The Synthesis of Glidobactin A[1]

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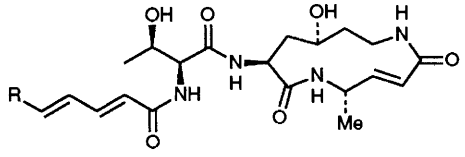
Glidobactin A, a member of the antibiotic families glidobactins and cepafungins, which was previously isolated from culture filtrates of the Gram-negative bacterium *Polyangium brachysporum* sp. nov., is synthesized.

The closely related and, in parts, identical glidobactins A to F (**1a–f**)[2] and cepafungins I to III[3] were isolated from the Gram-negative bacterium *Polyangium brachysporum* sp. nov. and from Pseudomonas species, respectively, by Japanese workers in 1988 and 1990 and their structures elucidated. These compounds contain a 12-membered cyclic diamide ring element (glidobamine) made up of the non-proteinogenic amino acids (4*S*)-amino-2(*E*)-pentenoic acid and (*S,S*)-4-hydroxylysine; the α-amino group of the latter amino acid is connected to an L-threonine unit. The glidobactins A–F and the cepafungins differ only in the unsaturated fatty acid moiety attached to the threonine residue. Some metabolites of these substances are cytotoxic towards P 388 leukaemia and B16 melanoma cell lines.

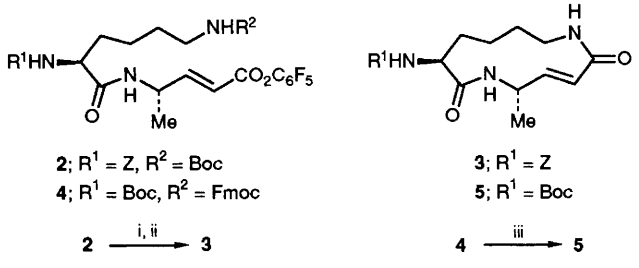
Glidobactin A has previously been synthesized from γ-aminopentenoic acid and hydroxylysine, obtained by hydrolysis of the natural compound, but the yield in the ring closure reaction was merely 2.3%.[1] Some unsuccessful attempts to prepare the model compound deoxyglidobamine have been reported.[4] We now report a total synthesis of glidobactin A. The main problems associated with this process were the ring closure reaction and the high tendency of hydroxylysine to undergo lactonization.

We have investigated the ring closure processes leading to the Z- and Boc-protected deoxyglidobamines **3** and **5** on the basis of numerous model reactions.[5] When the pentafluorophenyl esters **2** nd **4** are employed, this reaction is only possible at the ε-amino group of lysine under high dilution conditions at 95 °C and even then the yields are only moderate (39 and 26%, respectively). Attempts to perform the ring closure reaction in the two-phase system chloroform–aqueous sodium hydrogencarbonate gave rise to the product **3** in only 18% yield. Unfortunately, the Z-protecting group cannot be employed in the construction of the natural product; its subsequent hydrogenolytic cleavage is not feasible on account of the double bond in the ring.

L-*erythro*-δ-Hydroxylysine and its lactone have previously been prepared from lysine.[6] However, they could not be converted into protected derivatives suitable for use in the preparation of the glidobactin. Both amino groups need to be



II, 1a R = n-C_7H_{15}
1b R = n-C_5H_{11}–CH(*Z*)=CH–C_2H_4
1c R = n-C_8H_{19}
1d R = EtCH(OH)–C_4H_5
1e R = n-C_5H_{11}CH(OH)–CH_2
1f R = n-C_5H_{11}
I R = Pr^iC_5H_{10}
III R = Pr^iC_3H_6

