Amino Sugar Synthesis

Total Synthesis of Glycocinnasperimicin D**

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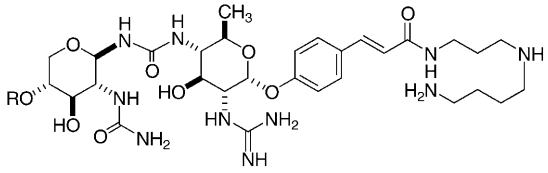
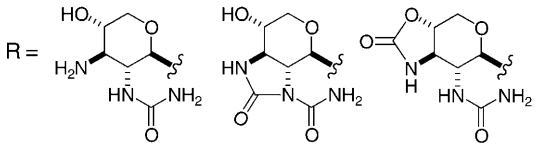
Glycocinnasperimicin D (**1**) was isolated from the fermentation broth of the producing strain (*Nocardia*), and its structure was elucidated by spectroscopic studies by Umezawa and his co-workers.[1] This molecule belongs to a family of glycocinnamoylspermidine antibiotics which also includes LL-BM123β (**2**), LL-BM123γ_1 (**3**), and LL-BM123γ_2 (**4**); these members contain three different types of unusual amino sugars.[2,3] Glycocinnasperimicin D contains the two highly functionalized amino sugars: 2-ureidopentose (left) and 2-guanidino-4-ureido-6-deoxy-α-D-glucopyranose (right) with the *p*-cinnamoylspermidine aglycone. Moreover, these two unusual amino sugars are joined through a unique glycosyl urea linkage.



glycocinnasperimicin D (**1**): R = H



LL-BM123β (**2**) LL-BM123γ_1 (**3**) LL-BM123γ_2 (**4**)

The amino sugar antibiotic **1** is of special interest because of its broad-spectrum activity against Gram-negative organisms; however, the natural product was no longer available as a result of mutation of the *Nocardia* strain.[4] Its intriguing structural features, coupled with its unique biological activity and the lack of availability from natural sources, encouraged us to explore the synthesis of this molecule. We report herein the first total synthesis of glycocinnasperimicin D (**1**).

It is evident that the construction of the urea glycoside in the presence of a variety of nitrogen-containing functional groups constitutes the major challenge in the total synthesis of **1**. Recently, we developed a new approach to the synthesis of urea glycosides which involves the reaction of a highly reactive glycosyl isocyanate with amines.[5] It was envisaged that our protocol could be applied to the synthesis of **1** as represented in the retrosynthetic analysis shown in Scheme 1. Oxidation of the glycosyl isonitrile **7** could generate the glycosyl isocyanate **5**, which would react with the amino sugar **6** at the position indicated. The amino sugar **6** could be obtained by the Heck reaction of the iodophenyl glycoside **8** with the acrylamide **9**, which contains the spermidine moiety. We anticipated that this convergent tactic for the synthesis of the cinnamoyl glycoside would avoid the problems associated with the glycosidation of a poorly nucleophilic phenol bearing an electron-withdrawing substituent.[6]

The synthesis of the left-hand amino sugar in the form of **7** began with the stereoselective synthesis of an allyl amine on the basis of a protocol developed recently by our research group[7] (Scheme 2). Thus, the enantioselective addition of diethylzinc to the α,β-unsaturated aldehyde **10** in the presence of the Soai catalyst **11**[8] proceeded smoothly to afford the allylic alcohol **12** in 79% yield and with high diastereoselec-

