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ACCESS TO THE SYNTHESIS OF WYBUTOSINE, THE FIRST TRICYCLIC FLUORESCENT NUCLEOSIDE ISOLATED FROM PHENYLALANINE TRANSFER RIBONUCLEIC ACIDS

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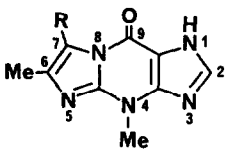
Abstract ——An improved synthesis of the key intermediate **5** for the chiral syntheses of wybutine (**1c**) and hydroxywybutine (**1d**) has been achieved by palladium-catalyzed vinylation, which has been utilized for the first synthesis of 3-β-D-ribofuranosylwybutine (**2c**).

Twenty years have passed since wybutosine, a unique fluorescent nucleoside, was reported to be isolated from yeast phenylalanine transfer ribonucleic acid ($tRNA^{Phe}$).[1,2] Its glycosyl bond is known to be remarkably sensitive to acid.[2] The structure of the base, wybutine, was determined to be **1c**,[3,4] whose congeners **1a,b,d–f** were thereafter isolated from tRNAs of various species.[5] Although the structures of the parent nucleosides of **1a–c**[1,2,6–8] have been accepted as **2a–c**, detailed identification of the position of glycosylation and the structure of the sugar moiety remains to be done because of the extremely minute amounts available. Of these latter three, **2a,b** have been synthesized.[9,10] This paper demonstrates the utility of the Heck reaction with an optically active vinyl compound **11** for the synthesis of 3-β-D-ribofuranosylwybutine (**2c**).

We have accomplished the synthesis of **5**, the key intermediate for the syntheses of wybutine (**1c**)[4] and hydroxywybutine [[*R*-(*R**,*S**)]-**1d** or [*S*-(*R**,*R**)]-**1d**],[11] in 5% yield by the Wittig reaction between 1-benzyl-7-formylwye (**3**) and phosphonium chloride **10** followed by methylation.[4] Unfortunately, similar treatment of 7-formyl-3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-wye[12] did not give the expected product. Although this type of compound should be prepared



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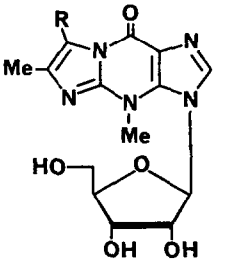