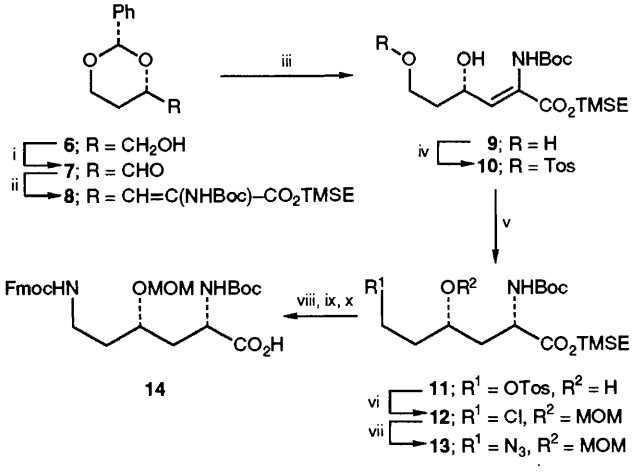


2; R^1 = Z, R^2 = Boc
4; R^1 = Boc, R^2 = Fmoc
2 —i, ii→ **3**

3; R^1 = Z
5; R^1 = Boc
4 —iii→ **5**

Abbreviations: Boc = *tert*-butoxycarbonyl; Fmoc = fluorenylmethoxycarbonyl; MOM = methoxymethyl; Ph = phenyl; Suc = succinimido; Tce = 2,2,2-trichloroethyl; TMSE = trimethylsilylethyl; Tos = *p*-$MeC_6H_4SO_2$; Z = benzyloxycarbonyl; cod = cycloocta-1,5-diene; dipamp = (*R,R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane.

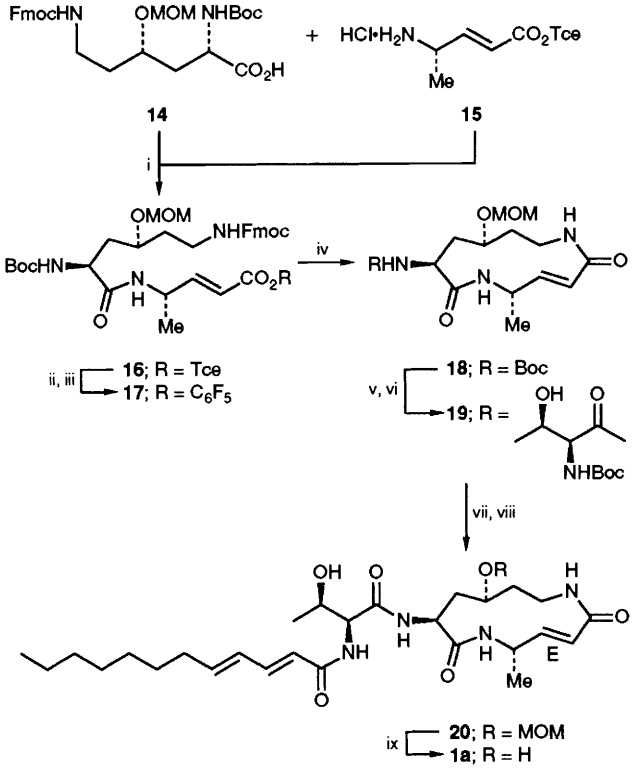
Scheme 1 *Reagents and conditions*: i, CF_3CO_2H; ii, dimethylaminopyridine (DMAP), dioxane, 95 °C, 13 h, i + ii, 39%; iii, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), dioxane, 95 °C, 13 h, 26%



6; R = CH_2OH
7; R = CHO
8; R = CH=C(NHBoc)–CO_2TMSE
9; R = H
10; R = Tos
11; R^1 = OTos, R^2 = H
12; R^1 = Cl, R^2 = MOM
13; R^1 = N_3, R^2 = MOM
14

Scheme 2 *Reagents and conditions*: i, dimethyl sulfoxide, $(COCl)_2$, ethyldiisopropylamine, CH_2Cl_2, −80 °C, 85%; ii, *N-tert*-butoxycarbonyl-(dimethoxyphosphoryl)glycine trimethylsilylethyl ester, DBU, room temp., 2 h, 95%; iii, acetic acid–H_2O (9 : 1), 50 °C, 1 h, 87%; iv, TosCl, pyridine, CH_2Cl_2, 0 to 25 °C, 20 h, 91%; v, [Rh(cod)(dipamp)]$^+BF_4^-$, H_2, MeOH, room temp., 48 h, 47%; vi, ethyldiisopropylamine, 0 to 25 °C, 20 h, 79%; vii, NaN_3, dimethylformamide, 70 °C, 12 h, 92%; vii, $Bu_4N^+F^-$, dimethylformamide, room temp., 2 h, 93%; ix, Pd/C, H_2, EtOH, room temp., 5 h, 91%; x, Fmoc–Cl, dioxane, $NaHCO_3$, 0 to 25 °C, 20 h, 72%

protected with different but compatible protecting functions. Furthermore, the hydroxy group must be masked in such a way that lactonization cannot occur during activation of the carboxy group. Finally, the protection of the hydroxy group must be susceptible to such a mild cleavage at the end of the