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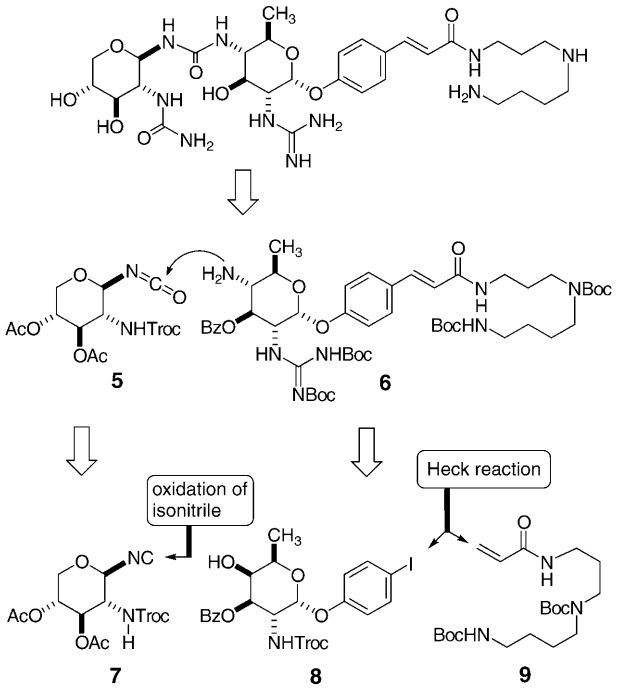
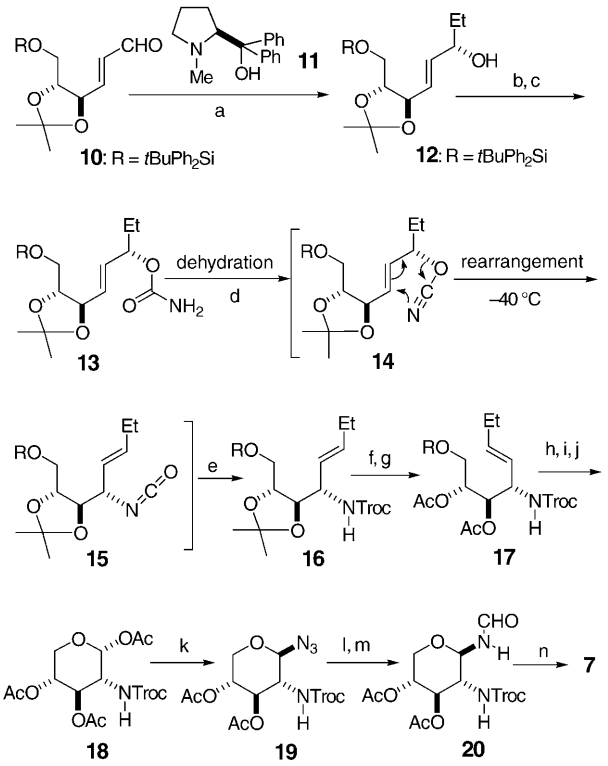


Scheme 1. Retrosynthetic analysis of glycocinnasperimicin D.



