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Construction of the Skeleton of Phthalascidin, Mechanism of the Formation of the Key Tricyclic Lactam Intermediate

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Abstract: The mechanism of the formation of a key tricyclic lactam intermediate **3** was studied. It was found that the E-form compound **3** was transformed from the Z-form compound **4**. The formation of **4** was a kinetically controlled process while the formation of **3** was a thermodynamically favorable one. A possible mechanism was given in this paper.

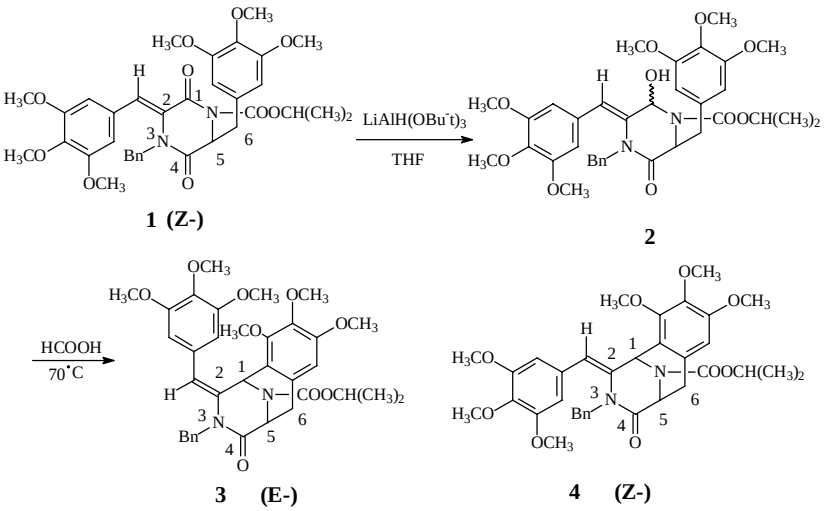
Keywords: Lactam, phthalascidin, mechanism, Et-743.

Phthalascidin is a structurally simplified version of Et-743, which is a potent anti-tumor marine natural product isolated from *Ecteinascidia turbinata*. Its antiproliferative activity is greater than that of the agents taxol, camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, and etoposide by 1-3 orders of magnitude. An elegant synthesis of Et-743 and phthalascidin has been reported by E. J. Corey and co-workers[1,2]. As part of our continuing program, we have also engaged in developing a simple and efficient approach of synthesizing phthalascidin and structurally related compounds and studying their structure-activity relationship. The synthetic strategy we utilized was partly based upon that developed by Naoki Saito *et al* in the synthesis of saframycins[3].

The Z-form piperizine-2,5-dione derivative **1** was prepared from two molecules of 3,4,5-trimethoxybenzaldehyde and one molecule of piperizine-2,5-dione by the known method[4]. **1** was then reduced regio-specifically to give the allylic alcohol **2**, which was then heated in formic acid to give the key E-form tricyclic lactam **3** (**Scheme 1**) .

In addition to the major E-form product **3**, in which the configuration of the C=C double bond was different from the starting material **1**, a small amount of the normal Z-form product **4** was also isolated. The structure of **3** and **4** was assigned with ^{1}H-NMR, ^{13}C-NMR, FAB-MS, HRMS, and IR as E- and Z- isomer respectively. From their spectroscopic data, it was apparent that, aside from other differences, the most obvious difference was the chemical shift of H-1. In the E-form **3**, it was 6.68, while in the Z-form **4**, it was 4.94. This big difference was in good agreement with their structure since in compound **3**, H-1was in the off-shielding area of the left benzene ring.