2

a: R = H wye

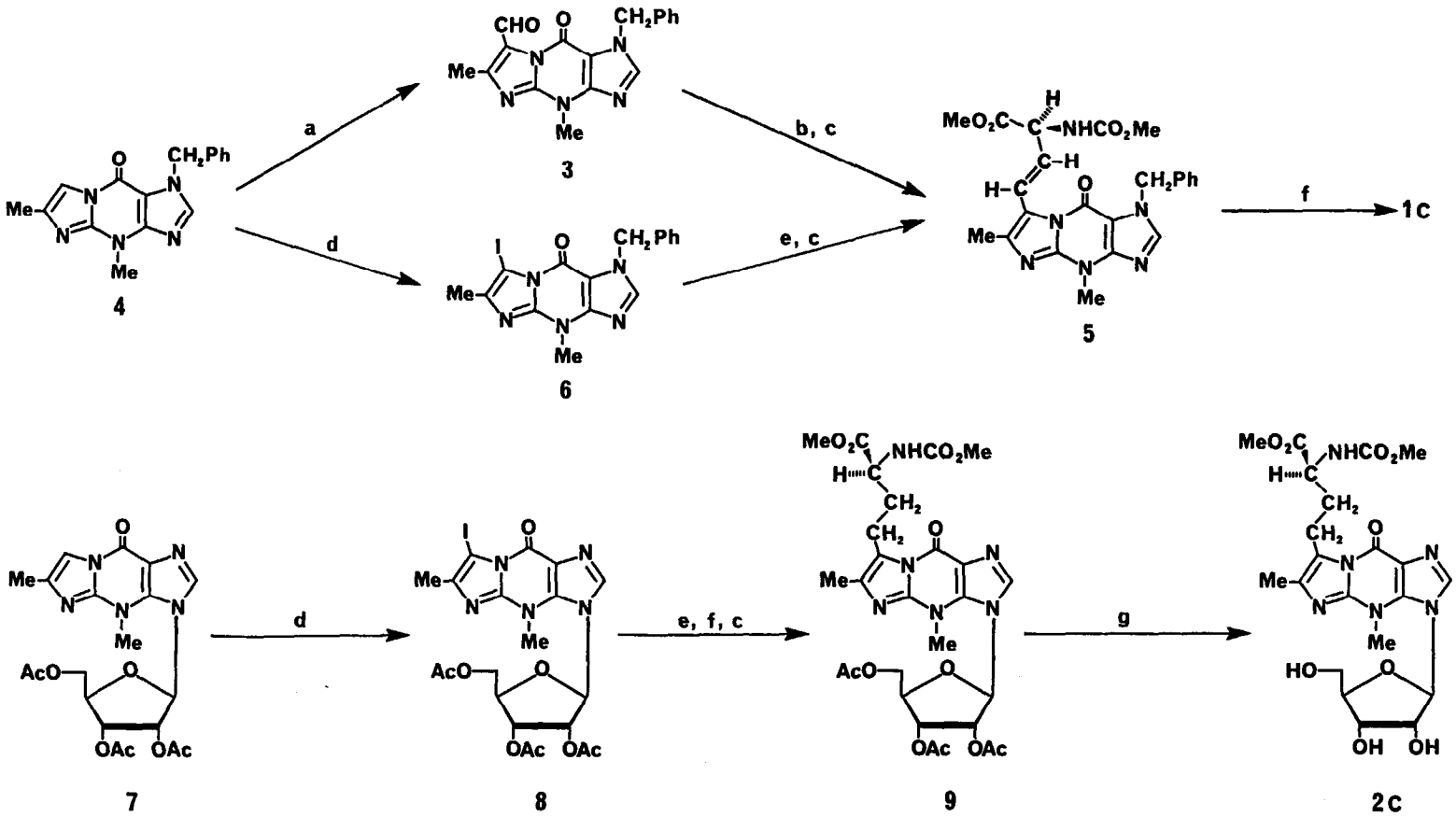
b: R = Me

c: R = $CH_2\overset{\gamma}{C}H_2-\overset{\beta}{C}H(NHCO_2Me)-\overset{\alpha}{C}O_2Me$

d: R = $CH_2CH(NHCO_2Me)CHCO_2Me$ (OH)

e: R = $CH_2CH(NHCO_2Me)CHCO_2Me$ (CO_2H)

f: R = $CH_2CH(NH_2)CHCO_2H$ (OH)



a) $POCl_3/Me_2NCHO$ b) $Ph_3P^+CH_2-C(H)(CO_2H)(NHCO_2Me)\ Cl^-$ /*n*-BuLi c) Me_3SiCHN_2/MeOH/benzene d) $I_2/NaHCO_3/CH_2Cl_2$

10

e) $CH_2=CH-C(H)(CO_2H)(NHCO_2Me)$ /$Pd(OAc)_2/Bu_4N^+Cl^-/NaHCO_3/Me_2NCHO$, 45°C, 24 h f) Pd-C/$H_2$ g) 0.1 M NaOMe, 0°C, 5 min

11

by the Heck reaction, it generally requires a high temperature.[13] We were afraid that the tricyclic nucleosides would undergo cleavage at the glycosyl bonds and that vinylglycine derivatives would racemize at the elevated temperature. However, recent reports on the Heck reaction at lower temperatures[14] as well as the syntheses of optically pure vinylglycine[15] encouraged us to devise the alternative synthesis of **5**.

Compound **4**[3d] was easily converted into 7-iodo derivative **6**, mp 165–167°C (dec.),[16] in 81% yield by treating with I_2 in CH_2Cl_2 in the presence of aq. $NaHCO_3$. The requisite olefin **11**[17] was obtained from L-vinylglycine[15b] in the usual manner. The Heck reaction of **6** with **11** was conducted in the presence of $Pd(OAc)_2$, $NaHCO_3$, and $Bu_4N^+Cl^-$ in Me_2NCHO according to the reported procedure[14a] at 45°C to give **5**, $[\alpha]_D^{14}$ +48° (*c* 0.37, MeOH) [lit.[4] $[\alpha]_D^{24}$ +44° (*c* 0.20, MeOH)] after methylation with Me_3SiCHN_2[4] in 24% yield. Careful examination of the products by NMR spectroscopy showed that the reaction proceeded in a regiospecific manner and that no (*Z*)-isomer was formed. The present procedure is superior to the reported one[4] in terms of yield and ease of handling.

