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SYNTHESIS OF (*S*)-(-)-WYBUTINE, THE FLUORESCENT MINOR BASE FROM YEAST PHENYLALANINE TRANSFER RIBONUCLEIC ACIDS

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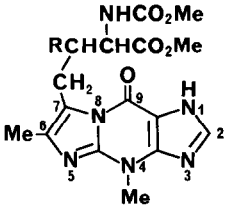
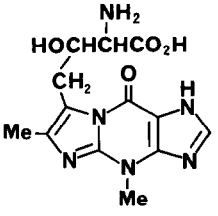
Abstract—— The Wittig reaction of 1-benzyl-7-formylwye (**12**) with (*R*)-[2-carboxy-2-[(methoxycarbonyl)amino]ethyl]triphenylphosphonium chloride (**8**) followed by successive methylation and reduction gave (-)-wybutine [(*S*)-**1a**].

The structures of the fluorescent minor bases from various eukaryotic $tRNAs^{Phe}$ have been elucidated as **1**.[1] An under-modified base **2** has been also isolated from tumor-specific $tRNAs^{Phe}$ in place of normal **1b**.[2] An (*S*) configuration has been assigned to the chiral center of wybutine (**1a**) from Saccharomyces cerevisiae $tRNA^{Phe}$ on the basis of the CD spectrum of a derivative of a degradation product of **1a**.[3] Nakanishi and his co-workers[3] reported the synthesis of (±)-**1a** by the cyclocondensation of 3-methylguanine with methyl 5-bromo-2-[(methoxycarbonyl)-amino]-6-oxoheptanoate (**3**). They reported also that the reaction of **3** with 7-benzyl-3-methylguanine (**15**) followed by hydrogenolysis gave the better results.[4] We now wish to record here the first synthesis of the optically active form of wybutine [(*S*)-**1a**].