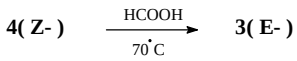
Scheme 1



1 (Z-) **2** **3 (E-)** **4 (Z-)**

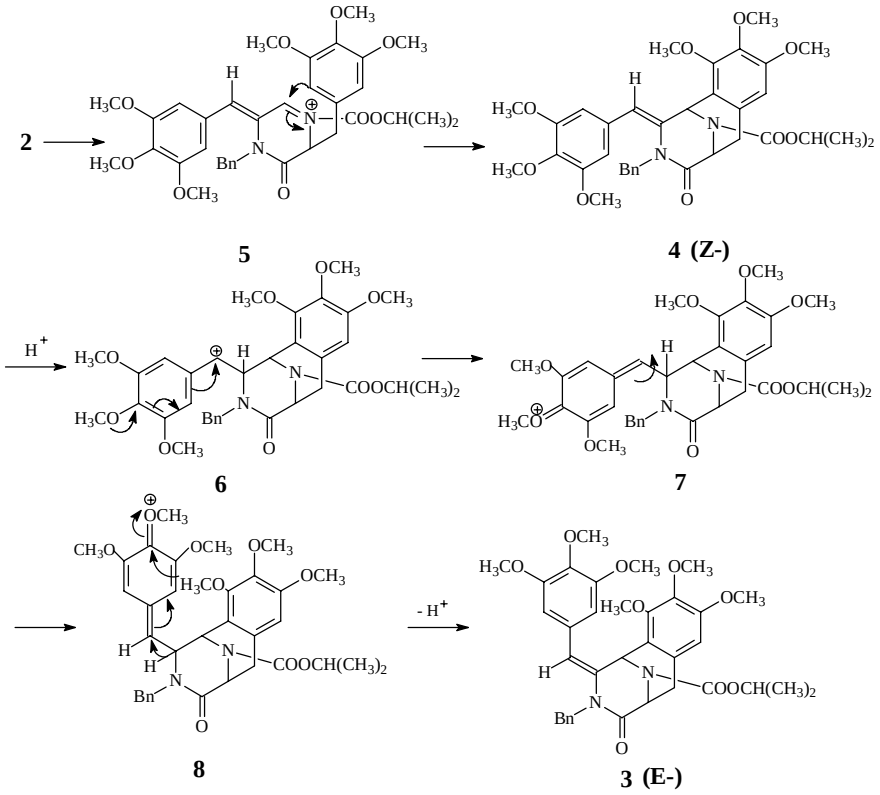
In order to study this phenomenon, the reaction was monitored with TLC carefully and it was found that the spot corresponding to compound **4** appeared at the earlier stage of the reaction and became smaller gradually, however in the meantime, the spot of compound **3** became larger. This phenomenon convinced us that compound **3** was transformed from compound **4**. In order to prove this hypothesis, the reaction was then stopped at certain time and a considerable amount of compound **4** was isolated. Then **4** was heated in formic acid at 70°C and indeed the same phenominon was observed and the pure E-form compound **3** was obtained. (**Scheme 2**)

Scheme 2



From all the above experimental facts, a rational mechanism was proposed, with which the process of the reaction could be satisfactorily explained. The allylic alcohol **2** lost H_2O through the action of the acid to produce the cation intermediate **5** which then readily underwent the Pictet-Spengler cyclization to form the Z-form tricyclic compound **4** with the configuration of the double bond intact. However, compound **4** was not a thermodynamically favorable molecule because of the congestion and repellence of the left benzene ring and the N-protective benzyl groups, which were spatially close to each other. Under the action of the formic acid, the double bond was protonated to give **6**, which could be stablized through its resonant form **7**. The rotation of the single C-C bond in **7** and the subsequent loss of a proton resulted in the thermodynamically stable compound **3**. (**Scheme 3**)

Scheme 3



In conclusion, it was proved through our study that the formation of the E-form compound **3** was transformed from the Z-form compound **4**. The formation of **4** was a kinetically controlled process while the formation of **3** was a thermodynamically favorable one.