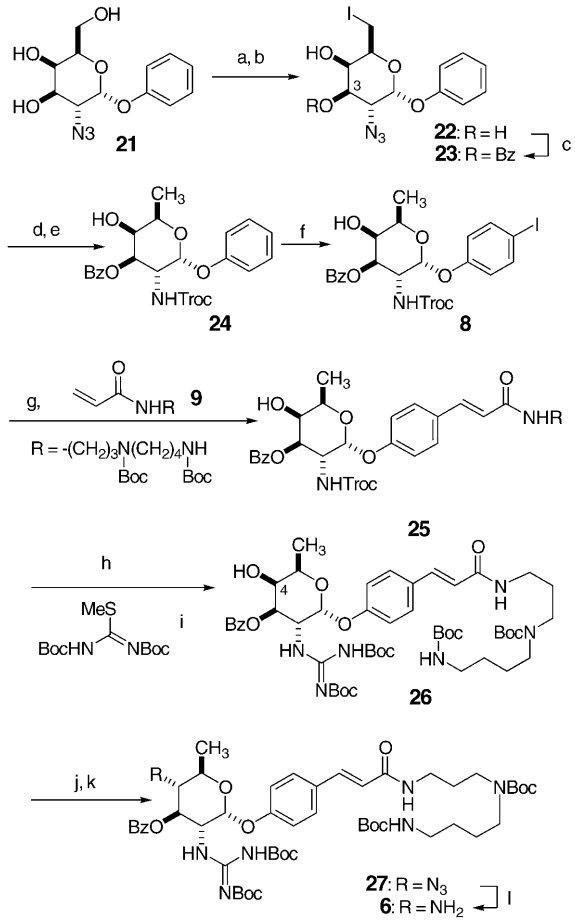
Scheme 2. Synthesis of the left-hand amino sugar moiety: a) Et_2Zn, cyclohexane, 0 °C→RT (79%); b) CCl_3CONCO, CH_2Cl_2; c) aqueous K_2CO_3, MeOH (93% over two steps); d) PPh_3, CBr_4, Et_3N, CH_2Cl_2, −40 °C; e) CCl_3CH_2OH, room temperature, overnight (82% over two steps); f) $FeCl_3{\cdot}6H_2O$, $CHCl_3$; g) Ac_2O, pyridine (80%); h) HF·pyridine, THF; i) O_3, CH_2Cl_2, Me_2S; j) Ac_2O, DMAP, pyridine (71% over three steps); k) $TMSN_3$, $SnCl_4$, CH_2Cl_2, (86%); l) PPh_3, THF, H_2O; m) AcOCHO (72% over two steps); n) PPh_3, CBr_4, Et_3N, CH_2Cl_2, (85%). DMAP = 4-dimethylaminopyridine, TMS = trimethylsilyl, Troc = 2,2,2-trichloroethoxycarbonyl.

tivity (15:1, checked by ^1H NMR spectroscopic analysis of the corresponding acetates). The allylic alcohol **12** was then transformed into the allyl carbamate **13** by treatment with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol. Upon dehydration of the carbamate **13** with triphenylphosphane, carbon tetrabromide, and triethylamine at −40 °C, the resulting allyl cyanate **14** underwent a spontaneous [3,3] sigmatropic rearrangement to afford the allyl isocyanate **15** with a high degree of 1,3-chirality.[9] Subsequent trapping of **15** with 2,2,2-trichloroethanol gave the Troc carbamate **16** in 82% yield from **13**.[10]

Hydrolysis of the isopropylidene ketal in **16** was more problematic than we had initially anticipated; the acetonide **16** was subjected to a number of deprotection protocols without success, possibly as a result of silyl-group migration to the adjacent hydroxy groups. Fortunately, Lewis acid catalyzed deprotection with ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$) was found to be successful.[11] After treatment of **16** with $FeCl_3{\cdot}6H_2O$ in chloroform followed by workup, the resulting mixture was treated immediately with acetic anhydride and pyridine to prevent silyl-group migration. The required acetate **17** was obtained in acceptable yield (80% based on the consumed starting material) along with recovered **16** (23%). Careful cleavage of the *tert*-butyldiphenylsilyl ether **17** (HF·pyridine, THF)[12] followed by oxidative cleavage of the alkene (O_3, CH_2Cl_2, −78 °C) gave the corresponding lactol, which was subsequently treated with acetic anhydride and pyridine to furnish predominantly the α-*O*-acetyl glycoside **18** in 71% yield over three steps. Treatment of **18** with trimethylsilyl azide in the presence of tin(VI) chloride furnished the β-glycosyl azide **19** exclusively (86%).[13] The isonitrile group at the anomeric position was constructed in a three-step sequence by 1) Staudinger reaction of the glycosyl azide **19**, 2) formylation of the resulting iminophosphorane with acetic formic anhydride (72% yield over two steps), and 3) dehydration of the formamide **20** by the modified Appel procedure[14] to afford the isonitrile glycoside **7** (85% yield).