a: R = H
b: R = OH
c: $R = O_2H$

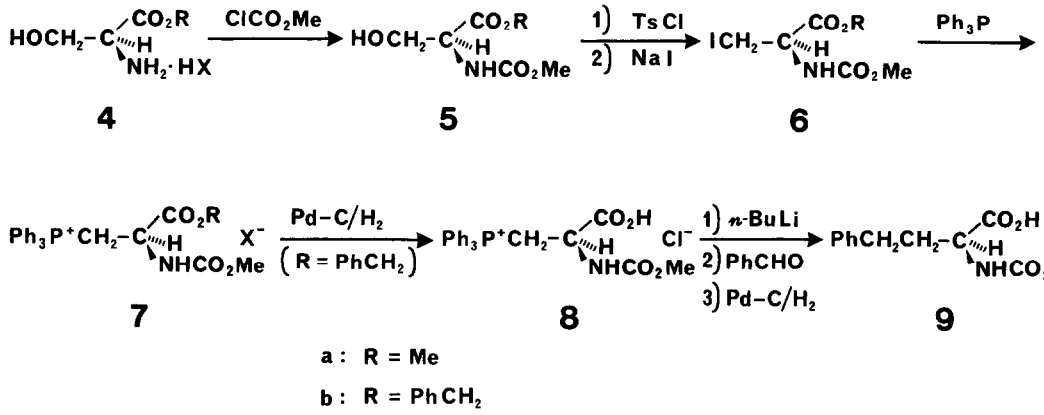
1

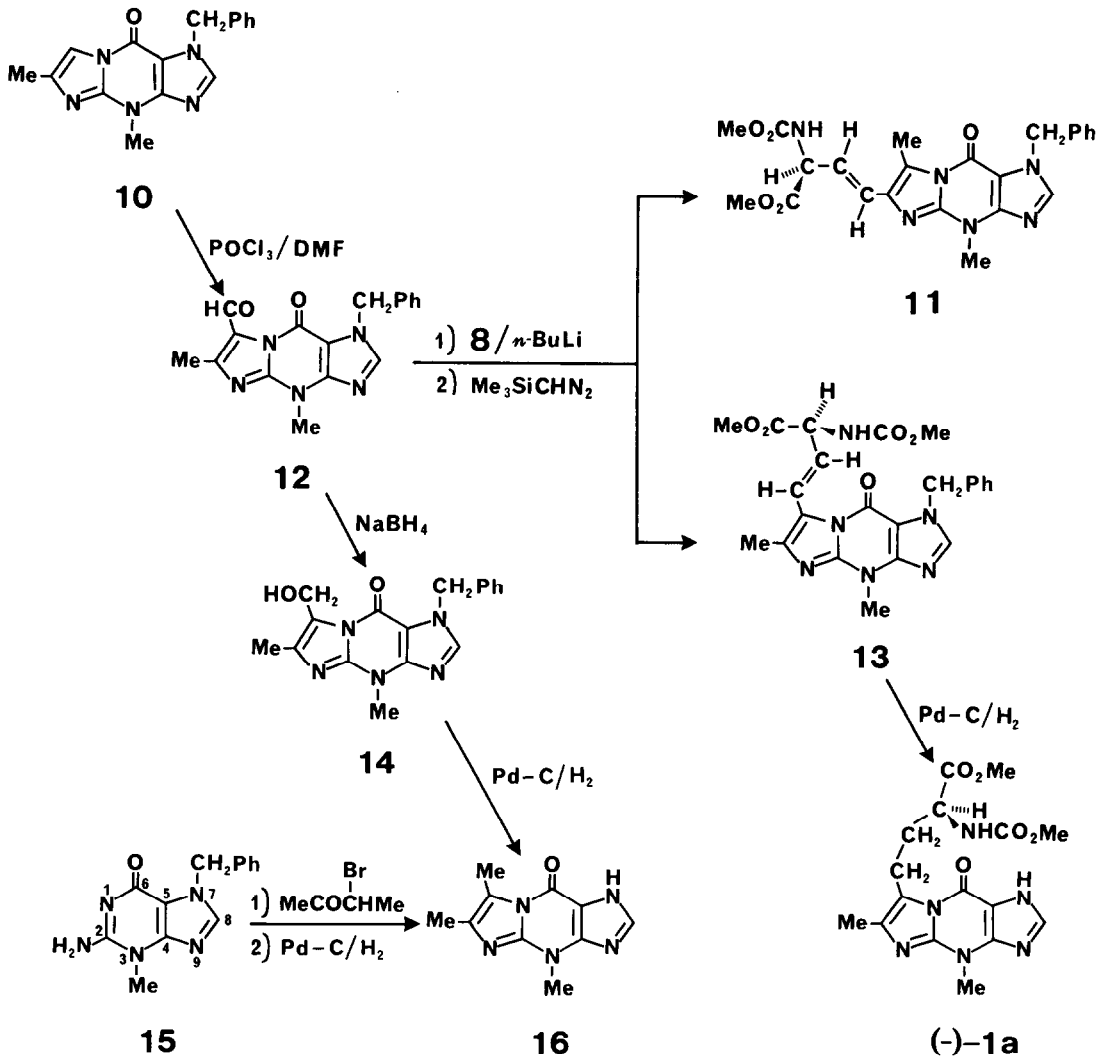


2

Since it seemed difficult to obtain the optically active bromoketone **3**, we designed a different method from that of the precedents.[3,4] Although several attempts failed in introducing a carbon side chain at the 7-position of 1-benzylwye (**10**),[4] the Vilsmeier-Haack reaction of **10** ($POCl_3$–DMF) successfully gave 1-benzyl-7-formylwye [**12**: 100% yield; mp 228–229°C; ^{1}HNMR ($CDCl_3$) δ: 2.70 (s, CMe), 4.01 (s, NMe), 5.65 (s, CH_2), 7.37 (s, Ph), 7.76 (s, $C_{(2)}$-H), 10.88 (s, CHO)].[5] The site of the formyl group was confirmed by conversion of **12** into 7-methylwye [**16**: monohydrate; mp>300°C; ^{1}HNMR (Me_2SO-d_6) δ: 2.11 (s, $C_{(6)}$-Me), 2.56 (s, $C_{(7)}$-Me), 3.73 (s, NMe), 8.12 (s, $C_{(2)}$-H), 13.51 (br, NH)] through the alcohol **14** by $NaBH_4$ reduction followed by catalytic hydrogenolysis over Pd–C. The structure **16** was supported by direct comparison with a sample prepared by the reaction of **15** and 3-bromo-2-butanone followed by hydrogenolysis.

The Wittig reaction of **12** with an appropriate ylide would give a type of compound **13**, which appears to be a good intermediate for the synthesis of not only **1a** but also the other congeners,


HOCH2–C(CO2R)(H)(NH2·HX)
ClCO2Me
HOCH2–C(CO2R)(H)(NHCO2Me)
1) TsCl
2) NaI
ICH2–C(CO2R)(H)(NHCO2Me)
Ph3P
4
5
6
Ph3P+CH2–C(CO2R)(H)(NHCO2Me) X−
Pd–C/H2
(R = PhCH2)
Ph3P+CH2–C(CO2H)(H)(NHCO2Me) Cl−
1) n-BuLi
2) PhCHO
3) Pd–C/H2
PhCH2CH2–C(CO2H)(H)(NHCO2Me)
7
8
9
a : R = Me
b : R = PhCH2


10
POCl3/DMF
12
1) 8/n-BuLi
2) Me3SiCHN2
11
13
NaBH4
14
Pd–C/H2
Pd–C/H2
1) MeCOCHMeBr
2) Pd–C/H2
15
16
(-)–1a

1b,c and **2**. (*S*)-Serine methyl ester hydrochloride (**4a**: X = Cl)[6] was treated with methyl chloroformate in aqueous $NaHCO_3$ and the carbamate **5a** thus obtained was transformed into the iodide **6a** (53% overall yield; mp 105–106°C) through the tosylate according to reported procedures.[7,8] On treatment with triphenylphosphine in toluene (50°C, 34 days), **6a** gave the phosphonium iodide **7a** [X = I; 76% yield; mp 148–153°C (dec.)]. However, the Wittig reaction with **7a** (*n*-BuLi/THF; -78°C) failed owing to tendency of this type of compound to suffer β-elimination.[9]

