Tetrahedron Letters,Vol.25,No.35,pp 3865-3868,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (+)-TRYPTOQUIVALINE

Masako Nakagawa,* Manabu Ito, Yuko Hasegawa, Satoko Akashi, and Tohru Hino*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Chiba-shi, 260, Japan

Summary : We report the first total synthesis of (+)-tryptoquivaline **1a** and of a key precursor, 2,3-dialkylquinazolinone **13b**.

We have recently described a method for synthesizing imidazo[1,2-a] indole-spirolactone ring system in one step by oxidative double cyclization of 1-(N-alkoxycarbonylalanyl)-3-indolepropionic acids with NBS[1] and we have achieved a short-step synthesis of tryptoquivaline G **1b** and L[2] which have been synthesized first by Büchi and coworkers.[3]

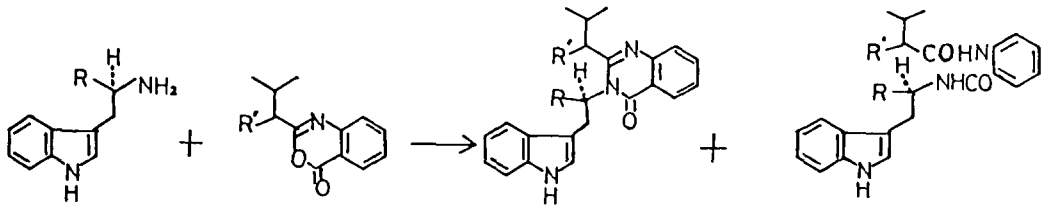
Tryptoquivaline **1a**, a tremorgenic mycotoxin, is the major metabolite among 14 tryptoquivalines isolated from Aspergillus clavatus[4] and fumigatus.[5] It has a highly sterically hindered substituent at the 2 and 3 positions of the quinazolinone ring.

The lack of standard method for the synthesis of sterically hindered 2,3-dialkylquinazolinone in the literature[6] has prevented the total synthesis of tryptoquivaline itself. The congested 2-ethylquinazolinone by condensation of L-tryptophan methyl ester with N-propionylanthranilic acid using $POCl_3$ has been synthesized by Ohnuma and Ban and they succeeded in the formal synthesis of (+)-**1b**[7] but this method could not be extended to the synthesis of the 2-isobutyl derivative.

We report here an easy and probably general procedure for the preparation of the 2,3-dialkyl-4-quinazolinone and the first total synthesis of (+)-tryptoquivaline **1a**.

We first examined the utility of 2-substituted benzoxazolinone **3**. Condensation of tryptamine **2a** with 2-isobutylbenzoxazolinone **3a** (200°C , 1.5 h) gave the corresponding quinazolinone **4a** (41%)[8] and the amide **5a** (16%). However, the similar reaction of L-tryptophan benzyl ester **2b** with **3a** gave only a trace amount of **4b** (1%) and **5b** (7%). The reaction of **2a** with **3b** gave **4c** (14%) and **5c** (27%) whereas the amide **5d** was the only product obtained in 32% by the reaction of **2b** with **3b**.

The dehydrocyclization of the amide **5a** and **5b** by use of Meerwein reagent in refluxing CH_2Cl_2 gave **4a** and **4b** in 13% yields, respectively, but **5d** did not cyclized to give **4d** under the similar conditions. An attempted ring



2 a, R=H
b, R=CO_2Bzl

3 a, R'=H
b, R'=OAc

L-tryptophan series

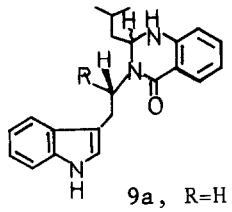
4 a, R=R'=H
b, R=CO_2Bzl, R'=H
c, R=H, R'=OAc
d, R=CO_2Bzl, R'=OAc

5 a, R=R'=H
b, R=CO_2Bzl, R'=H
c, R=H, R'=OAc
d, R=CO_2Bzl, R'=OAc

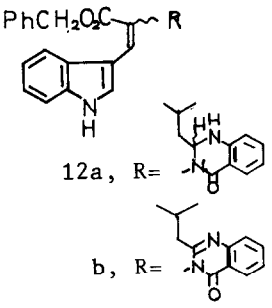
cyclization of 5 by BF_3-AcOH failed to proceed although a series of 3-arylquinazolinone has been obtained by the reaction of the corresponding diamides with BF_3-AcOH in high yield.[6g)]

Next approach was to use trialkyl orthoester and the reaction of **2b** with trimethyl orthoisovalerate in xylene for 3 h was found to give **4b**(85%). However, the oxidation of isobutyl groups in **4b** and its N-acyl derivative with SeO_2 or $(PhSeO)_2O$ to isobutyryl group was unsuccessful.