References and Notes

1. R. J. Martinez, T. Owa *et al., Proc. Natl. Acad. Sci. USA*, **1999**, *96*, 3496.
2. E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.*, **1996**, *118*, 9202.
3. A. Kubo, N. Saito *et al., J. Org. Chem.*, **1988**, *53*, 4295.
4. A. Kubo, N. Saito *et al., Chem. Pharm. Bull.*, **1987**, *35* (6), 2525.
5. Data of compound **1**: ^{1}H-NMR (300MHz, $CDCl_3$): δ ppm 7.2 (m,3H,Ar-H), 7.1 (s,1H,alkene-H), 6.9 (m,2H,Ar-H), 6.5 (s,2H,Ar-H), 6.4 (s,2H,Ar-H), 5.23 (d,1H,J=14.4Hz,$ArCH_2$**N**), 5.2 (dd,1H, J=7.8,5.4Hz,H-5), 4.9 (sept,1H,J=6.3Hz,$CH(CH_3)_2$), 4.2 (d,1H,J=14.4Hz,$ArCH_2N$), 3.9 (s,3H, OCH_3), 3.85 (s,6H,OCH_3), 3.80 (s,6H,OCH_3), 3.65 (3 s,H,OCH_3), 3.2 (dd,1H,J=19.2,5. 4Hz,H-6), 3.1 (dd,1H,J=19.2,7.8Hz,H-6′), 1.28 (d,3H,J=6.3Hz,$CHCH_3$), 1.23 (d,3H, J=6.3Hz,$CHCH_3$); IR (KBr , cm^{-1}): 1774 (C=O), 1722 (C=O), 1691 (C=O), 1624 (C=C) ; FAB-MS: 648 (*m/z*), 604, 557.
6. Data of compound **3**: ^{1}H-NMR (300MHz, $CDCl_3$): δ ppm 7.1 (m,3H, Ar-H), 6.75 (m,4H,Ar-H), 6.68 (1 s,H,H-1), 6.4 (s,1H,Ar-H), 5.94 (s,1H,alkene-H), 5.3 (1 d,H,J=15Hz,$ArCH_2N$), 5.2 (m,1H,H-5), 5.0 (m,1H,$CH(CH_3)_2$), 4.7 (d,1H,J=15Hz,$ArCH_2N$), 3.9 (s,6H,2 OCH_3), 3.85 (s,3H, OCH_3), 3.83 (s,3H,OCH_3), 3.7 (s,3H,OCH_3), 3.2 (m,2H,H-6), 3.0 (s,3H,OCH_3), 1.31

(d,3H, J=6.3Hz, $CHCH_3$), 1.26 (d,3H,J=6.3Hz,$CHCH_3$); ^{13}C-NMR ($CDCl_3$): δ ppm 168.57(s), 153.56(s), 153.25(s), 152.95(s), 151.19(s), 140.5(s), 136.40(s, x2), 135.94(s), 131.88(s), 128.59(d, x2), 128.29(s), 127.18(d), 126.69(d, x2), 119.54(s), 112.02(d), 107.89(s), 107.23(d), 106.91(d, x2), 69.74(d), 61.15(q), 60.83(q), 60.61(q), 59.72(q), 59.64(q), 56.24(q), 54.12(d), 45.94(d), 45.21(t), 33.22(t), 22.43(q, x2); IR (KBr, cm^{-1}): 1738 (C=O), 1689 (C=O), 1643 (C=C); FAB-MS: 632 (*m/z*), 591,547,306,264, 220; HRMS (FAB): calcd. for $C_{35}H_{40}N_2O_9$ 632.273381, found 632.273348.

7. Data of compound **4**: ^{1}H-NMR (300HMz, $CDCl_3$): δppm 7.0 (t,1H,J=7.5Hz,Ar-H), 6.8 (t,2H, J=7.5Hz,Ar-H), 6.69 (br,1H,Ar-H), 6.4 (s,2H,Ar-H), 6.0 (d,2H,J=7.5Hz,Ar-H), 6.02 (s,1H, alkene-H), 5.62 (d,1H,J=15Hz,$ArCH_2N$), 5.3 (d,1H,J=15Hz,$ArCH_2N$), 4.94 (br,1H,H-1), 4.87 (t,1H,J=6Hz,H-5), 4.0 (hept,1H,J=7.2Hz,$CH(CH_3)_2$), 3.83 (s,3H,OCH_3), 3.74 (s,6H,2OCH_3), 3.7 (s,3H,OCH_3), 3.69 (s,3H,OCH_3), 3.34 (s,3H,OCH_3), 3.2 (dd,1H,J=12.6,6Hz,H-6), 3.1 (dd,1H, J=12.6,6Hz,H-6'), 1.17 (t,6H,J=7.2Hz,$CH(CH_3)_2$); ^{13}C-NMR ($CDCl_3$): δ ppm 168.56(s), 153.3(s), 153.0(s, x2), 152.5(s), 149.9(s), 140.1(s), 137.0(s), 136.5(s), 136.2(s), 134.2(s), 130.7(s), 128.0(d), 127.4(d), 126.6 (d), 126.5(d, x2), 117.9(d), 112.1(d), 107.6(d), 106.7(d, x2), 69.2(d), 60.2(q), 60.1(q), 59.6(q), 56.0(q, x2), 53.4(q), 52.7(d), 52.4(d), 45.0(t), 33.1(t), 21.9(q, x2); IR (KBr ,cm^{-1}): 1699 (C=O), 1689 (C=O), 1647 (C=C); FAB-MS: *m/z* M^+633, 591,547,306,264, 220; HRMS (FAB): calcd. for $C_{35}H_{40}N_2O_9$ 632.273381, found 632.273351.

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