Successful reactions of the ylide from (2-carboxyethyl)triphenylphosphonium chloride with ketones have been reported.[10] For the synthesis of the requisite carboxylic acid **8**, the benzyl ester **7b** [X = I; mp 143–146°C (dec.)] was prepared from (*S*)-serine benzyl ester tosylate (**4b**: X = TsO)[11] in a manner similar to that described for **7a** in 67% overall yield. Compound **7b** (X = I) was transformed into the chloride with Amberlyst A-26 (Cl^-) and then hydrogenated over Pd–C to give **8** [96% yield; ^{1}HNMR (Me_2SO-d_6) δ: 3.30 (s, Me), 3.70–4.50 (br, CH_2CH), 7.50 (br, NH), 7.60–8.00 (m, Ph); $[\alpha]_D^{24}$ +52° (c=0.50, $CHCl_3$)] as a glass. The Wittig reaction of **8** with benzaldehyde (*n*-BuLi/THF–HMPA; -78–-18°C) followed by catalytic hydrogenation over Pd–C gave **9** [mp 102–105°C; $[\alpha]_{365}^{24}$ +29.9 ± 0.4° (c=0.538, MeOH)] in 13% yield. It was shown that the configuration of the chiral center was fairly retained through the reaction sequence by comparison of this sample with an authentic **9** [$[\alpha]_{365}^{25}$ +30.2 ± 0.4° (c=0.540, MeOH)] derived from (*S*)-2-amino-4-phenylbutyric acid.[12]

The tricyclic aldehyde **12** was finally treated with **8** (*n*-BuLi/THF–HMPA; -78–-15°C) to afford the desired **13** [5% yield; mp 176–178°C; ^{1}HNMR ($CDCl_3$) δ: 2.39 (s, CMe), 3.72 and 3.81 (s each, OMe), 3.90 (s, NMe), 5.10 (br, $C_{(3')}$-H), 5.60 (s, CH_2), 5.78 (d-d, J = 8 and 16 Hz, $C{=}C_{(2')}$-H), 7.35 (s, Ph), 7.64 (s, $C_{(2)}$-H), 7.68 (d, J = 16 Hz, $C{=}C_{(1')}$-H); $[\alpha]_D^{24}$ +44 ± 2° (c = 0.20, MeOH)] and a trace of a rearranged product **11** [^{1}HNMR ($CDCl_3$) δ: 2.73 (CMe)][13] after methylation with trimethylsilyldiazomethane.[14] Differentiation between the two structures **11** and **13** is based on the chemical shifts of the C-methyl groups.[1a,3,4,15] A (*E*) configuration is assignable to **13** on the basis of the coupling constants for the olefinic protons and no (*Z*)-isomer of **13** was detected in this reaction. Catalytic reduction of **13** over Pd–C achieved hydrogenation of the double bond of the side chain and subsequent debenzylation over Pd–C in the presence of $HClO_4$ afforded (-)-wybutine [(*S*)-**1a**: 74% yield; mp 200–204°C (dec.); $[\alpha]_D^{26}$ -40 ± 1° (c = 0.14, MeOH)]. The structure of this compound was supported by direct comparison with (±)-**1a**, which was prepared according to the reported procedure.[4,16] The negative Cotton effects reported for the CD spectrum of wybutine[1a,b,e] are consistent with those of the present sample of (*S*)-**1a** [(10% MeOH) $\Delta\varepsilon_{264}$ -1.1 ± 0.1, $\Delta\varepsilon_{235}$ -4.4 ± 0.3], confirming that the chiral center of wybutine has an (*S*) configuration.[17]

The present work has illustrated the usefulness of **8** as a chiral building block for construction of homologues of alanine.

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16. We obtained **3** by bromination of the corresponding ketone in 22% yield after repeated column chromatography. Cyclocondensation of **12** with **3** gave (±)-1-benzylwybutine (mp 176–177°C) in 6% yield (lit.[4] 20% yield). Hydrogenolysis of this compound was achieved over Pd–C in MeOH in the presence of $HClO_4$ to give (±)-**1a** [89% yield; mp 214–215°C (dec.) (lit.[3] mp 204–206°C); UV λ_{max} (95% EtOH) 235 nm (ε 34500), 257 (sh) (5700), 309 (5500); ^{1}HNMR (Me_2-SO-d_6) δ: 1.92 (m, $C_{(2')}$-H_2), 2.10 (s, CMe), 3.06 (m, $C_{(1')}$-H_2), 3.56 and 3.58 (s each, OMe), 3.76 (s, NMe), 3.88 (m, CH), 7.64 (d, J = 7 Hz, N<u>H</u>CO_2Me), 8.16 (s, $C_{(2)}$-H), 13.54 (br, $N_{(1)}$-H)].
17. The assignment of the configuration by Funamizu *et al.*[3] is somewhat puzzling . They reported that wybutine afforded dimethyl [(methoxycarbonyl)amino]glutarate with negative and positive CD Cotton effects, respectively, at 232 and 207 nm, which are inconsistent with those [Δε –0.14 (232 nm), –0.76 (206)] reported for an authentic sample derived from (*S*)-glutamic acid.

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