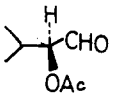
The elaboration of the quinazolinone ring which has the (S)-α-acetoxyisobutyl group at 2-position started first with the condensation of the amide **6a** and **6b**[2)] with isovaleraldehyde in boiling EtOH-AcOH (6a,10:1; 6b,1:1) to give the dihydroquinazolinone **9a**(81%)[9)] and **9b**(85%)[10)], respectively. The condensation of (S)-α-acetoxyisovaleraldehyde **7**, prepared by the reduction[11)] of (S)-α-acetoxyisovaleric acid[12)], with **6b** did not proceed to give **8** under the similar condition to that of isovaleraldehyde. However, **8**(two diastereoisomers) was obtained in 60% yield when **7** and **6b** in CH_2Cl_2 were stirred for 4 h in the presence of TsOH and molecular sieves 4A. Dehydrogenation of **9b** with DDQ afforded **4b**[13)](24%), **12a**(35%), and **12b**(21%), indicating that the oxidation of the indole ring was preferred over that of sterically hindered dihydroquinazolinone ring. Therefore, the acylation of **8** was carried out before dehydrogenation. Treatment of **8** with N-trichloroethoxycarbonylmethylalanine p-nitrophenyl ester **10**[1,2)] gave **11**(two diastereoisomers) (57%). Subsequent dehydrogenation of **11** with DDQ gave the quinazolinone **13a** (91%) which was debenzylated to give the acid **13b**[14)] quantitatively. Oxidative double cyclization was carried out by addition of NBS to a solution of **13b** in CF_3CO_2H to give **14a**(16.3%) and **15a** (32%). By use of NIS in CF_3CO_2H the yield of desired **14a** increased up to 24.3%. Deprotection of **14a** with Zn in AcOH provided the amine **14b**(66%). Finally, on treatment with MCPBA in CH_2Cl_2 at room temperature for 2 h, **14b** was effectively converted to (+)-tryptoquivaline **1a**(93%), mp 214-217°C, $[\alpha]_D$ +160° (c 0.10, $CHCl_3$) which was identical (mp, $[\alpha]_D$, UV, IR, NMR, and Mass) with the specimen[5b)] obtained from Aspergillus fumigatus.



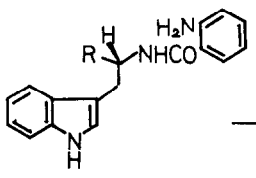
9a, R=H
b, R=CO_2Bzl



12a, R=
b, R=

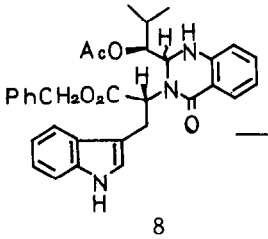


7



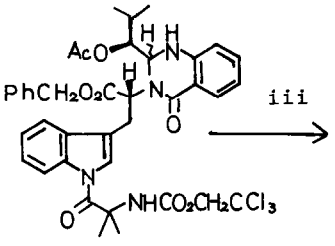
6a, R=H
b, R=CO_2Bzl
D-tryptophan series

i



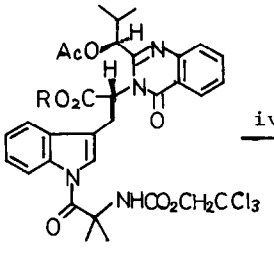
8

ii



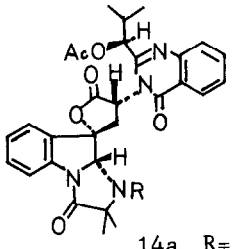
11

iii



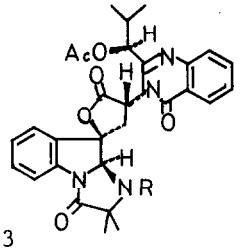
13a, R=Bzl
b, R=H

iv, v
vi



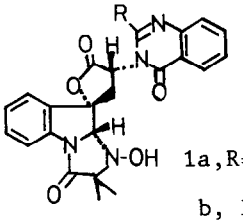
14a, R=$CO_2CH_2CCl_3$
b, R=H

+



15a, R=$CO_2CH_2CCl_3$
b, R=H

vii



1a, R=
b, R=H

(+)-tryptoquivaline
(+)-tryptoquivaline G

i, 7, molecular sieves 4A, TsOH, CH_2Cl_2, r.t.; ii, $CCl_3CH_2O_2CNHCMe_2CO_2C_6H_4$-p-$NO_2$, 10, KF,MeCN, 18-crown-6, $EtN(i\text{-}Pr)_2$, 35°C, 4 h; iii, DDQ, $CHCl_3$, 30°C, 3 h; iv, H_2, Pd/C; v, N-iodosuccinimide(3 equiv), CF_3CO_2H, reflux; vi, Zn, AcOH; vii, m-$ClC_6H_4CO_3H$.

Acknowledgements We thank Prof. Mikio Yamazaki, Chiba University, for a generous gift of natural tryptoquivaline. We are grateful to Prof. Yoshio Ban, Hokkaido University, for discussions and encouragement. The financial support of this research by Grant-in-Aid for Scientific Research given from the Ministry of Education, Science, and Culture is greatly appreciated.