The synthesis of the right-hand amino sugar in the form of **6** commenced with the α-phenyl 2-azido-D-galactoside **21**,[15] which was prepared from D-galactal in a four-step sequence (Scheme 3). Tosylation of the primary alcohol in **21** followed by displacement with iodide anion gave the iodide **22** in 73% yield over two steps. After selective protection of the equatorial hydroxy group at C3 in **22** as a benzoate group (93% yield), reductive hydrogenolysis of the iodide **23** was carried out with concomitant reduction of the azide group. Subsequent protection of the resulting amine as its Troc carbamate gave the 6-deoxypyranose **24** in 81% yield.[16]

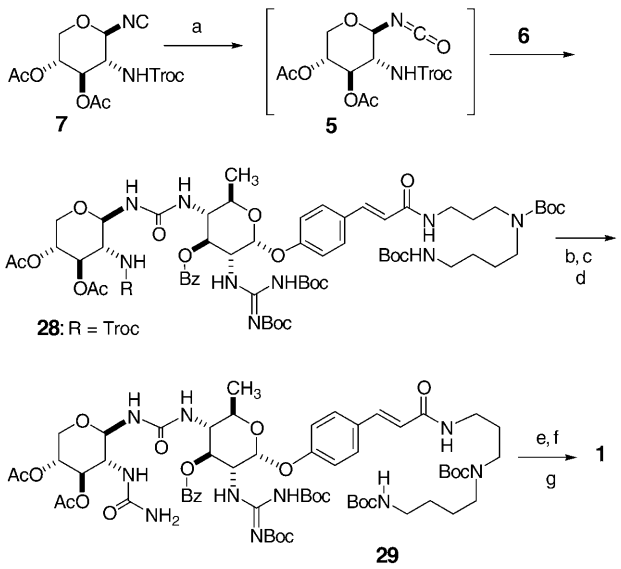
The cinnamic spermidine amide attached to the amino sugar was constructed from the phenyl glycoside **24** by a two-step protocol. Thus, treatment of **24** with ceric ammonium nitrate (CAN) and an iodine salt (nBu_4NI) in acetonitrile at 70 °C furnished the iodophenyl galactoside **8** in 86% yield.[17] The Heck reaction of **8** with acrylamide **9** proceeded smoothly to furnish the cinnamoyl galactoside **25** in 73% yield. Cleavage of the Troc carbamate in **25** (Zn, AcOH, THF) followed by treatment of the resulting amine with *N*,*N*-di-(*tert*-butoxycarbonyl)-*S*-methylisothiourea and mercuric



Scheme 3. Synthesis of the right-hand amino sugar unit: a) TsCl, pyridine (81%); b) NaI, nBu$_4$NI, DME (91%); c) BzCl, pyridine (93%); d) H_2, Pd-C (5%), Et_3N, EtOH; e) TrocCl, pyridine (81% over two steps); f) nBu$_4$NI, CAN, CH_3CN (86%); g) Pd(OAc)$_2$, P(*o*-Tol)$_3$, Et_3N, CH_3CN, 70°C (73%); h) Zn, AcOH, THF; i) $HgCl_2$, Et_3N, DMF (72% over two steps); j) Tf_2O, pyridine, CH_2Cl_2; k) NaN_3, DMF (73% over two steps); l) HS(CH$_2$)$_3$SH, Et_3N, MeOH (73%). Boc = *tert*-butoxycarbonyl, Bz = benzoyl, DME = dimethoxyethane, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, Tol = tolyl.

chloride in DMF afforded the bis(Boc)-protected guanidine **26** in 72% yield for the two steps.[18] The amino group at C4 was introduced by S_N2 displacement of a triflate with azide anion; thus the hydroxyl group in **26** was transformed into the corresponding triflate, and the rather unstable product was subjected immediately to treatment with sodium azide in DMF to furnish **27** in 73% yield over two steps. Whereas reduction of the azide group in **27** with PPh_3, $SnCl_2$,[19] nBu$_3$SnH,[20] or H_2/Pd-C[21] was unsuccessful, careful treatment with propanedithiol and triethylamine in MeOH[22] furnished the amino sugar **6** in 73% yield to set the stage for the coupling reaction.