16; R = Tce
17; R = C_6F_5
18; R = Boc
19; R =
20; R = MOM
1a; R = H

Scheme 3 *Reagents and conditions*: i, cyanuric fluoride, pyridine, CH_2Cl_2, −10 °C, 2 h; H_2O, $NaHCO_3$, CH_2Cl_2, room temp., 3 h, 63%; ii, 90% acetic acid, Zn, room temp., 20 h, quant.; iii, $CF_3CO_2C_6F_5$, pyridine, 0 to 25 °C, 20 h; iv, DBU, 4-pyrrolidinylpyridine (pyrpyr), dioxane, Bu^{t}OH, 95 °C, 13 h, 20% (iii + iv); v, CF_3CO_2H, tetrahydrofuran (THF), 0 to 20 °C, 30 min; vi, Boc-Thr-Suc, DMAP, dimethylformamide, room temp., 24 h, v + vi, 72%; vii, CF_3CO_2H, THF, 0 to 20 °C, 25 min; viii, 2(*E*),4(*E*)-dodecadienoic acid succinimido ester, *N*-methylmorpholine, dimethylformamide, room temp., 24 h, vii + viii, 41% **20** + 26% **1a**; ix, CF_3CO_2H, THF, 0 °C, 6 h, quant.

sequence that no amide cleavage with concomitant lactonization can take place.†

The transparent and stereoselective construction of a suitably protected hydroxylysine starts from the butanetriol derivative **6**, obtainable in 90% yield from malic acid.[8] The reaction sequence consists of Swern oxidation[9] to the aldehyde **7**, condensation to the didehydroamino acid ester **8** (98% *E*),[10] formation of the tosyl ester **10**, and hydrogenation using the homogeneous catalyst Rh–dipamp[11] to the amino acid derivative **11**. This hydrogenation reaction is highly diastereoselective but gives rise to a yield of only 47% since an appreciable amount of **11** undergoes lactonization during the long reaction period (3 days).‡

The hydroxy group in **11** is masked by treatment with methoxymethyl chloride; the tosyl ester function is concomitantly exchanged for chlorine to give the chloride **12**. The protected hydroxylysine **14** can now be obtained without difficulty by way of the azide **13**. Coupling with the trichloroethyl (4*S*)-amino-2(*E*)-pentenoate **15**§ to furnish the amide **16** was preferentially performed with the acid fluoride of **14**.[14]

† γ-Hydroxyisocapronic amides are easily cleaved with concomitant formation of γ-isocapronic acid lactone.[7]

‡ Lactone formation occurs exclusively with the corresponding methyl ether; a *tert*-butyl ester analogue of **10** cannot be hydrogenated.

§ (4*S*)-Amino-2(*E*)-pentenoic acid was obtained *via* a Horner condensation[12] and the corresponding trichloroethyl ester was prepared by standard methods.[13]

After conversion of the trichloroethyl ester into the pentafluorophenyl ester,[15] cleavage of the Fmoc protecting group[16] and simultaneous ring closure[17] was achieved by heating for 13 h with DBU and 4-pyrrolidinylpyridine in dioxane under high dilution conditions. As found in the model experiments on the formation of **5**, the reaction to form **18**, also proceeded with a low yield (20%).

The side chain was built up in two steps.¶ The methoxymethyl ether derivative, which was obtained intact after cleavage of the Boc group from **18**, was then converted to the Boc-threonine compound **19**. After cleavage of the Boc group from **19** using trifluoroacetic acid, acylation with dodecadienoic acid‖ hydroxysuccinimide ester gave rise to a mixture of glidobactin A (**1a**) and its methoxymethyl ether **20** which could be separated easily. The protecting group was quantitatively cleaved from **20** by treatment with trifluoroacetic acid. The synthetic product was identical in all respects with the naturally occurring compound.

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¶ An attempted one-step acylation with dodecadienoylthreonine resulted in partial epimerization of the threonine.

‖ The synthesis of 2(*E*),4(*E*)-dodecadienoic acid has been reported.[18] However, condensation of (*E*)-dodec-2-enal with ethyl (diethoxyphosphoryl)acetate proved to be a more favourable procedure.

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