 98%; (f)  $Me_4NBH(OAc)_3$ , AcOH, THF, -20 °C, 24 h, 86%; (g)  $^{1}Bu_2Si(OTf)_2$ , 2,6-lutidine,  $CH_2Cl_2$ , 4 h, 67%; (h) OsO<sub>4</sub>, NMO, acetone, H<sub>2</sub>O, 18 h; (i) NaIO<sub>4</sub>, phosphate buffer (pH 6.86), THF, 1.5 h, 76% (2 steps).

hydroxylamine hydrochloride followed by protection of the C23 hydroxyl group as a triethylsilyl ether afforded the Weinreb amide 23 in 73% yield. Treatment of 23 with 2-methylenebutylmagnesium bromide in ether led to the ketone 24, which upon desilylation gave the  $\beta$ -hydroxy ketone 25 in 80% overall yield. Directed reduction of 25 with Me<sub>4</sub>NBH(OAc)<sub>3</sub> under Evans' conditions<sup>23</sup> afforded the diol 26 as a 10: 1 mixture of anti to syn diastereomers. Protection of 26 as a di-*tert*-butylsilylene acetal<sup>24</sup> was followed by unmasking of the carbonyl functionality to give, after separation from the syn diastereomer, the target fragment 4 in 76% yield.

With the successful construction of the key building blocks developed, the stage was now set for the macrolactonization and fragment assemblage that led to the completion of the total synthesis of hygrolidin.<sup>15</sup>

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