With both key amino sugars **6** and **7** in hand, we next investigated their coupling to construct the urea glycosyl linkage (Scheme 4). In the event, oxidation of the isonitrile **7** with pyridine *N*-oxide in the presence of 3-Å molecular sieves and a catalytic amount of iodine in acetonitrile generated the isocyanate **5**,[5] which was treated directly with the amino



Scheme 4. Final coupling and completion of the synthesis of glycocinnasperimicin D (**1**): a) pyridine *N*-oxide, I_2 (cat.), 3-Å molecular sieves, CH_3CN (85% for **28**); b) Zn, AcOH, THF; c) CCl_3CONCO, CH_2Cl_2; d) Et_3N, MeOH (77% over two steps); e) TFA, CH_2Cl_2; f) 28% aqueous NH_3, CH_3OH; g) HPLC purification, lyophilization (23%). TFA = trifluoroacetic acid.

sugar **6**. Gratifyingly, this procedure gave the desired coupling product **28** in good yield (85%). Removal of the Troc group in **28** and subsequent treatment of the resulting amine with trichloroacetyl isocyanate, followed by methanolysis, gave the fully protected glycocinnasperimicin D **29** in 77% yield. Finally, removal of the Boc group in **29** with trifluoroacetic acid and subsequent cleavage of the benzoyl and two acetyl groups in a mixture of aqueous ammonia and methanol yielded glycocinnasperimicin D (**1**). To our delight, careful and laborious purification by HPLC provided pure synthetic material **1** (23% yield, isolated as the hydrochloride), the spectral data (^{1}H NMR, ^{13}C NMR, HRMS), TLC behavior, and antimicrobial activity of which were in good agreement with those of the natural glycocinnasperimicin D.

In conclusion, the first total synthesis of glycocinnasperimicin D (**1**) has been carried out by a convergent route on the basis of a three-fragment coupling strategy. Our synthesis features a Heck reaction to form the cinnamoyl glycoside, the stereoselective formation of an allyl amine by the [3,3] sigmatropic rearrangement of an allyl cyanate, and the construction of the urea glycoside by the coupling of a glycosyl isocyanate with an amino sugar. In particular, the oxidation of an isonitrile glycoside afforded a highly reactive isocyanate glycoside, which was key to the crucial coupling step.

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[1] K. Dobashi, K. Nagaoka, Y. Watanabe, M. Nishida, M. Hamada, H. Naganawa, T. Takita, T. Takeuchi, H. Umezawa, *J. Antibiot.* **1985**, 1166.

[2] a) G. A. Ellestad, D. B. Cosulich, R. W. Broschard, J. H. Martin, M. P. Kunstmann, G. O. Morton, J. E. Lancaster, W. Fulmor, F. M. Lovell, *J. Am. Chem. Soc.* **1978**, *100*, 2515; b) S. H. L. Chiu, R. Fiala, R. Kennett, L. Wozniak, M. W. Bullock, *J. Antibiot.* **1984**, 1000; c) H.-R. Tsou, R. R. Fiala, P. C. Mowery, M. W. Bullock, *J. Antibiot.* **1984**, 1382.

[3] For synthetic studies of glycocinnamoylspermidine antibiotics, see: a) K. Araki, K. Miyazawa, H. Hashimoto, J. Yoshimura, *Tetrahedron Lett.* **1982**, *23*, 1705; b) K. Araki, H. Hashimoto, J. Yoshimura, *Carbohydr. Res.* **1982**, *109*, 143; c) K. Araki, M. Kawa, K. Miyazawa, H. Hashimoto, J. Yoshimura, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3137.

[4] Personal communication from Dr. H. Naganawa and Dr. Y. Takahashi.