For the synthesis of **2c**, nucleoside **7**[10] was iodinated similarly as described above to give **8**[18,19] in 93% yield. The Heck reaction of **8** with **11** under conditions similar to those described above, followed by catalytic hydrogenation over Pd–C and methylation with Me_3SiCHN_2 gave **9**[20] in 19% yield. This compound was then treated with 0.1 M NaOMe at 0°C to give **2c**[21] in 81% yield. Compound **2c** underwent hydrolysis of the glycosyl bond at the rate (rate constant 4.7 x 10^{-1} min^{-1}, half life 88 s) comparable to the rates of **2a** (4.4 x 10^{-1} min^{-1})[9b,c] and **2b** (4.7 x 10^{-1} min^{-1})[10] in 0.1 N aq. HCl at 25°C to give **1c**[4] in 88% yield, confirming the correctness of the structure **2c**. However, optical purity of the present sample of **1c**, $[\alpha]_D^{14}$ -34 ± 1° (*c* 0.20, MeOH) [lit.[4] $[\alpha]_D^{26}$ -40 ± 1° (*c* 0.14, MeOH)], suggests that **2c** thus obtained was contaminated by the diastereomer to some extent. We have not yet determined which step caused this trouble.

The first syntheses of **1e,f** should be facilitated by the present method, which permits the large-scale synthesis of the key intermediate **5**. Moreover, the above synthesis of **2c**, though it was not pure in a stereochemical sense, should help towards unambiguous identification of the structure of wybutosine.

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REFERENCES AND NOTES

1) U. L. RajBhandary, R. D. Faulkner, and A. Stuart, J. Biol. Chem., 243, 575 (1968).
2) R. Thiebe and H. G. Zachau, Eur. J. Biochem., 5, 546 (1968).
3) a) K. Nakanishi, N. Furutachi, M. Funamizu, D. Grunberger, and I. B. Weinstein, J. Am. Chem. Soc., 92, 7617 (1970); b) R. Thiebe, H. G. Zachau, L. Baczynskyj, K. Biemann, and J. Sonnenbichler, Biochim. Biophys. Acta, 240, 163 (1971); c) M. Funamizu, A. Terahara, A. M. Feinberg, and K. Nakanishi, J. Am. Chem. Soc., 93, 6706 (1971); d) C. R. Frihart, A. M. Feinberg, and K. Nakanishi, J. Org. Chem., 43, 1644 (1978).
4) T. Itaya and A. Mizutani, Tetrahedron Lett., 26, 347 (1985).
5) References cited in ref. 10.
6) S. Takemura, H. Kasai, and M. Goto, J. Biochem., 75, 1169 (1974).
7) J. A. McCloskey, P. F. Crain, C. G. Edmonds, R. Gupta, T. Hashizume, D. W. Phillipson,

and K. O. Stetter, Nucleic Acids Res., 15, 683 (1987).

8) S. H. Blobstein, R. Gebert, D. Grunberger, K. Nakanishi, and I. B. Weinstein, Arch. Biochem. Biophys., 167, 668 (1975).

9) a) S. Nakatsuka, T. Ohgi, and T. Goto, Tetrahedron Lett., 1978, 2579; b) T. Itaya, T. Watanabe, and H. Matsumoto, J. Chem. Soc., Chem. Commun., 1980, 1158; c) T. Itaya, H. Matsumoto, T. Watanabe, and T. Harada, Chem. Pharm. Bull., 33, 2339 (1985); d) B. Golankiewicz and W. Folkman, Nucleic Acids Res., 11, 5243 (1983); e) H. Bazin, X-X. Zhou, C. Glemarec, and J. Chattopadhyaya, Tetrahedron Lett., 28, 3275 (1987).

10) T. Itaya, Chem. Pharm. Bull., 35, 4372 (1987).

11) T. Itaya, N. Watanabe, and A. Mizutani, Tetrahedron Lett., 27, 4043 (1986).

12) Details for the synthesis of this compound will be reported elsewhere.

