THE SYNTHESIS OF DIPHENYL ETHERS HAVING TYROSINE MOIETY

Tsutomu Inoue, Kenji Naitoh, Seiji Kosemura, Isao Umezawa,
Thoru Sonobe, Nobuaki Serizawa, and Noboru Mori

Ohmori Research Laboratory, Tobishi Pharmaceutical Co,.Ltd
1-16-18 Ohmori Nishi, Ohtaku, Tokyo, 143, Japan

Hideji Itokawa

Tokyo College of Pharmacy
Horinouchi 1432-1, Hachioji, Tokyo, 192-03, Japan

Abstract— Dienone mono-epoxides (13) and (14) were readily reacted with potassium phenoxides to give intermediates (17) and (18) which were subjected to methylation followed by reduction with Zn/AcOH to give the desired diphenyl ethers (15a)-(15f) in good yield.

Two bicyclic peptides, bouvardin (1) and deoxybouvardin (2)[1] are known to possess the inhibitory activity toward the P-388 lymphocytic leukemia. Since Kriek[2] reported the hexapeptide (3) lacking the diphenyl ether bond was devoid of anti-tumor activity, the 14-membered ring of (1) and (2) which contains an ether bond seems to be very important for the biological activity.

For synthesis of the 14-membered ring, first of all we attempted to build up an ether linkage by using Ullmann reaction of N-benzyloxycarbonyl-N-methyl-3-bromo-4-methoxy-L-phenylalanine methyl ester (7) or N-benzyloxycarbonyl-N-methyl-3-iodo-4-methoxy-L-phenylalanine methyl ester (8) with benzyl N-methyl-N-t-butoxycarbonyl-L-tyrosinate (16), however in all cases intractable mixtures were produced contrary to our expectation.

Scott et al. already reported that the electrooxidation of the N-carbomethoxy-tyrosine (9) afforded the spirodienone lactone (11) in low yield (15%)[3].

Therefore, we turned our attention to the reaction of a dienone with a certain phenol in the hope of getting a C-O-C coupling product. The dienone lactone (10)[4] was prepared from N-methyl-N-benzyloxycarbonyl-L-tyrosine (6) by oxidation with thallic nitrate in 60% yield. Despite of numerous efforts, the reaction afforded a C-C coupling compound instead of a desirable C-O-C. For instance, the reaction of (10) with p-cresol in the presence of $BF_3 \cdot (Et)_2O$ gave (19)[5] in 20% yield.

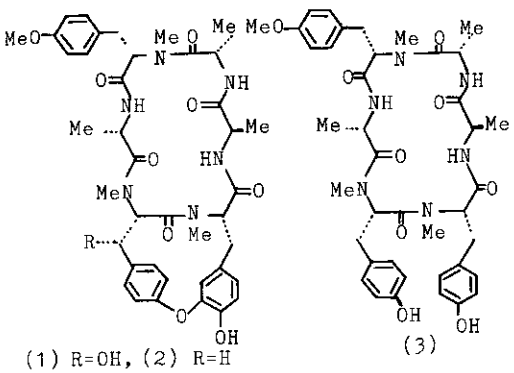
This result was coincided with earlier observations[6] and also explicable in terms of HSAB rule.

Since the reaction of 2,3-epoxy-3-methylcyclohexanone (4) with o-cresol is known to give 2-(2-methylphenoxy)-3-methyl-2-cyclohexen-1-one (5)[7], we decided to apply the reaction to the dienone mono-epoxide derivable from (10).

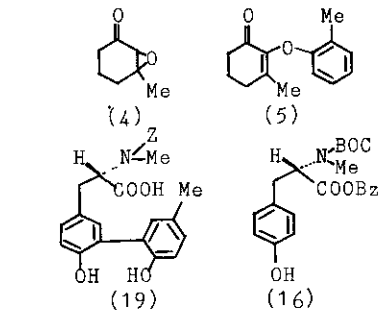
Fortunately mono-epoxidation was readily achieved by using 30% H_2O_2-Triton B (40% in MeOH) in $CHCl_3$-EtOH to afford (12).

Thus methylation of (12) with CH_2N_2 afforded an oily epoxy ester (13)[8] as the sole product (81%).

The ester (13) and the carboxylic acid (12) were smoothly lactonized to give the lactone (14)[9] when treated with t-BuOK and DCC respectively.