[5] a) Y. Ichikawa, T. Nishiyama, M. Isobe, *Synlett* **2000**, 1253; b) Y. Ichikawa, T. Nishiyama, M. Isobe, *J. Org. Chem.* **2001**, *66*, 4200.

[6] T. Nishiyama, Y. Ichikawa, M. Isobe, *Synlett* **2004**, 89.

[7] a) Y. Ichikawa, T. Ito, T. Nishiyama, M. Isobe, *Synlett* **2003**, 1034; b) Y. Ichikawa, T. Ito, M. Isobe, *Eur. J. Org. Chem.* **2005**, 1949.

[8] K. Soai, A. Ookawa, T. Kaba, K. Ogawa, *J. Am. Chem. Soc.* **1987**, *109*, 7111.

[9] For representative examples of the allylic cyanate-to-isocyanate rearrangement, see: a) C. Christophersen, A. Holm, *Acta Chem. Scand.* **1970**, *24*, 1512; b) L. E. Overman, M. Kakimoto, *J. Org. Chem.* **1978**, *43*, 4564; c) Y. Ichikawa, *Synlett* **1991**, 238; d) K. Banert, S. Groth, *Angew. Chem.* **1992**, *104*, 865; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 866.

[10] a) Y. Ichikawa, K. Tsuboi, M. Isobe, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2791; b) Y. Ichikawa, M. Osada, I. Ohtani, M. Isobe, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1449.

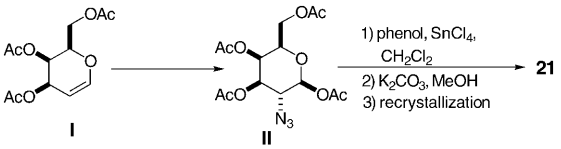
[11] K. S. Kim, Y. H. Song, B. H. Lee, C. S. Hahn, *J. Org. Chem.* **1986**, *51*, 404.

[12] D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.* **1990**, *112*, 7001.

[13] H. Paulson, Z. Gyorgydeak, M. Friedman, *Chem. Ber.* **1974**, *107*, 1568.

[14] a) Y. Ichikawa, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2135; b) I. A. O'Neil in *Comprehensive Organic Functional Group Transformations*, *Vol. 3* (Eds.: A. Katritzky, O. Meth-Cohn, C. W. Ress), Pergamon, Oxford, **1995**, pp. 696.

[15] Multigram quantities of the phenyl glycoside **21** were readily obtained in 51% yield from D-galactal by the following three-step synthesis: 1) azidonitration of the D-galactal **I** followed by acetolysis to give **II** (see: R. U. Lemieux, R. M. Ratcliffe, *Can. J. Chem.* **1979**, *57*, 1244), 2) Lewis acid catalyzed glycosylation of **II** with phenol (86%, α/β 4:1), and 3) deprotection of the acetyl groups and purification of the resulting triol by recrystallization.



[16] For recent examples of C6 deoxygenation, see: A. Medgyes, E. Farkas, A. Liptak, V. Pozsgay, *Tetrahedron* **1997**, *53*, 4159.

[17] T. Sugiyama, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2847.

[18] Z. X. Guo, A. N. Cammidge, D. Horwell, *Synth. Commun.* **2000**, *30*, 2933.

[19] S. N. Maiti, J. Beres, M. P. Singh, R. G. Micetich, *Tetrahedron Lett.* **1986**, *27*, 1423.

[20] H. H. Wasserman, K. R. Brunner, J. D. Buynak, C. G. Carter, T. Oku, R. P. Robinson, *J. Am. Chem. Soc.* **1985**, *107*, 519.

[21] E. J. Corey, K. C. Nicolaou, R. D. Balanson, Y. Machida, *Synthesis* **1975**, 590.

[22] H. Bayley, D. N. Stadring, J. R. Knowles, *Tetrahedron Lett.* **1978**, *19*, 3633.