REFERENCES AND NOTES

1. M. Nakagawa, M. Sodeoka, K. Yamaguchi, and T. Hino, Chem.Pharm.Bull., 32, No.4, (1984) in press.
2. M. Nakagawa, M. Taniguchi, M. Sodeoka, M. Ito, K. Yamaguchi, and T. Hino, J.Am.Chem.Soc., 105,3709 (1983).
3. G. Büchi, P.R. DeShong, S.Katsumura, and Y. Sugimura, J.Am.Chem.Soc., 101, 5084 (1979).
4. a) J. Clardy, J.P. Springer, G. Büchi, K. Matsuo, and R. Wightman, J.Am.Chem.Soc., 97,663 (1975) ; b) G. Büchi, K.C. Luk, B. Koffe, and J.M. Townsend, J.Org.Chem., 42,244 (1977) ; c) J.P. Springer, Tetrahedron Lett., 1979,339.
5. a) M. Yamazaki, H. Fujimoto, and E. Okuyama, Tetrahedron Lett., 1976, 2861 ; b) Idem, Chem.Pharm.Bull., 25,2554 (1977) ; c) Idem, ibid., 26, 111 (1978) ; d) M. Yamazaki, E. Okuyama, and Y. Maebayashi, ibid., 27, 1611 (1979).
6. a) W.L.F. Armarego, ''Advances in Heterocyclic Chemistry'' Ed. by A.R. Katritzkey, vol 1, 254, Wiley, New York, 1963 ; b) idem, ibid., vol 24, 1 (1979) ; c) M. Sainsbury'' Chemistry of Carbon Compounds. IVH, Heterocyclic Compounds'' Ed. by S. Coffey ; d) L.A. Errede, J.R. Hill, and J.J. McBrady, J.Org.Chem., 47, 3829 (1982); e) D.T. Zentmyer and E.C. Wagner, J.Org.Chem., 14,967 (1949) ;f) T. Hisano, M. Ichikawa, A. Nakagawa, and M. Tsuji, Chem.Pharm.Bull., 23, 1910 (1975) ; g) J. Tani, Y. Yamada, T. Ochiai, R. Ishida, I. Inoue, and T. Oine, Chem.Pharm.Bull.,27,2675(1979).
7. T. Ohnuma, Y. Kimura, and Y. Ban, Tetrahedron Lett., 22,4969 (1981).
8. **4a**, mp 158-158.5°C.
9. **9a**, mp 144-145.5°C; λmax (ε) 224.5(46500), 258sh(8200),274sh(7000), 281 (7100), 291(6100), 344(3100); δ ($CDCl_3$) 4.15(1H, br.s, N_1-H), 7.94(1H, dd, C_5-H); m/z 347 M^+.
10. **9b**: less polar isomer, colorless amorphous; λmax(EtOH) nm: 225,258,275sh, 284,291,344. δ ($CDCl_3$) 4.22(1H, s, N_1-H, exchangeable), 4.75(1H, d, J=10 Hz, C_2-H), 5.24(1H, dd, J=8.9 and 6.6 Hz, $C\underline{H}CO_2Bzl$), 7.92(1H, d, J=7.9 Hz, C_5-H) ; m/z 481 M^+; more polar isomer, colorless amorphous; δ ($CDCl_3$) 3.80(1H, br.s, N_1-H), 4.02(1H, dd, J=10.5 and 2.3 Hz, C_2-H), 4.39(1H, dd, J=9.9 and 5.6 Hz, $C\underline{H}CO_2Bzl$), 7.91(1H, d, J=7.6 Hz, C_5-H).
11. T. Fujisawa, T. Mori, S, Tsuge, and T. Sato, Tetrahedron Lett., 24,1543 (1983).
12. M. Taniguchi, K. Koga, and S. Yamada, Chem.Pharm.Bull., 20,1438(1972).
13. **4b**: D-series, amorphous, $[\alpha]_D$ + 307°(c 1.00, acetone), δ ($CDCl_3$) 4.95 (1H, m, $C\underline{H}CO_2Bzl$), 8.28(1H, dd, J=7.9 and 1.0 Hz, C_5-H); Exact Mass : Calcd. for $C_{30}H_{29}N_3O_3$ 479.2206. Found, 479.2179.
14. **13b**, amorphous, $[\alpha]_D$ + 176° (c 1.00, acetone). λmax(EtOH) nm: 229,234sh, 269,275sh,293,303,320sh; νmax(KBr) cm^{-1} : 3300,2960,1760-1670,1590,1510; δ (DMSO-d_6) 0.22(3H, d, J=6.6 Hz, Me), 0.68(3H, d, J=6.3 Hz, Me),1.18 (3H, s, CMe), 1.50(3H, s, C-Me), 1.83(1H, m, $Me_2C\underline{H}$), 1.92(3H, s,Ac), 3.66 (2H, d, J=5.9, Ind-CH_2), 4.58(2H, d, J=5.9, CH_2CCl_3),5.03(1H, d,J=8.6, AcOC$\underline{H}$), 5.24(1H, t, J=7.9 and 6.6, $C\underline{H}CO_2H$).

(Received in Japan 11 May 1984)