(1) R=OH, (2) R=H



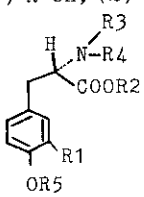
(3)

(4)

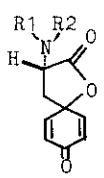
(5)

(19)

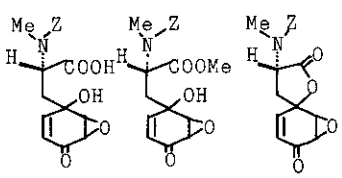
(16)



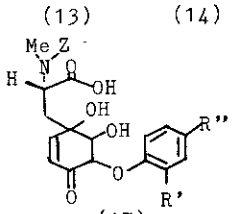
	R1	R2	R3	R4	R5
(6)	H	H	Z	Me	H
(7)	Br	Me	Z	Me	Me
(8)	I	Me	Z	Me	Me
(9)	H	H	COOMe	H	H



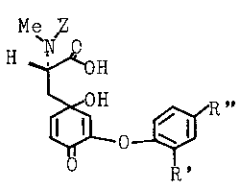
	R1	R2
(10)	Z	Me
(11)	COOMe	H



(12) (13) (14)



(17)

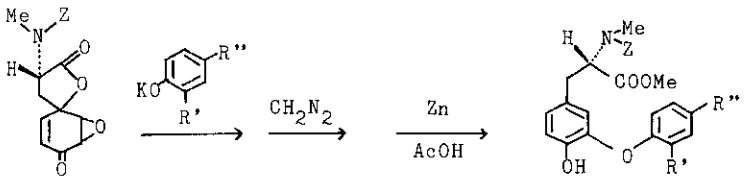


(18)

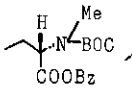
Z=$PhCH_2OCO$-,
Bz=$PhCH_2$-,
BOC=$(Me)_3COCO$-,

Both the ester (13) and the lactone (14) were readily reacted with potassium phenoxides at room temperature to give the desirable products (17) and (18) which were subjected to methylation followed by reduction with Zn/90%-AcOH at room temperature to give the expected diphenyl ether (15) in good yield[10].

Thus, the above dienone mono-epoxides were proved to be a useful candidate for the synthesis of diphenyl ethers having tyrosine moiety under mild reaction condition. Table 1 summarizes the yields of diphenyl ethers prepared in this way.



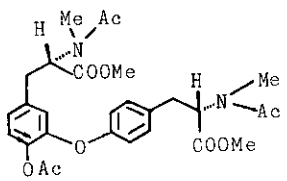
(14) (15)

	15a	15b	15c	15d	15e	15f
R'	H	OMe	H	OMe	H	H
R''	Me	H	OMe			
Yield g) %	61.0	56.5	33.1	60.3	64.5	71.5

g) Isolated yield by column chromatography on silica gel.

Table 1: Yield of Diphenyl Ethers.

Structure of the diphenyl ether (15e) was unequivocally determined on the basis of the following experiment. Namely, a sequence of reactions of (15e) 1) Ac_2O-pyridine, 2) H_2, 5%Pd-C/MeOH, 3) CH_2N_2, 4) CF_3CO_2H-anisole, 5) Ac_2O-pyridine gave 2-[p-2'(S)-(N-acetyl-N-methylamino-2'-methoxycarbonylethylphenoxy]-4-[2'(S)-(N-acetyl-N-methylamino)-2'-methoxycarbonylethyl]-phenylacetate (20), which was entirely coincided with the authentic compound from deoxybouvardin [1) 6N-HCl, 2) Ac_2O-5%-NaOH, 3) CH_2N_2] by comparison of each IR spectrum and TLC behavior. Unfortunately, however, each observed $[\alpha]_D$ value was not identical [the authentic (20): $[\alpha]_D^{25}$ $-17°$ (c=2.8, $CHCl_3$); the synthetic (20): $[\alpha]_D^{21}$ $-4.25°$ (c=0.94, $CHCl_3$)], pointing out that the unwanted racemization occurred partially under the reaction conditions. Now we are investigating the proper conditions to minimize the racemization and the effective lactamization.



(20)

ACKNOWLEDGEMENT The authers are grateful to prof. Bunsuke Umezawa, Prof. Osamu Hoshino, and Dr. Hiroshi Hara of the Science University of Tokyo for helpful suggestion.