13) R. F. Heck, "Palladium Reagents in Organic Syntheses," Academic Press, New York, 1985, pp. 276–287.

14) a) T. Jeffery, J. Chem. Soc., Chem. Commun., 1984, 1287; b) M. Somei, Y. Makita, and F. Yamada, Chem. Pharm. Bull., 34, 948 (1986).

15) a) A. Afzali-Ardakani and H. Rapoport, J. Org. Chem., 45, 4817 (1980); b) S. Hanessian, and S. P. Sahoo, Tetrahedron Lett., 25, 1425 (1984); c) D. H. R. Barton, D. Crich, Y. Hervé, P. Potier, and J. Thierry, Tetrahedron, 41, 4347 (1985).

16) Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds described herein.

17) Colorless scales from benzene, mp 92–92.5°C, $[\alpha]_{365}^{14}$ -60° (*c* 0.20, MeOH).

18) Compound **8**: slightly yellow foam, ^{1}H NMR ($CDCl_3$) δ: 2.10 (s, Ac), 2.19 (s, two Ac's), 2.27 (s, CMe), 4.14 (s, NMe), 4.30 (d, J = 3 Hz, CH_2), 4.49 [m, J = 3 and 4 Hz, C(4')H], 5.48 [dd, J = 4 and 5 Hz, C(3')H], 5.90 [dd, J = 5 and 6 Hz, C(2')H], 6.24 [d, J = 6 Hz, C(1')H], 7.64 [s, C(2)H].

19) Synthesis of this compound by the reaction of **7** with I_2 in the presence of CF_3COOAg was reported recently [C. Glemarec, J-C. Wu, G. Remaud, H. Bazin, M. Oivanen, H. Lönnberg, and J. Chattopadhyaya, Tetrahedron, 44, 1273 (1988)].

20) Compound **9**: colorless glass, ^{1}H NMR ($CDCl_3$) δ: 2.0 [m, C(β)H_2], 2.11, 2.14, and 2.18 (s each, three Ac's), 2.20 (s, CMe), 3.0 [m, C(γ)H_2], 3.70 (s, two OMe's), 4.11 (s, NMe), 4.32, [d, J = 3 Hz, overlapped with a multiplet due to C(α)H, C(5')H_2], 4.50 [m, J = 3 and 4 Hz, C(4')H], 5.49 [dd, J = 4 and 5 Hz, C(3')H], 5.85 [dd, J = 5 and 6 Hz, overlapped with a signal due to NH, C(2')H], 6.21 [d, J = 6 Hz, C(1')H], 7.71 [s, C(2)H]; EI MS *m/z*: calcd. for M^+ 634.2232, found 634.2242; $[\alpha]_D^{21}$ -35° (*c* 0.20, MeOH); CD (MeOH) $[\theta]_{268}^{20}$ -3600 (neg. max.).

21) Compound **2c**: colorless powder, UV $\lambda_{max}^{95\%\ EtOH}$ 239 nm (ϵ 29800), 296 (6000); $\lambda_{max}^{H_2O}$ (pH 2) 233 (29800), 277 (10200); $\lambda_{max}^{H_2O}$ (pH 7) 240 (30600), 299 (5700); $\lambda_{max}^{H_2O}$ (pH 13) 240 (31200), 299 (5700); ^{1}H NMR [$(CD_3)_2SO$] δ: 2.0 [m, C(β)H_2], 2.08 (s, CMe), 3.05 [m, C(γ)H_2], 3.56 and 3.58 [s each, overlapped with a multiplet due to C(5')H_2, two OMe's], 4.03 [s, overlapped with two multiplets due to C(4')H and C(α)H, NMe], 4.14 [m, C(3')H], 4.45 [m, C(2')H], 5.12 (t, J = 5 Hz, 5'-OH), 5.31 (d, J = 5 Hz, 3'-OH), 5.70 (d, J = 6 Hz, 2'-OH), 6.10 [d, J = 5 Hz, C(1')H], 7.65 (d, J = 8 Hz, NH), 8.20 [s, C(2)H]; FAB MS *m/z*: 509 (MH^+); $[\alpha]_D^{15}$ -46° (*c* 0.20, MeOH); CD (H_2O) $[\theta]_{243}^{13}$ -7800 (neg. max.), $[\theta]_{267}^{13}$ -3700 (neg. max.).

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