REFERENCES AND NOTES

1. S.D.Jolad, J.J.Hoffman, S.T.Torrance, R.N.Wiedhopf, J.R.Cole, S.K.Arora, R.B.Bates, R.L.Gargiuro, and G.R.Kriek, J.Am.Chem.Soc., 99, 8040(1977). The isolation of deoxybouvardin and its related compound from Rubia Cordiforia was reported by Itokawa et al. at 41th Annual Meeting of Japanese Cancer Association (Osaka, August 1982).
2. G.R.Kriek, Dissertation Abstructs International, 41 (2), 572-B, 573-B(1980).
3. A.I.Scott, P.A.Dodoson, F.McCapra, and M.B.Meyers, J.Am.Chem.Soc.,85, 3702(1963).
4. m.p. 97.5-100°c(EtOH-n-hexane). PMR(60 MHz $CDCl_3$)δ: 2.53(2H, d, J=10Hz), 3.03(3H, s), 4.7(1H, t, J=10Hz), 5.13(2H, s), 6.20, 6.83(each 2H, d, J=10Hz), 7.32(5H, s). IR(KBr): 1770, 1670, 1630 cm^{-1}.
5. Data of diacetate of methyl ester; PMR(60 MHz $CDCl_3$)δ: 1.93(3H, s), 2.0(3H, s), 2.2(3H, s), 2.8(3H, s), 2.9-3.4(2H, complex), 3.63(3H, s), 4.5-5(1H, complex), 5.03(2H, s), 6.9-7.4(11H, complex). IR(KBr): 1760, 1740, 1700 cm^{-1}. m/z: 533(M^+).
6. H.Hara, O.Hoshino, and B.Umezawa, Heterocycles, 15, 911(1981).
7. Y.K.Yee and A.G.Schultz, J.Org.Chem., 44, 719(1979).
8. PMR(100 MHz $CDCl_3$)δ: 2.3-2.6(2H, complex), 2.93(3H, s), 3.34, 3.5(each 1H, bs), 3.66, 3.76[3H, two s(1:3)], 5.13(2H, s), 5.8, 6.4(each 1H, bd, J=10Hz), 7.23(5H, s). IR(KBr): 1740, 1685 cm^{-1}. CI-MS(isobutane): m/z 376(M^++1).
9. PMR(60 MHz $CDCl_3$)δ: 2.3-3.0(2H, complex), 3.03(3H, s), 3.52, 3.68(each 1H, complex), 5.12(2H, s), 5.96, 6.55(each 1H, bd, J=10Hz), 7.31(5H, s). IR(KBr): 1795, 1690 cm^{-1}. $[\alpha]_D^{25}$+151°(c=1.17, $CHCl_3$).
10. 15a; m/z: 449(M^+). PMR(100 MHz $CDCl_3$)δ: 2.32(3H, s), 2.8(3H, s), 2.8-3.3(2H, complex), 3.64, 3.7[3H, two s(1:2)], 4.5-5(1H, complex), 5.02, 5.08[2H, two bs (1:2)], 5.8(1H, bs), 6.5-7.4(12H, complex). IR(KBr): 1735, 1690 cm^{-1}. $[\alpha]_D^{28}$+31.7°(c=2.65, $CHCl_3$).
15b; m/z: 465(M^+). PMR(100 MHz $CDCl_3$)δ: 2.74(3H, s), 2.8-3.32(2H, complex), 3.56, 3.64[3H, two s(1:2)], 3.78(3H, s), 4.46-4.92(1H, complex), 4.96, 5.04[2H, two s(1:2)], 6.28(1H, s), 6.5-7.5(12H, complex). IR(KBr): 1740, 1700 cm^{-1}. $[\alpha]_D^{28}$+11.76°(c=3.35, $CHCl_3$).
15c; m/z: 465(M^+). PMR(100 MHz $CDCl_3$)δ: 2.78(3H, s), 2.8-3.3(2H, complex), 3.64, 3.68[3H, two s(1:2)], 3.76(3H, s), 4.5-5(1H, complex), 5.03, 5.08[2H, two bs(1:2)], 5.8(1H, bs), 6.5-7.4(12H, complex). IR(KBr): 1730, 1690 cm^{-1}. $[\alpha]_D^{28}$+2.98°(c=4.35, $CHCl_3$).
15d; m/z: 551(M^+). PMR(60 MHz $CDCl_3$)δ: 2.77(3H, s), 2.7-3.4(6H, complex), 3.67(3H, s), 3.7(3H, s), 4.5-4.9(1H, complex), 5.03(2H, bs), 6.1(1H, s), 6.5-7(6H, complex), 7.23(5H, bs). IR(KBr): 1735, 1700 cm^{-1}. $[\alpha]_D^{21}$+18.77°(c=2.27, $CHCl_3$).
15e; PMR(60 MHz $CDCl_3$)δ: 1.36(9H, s), 2.7(3H, s), 2.8(3H, s), 3.0-3.3(4H, complex), 3.7(3H, bs), 4.5-5.0(2H, complex), 5.03(2H, bs), 5.16(2H, s), 6.5-7.5(18H, complex). IR($CHCl_3$): 1730, 1680 cm^{-1}. $[\alpha]_D^{21}$ −6.76°(c=1.96, $CHCl_3$).
15f; m/z: 597(M^+). PMR(60 MHz $CDCl_3$)δ: 2.6-3.3(6H, complex), 2.67(3H, s), 3.6(3H, s), 5.0, 5.07[4H, two s(4:1)], 6.6-7.5(18H, complex) IR(KBr): 1735, 1700 cm^{-1}. $[\alpha]_D^{21}$ +20.92°(c=3.68, $CHCl_3$).

Received, 4th October, 1982