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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 65.[1] A STEREOSELECTIVE SYNTHESIS OF TILIVALLINE

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Abstract: Tilivalline (**1**), a metabolite from *Klebsiella*, has been efficiently and stereoselectively synthesized from diphenyl phosphorazidate (DPPA), the 2-oxazoline **2**, the L-proline derivative **5**, and indole; the key step is a Mannich type intramolecular cyclization accompanied with simultaneous and completely stereoselective introduction of indole.

Tilivalline (**1**) is a pyrrolo[2,1-c][1,4]benzodiazepine metabolite isolated from *Klebsiella pneumoniae* var. *oxytoca* by Mohr and Budzikiewicz.[3] The synthesis of **1** has also been accomplished by the same group,[3] but it is neither stereoselective nor efficient. Since the pyrrolo[2,1-c][1,4]benzodiazepine skeleton is the fundamental constituent of a series of antitumor anthramycin antibiotics,[4] we have had a keen interest on veiled biological activities of **1**. We now wish to report a completely stereoselective, efficient, and convenient synthesis of tilivalline (**1**) mainly based on the synthetic methodologies developed by our own group. Our basic scheme for the synthesis of **1** is shown in Chart 1. The key step in this convergent synthesis is construction of the 7-membered diazepine ring accompanied with simultaneous and stereoselective introduction of indole.

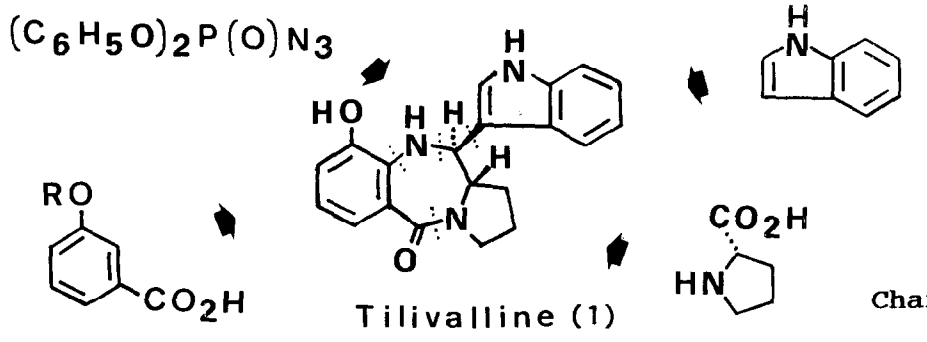


Chart 1.

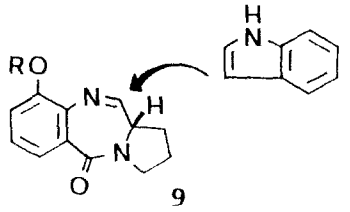
One important intermediate in the synthesis is 3-methoxy or 3-hydroxyanthranilic acid (**4a** or **4b**) which was obtained starting with the 2-oxazoline **2**, easily prepared from 3-methoxybenzoic acid and 2-amino-2-methylpropanol according to the literature.[5] Regioselective amination of **2** was achieved by our method[6] using diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$) as $^+NH_2$ synthon. Thus, sequential treatment of **2** in tetrahydrofuran with n-butyllithium (-45°, 1.5 h, under Ar),[5] DPPA (-70°, 1h), and sodium bis(2-methoxyethoxy)-aluminum hydride (-5°, 0.5h; room temp., 1h) afforded the amine **3**, mp 112°, in 67% yield (82% yield, based on consumed **2**). Hydrolysis of **3** with 3N hydrochloric acid (100°, 20 min)

followed by 20% sodium hydroxide in methanol (reflux, 0.5h) quantitatively gave 3-methoxyanthranilic acid (**4a**), mp 169°. 3-Hydroxyanthranilic acid (**4b**), mp 233-235°(decomp.), was also obtained in 86% yield by treatment of **3** with 55% hydriodic acid in the presence of red phosphorus in a sealed tube (100°, 14h).

A second key intermediate is the acetal **7** which was prepared as its hydrochloride in 59% overall yield by a sequence involving (1) racemization-free oxidation of N-tert-butyloxycarbonyl(Boc)-L-prolinol to Boc-L-prolinal (**5a**) by the method developed by us [7] with sulfur trioxide-pyridine and dimethylsulfoxide in the presence of triethylamine (room temp., 10 min, Ar), (2) conversion of **5a** to its dimethyl acetal **6a** with trimethyl orthoformate and ceric trichloride in methanol (room temp., 0.5h; 50°, 21h),[8] and (3) deprotection of the Boc group with 10% hydrogen chloride in methanol (room temp., 1h). No racemization was found to occur during the above conversion since the 3,5-dinitrobenzoyl derivative of **7** showed no peak of its antipodal D-isomer on HPLC using a Sumipax OA-1000 chiral column. Analogously, N-benzyloxycarbonyl-L-prolinal (**5b**)[7] afforded, with less efficiency, the acetal **7** via **6b** (Chart 2).

Condensation of 3-methoxyanthranilic acid (**4a**) with L-prolinal dimethyl acetal (**7**), used as its hydrochloride, was easily accomplished by the use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[9] in the presence of triethylamine and molecular sieves 4A in tetrahydrofuran (0°, 1h; room temp., 40 min) to give the amide **8a** as a colorless oil, $[\alpha]_D^{24}$-173°(c=1.2, MeOH), in 84% yield.

We considered that the final construction of the tilivalline skeleton would be attained from **8** by an intramolecular cyclization leading to the imine **9** followed by the nucleophilic introduction of the indole nucleus from the less hindered top face, as shown below. In fact, successive treatment of **8a** with chlorotrimethylsilane-sodium iodide, boron trifluoride etherate, followed by the 3-indolyl Grignard reagent afforded O-methyltilivalline (**10a**), but the yield was very poor (< 5%). However, dramatic improvement of the final construction was achieved by the sequential treatment of **8a** in a one-pot process with (1) chlorotrimethylsilane (3 eq)-sodium iodide (3 eq)-pyridine (4 eq) in acetonitrile (-20°, 0.5h, Ar), (2) indole (2 eq) (room temp., 0.5h), and (3) zinc chloride (2 eq) (room temp., overnight; 55°, 3h). This new Mannich type condensation afforded **10a** as an amorphous solid, mp ca. 200°, $[\alpha]_D^{19}$ +241°(c=0.56, MeOH), in 71% yield (93% yield, based on consumed **8a**), whose IR, ^{1}H-NMR, and mass spectral data were identical with those of O-methyltilivalline.[3,10] The reaction was completely stereoselective, and no isomer of **10a** could be found. Unfortunately, however, removal of the methyl group from **10a** was unsuccessful under a variety of reaction conditions (e.g., BBr_3, BCl_3, t-BuSLi/HMPA, or $AlCl_3$/EtSH).[11]



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In the preferred route to tilivalline (**1**), 3-hydroxyanthranilic acid (**4b**) was condensed with the acetal **7** by the DEPC method as described above to give the amide **8b** as a yellow oil in 69% yield. The simple one-pot Mannich type conversion of **8b** to tilivalline (**1**) was accomplished in a completely stereoselective manner analogously as above in 83% yield. The spectral data (IR, ^{1}H-NMR, mass, and UV) of the synthetic specimen[12] were completely identical with those of natural tilivalline.[3,10]

Incidentally, 3-benzyloxyanthranilic acid (**4c**)[13] was condensed with the acetal **7** by the

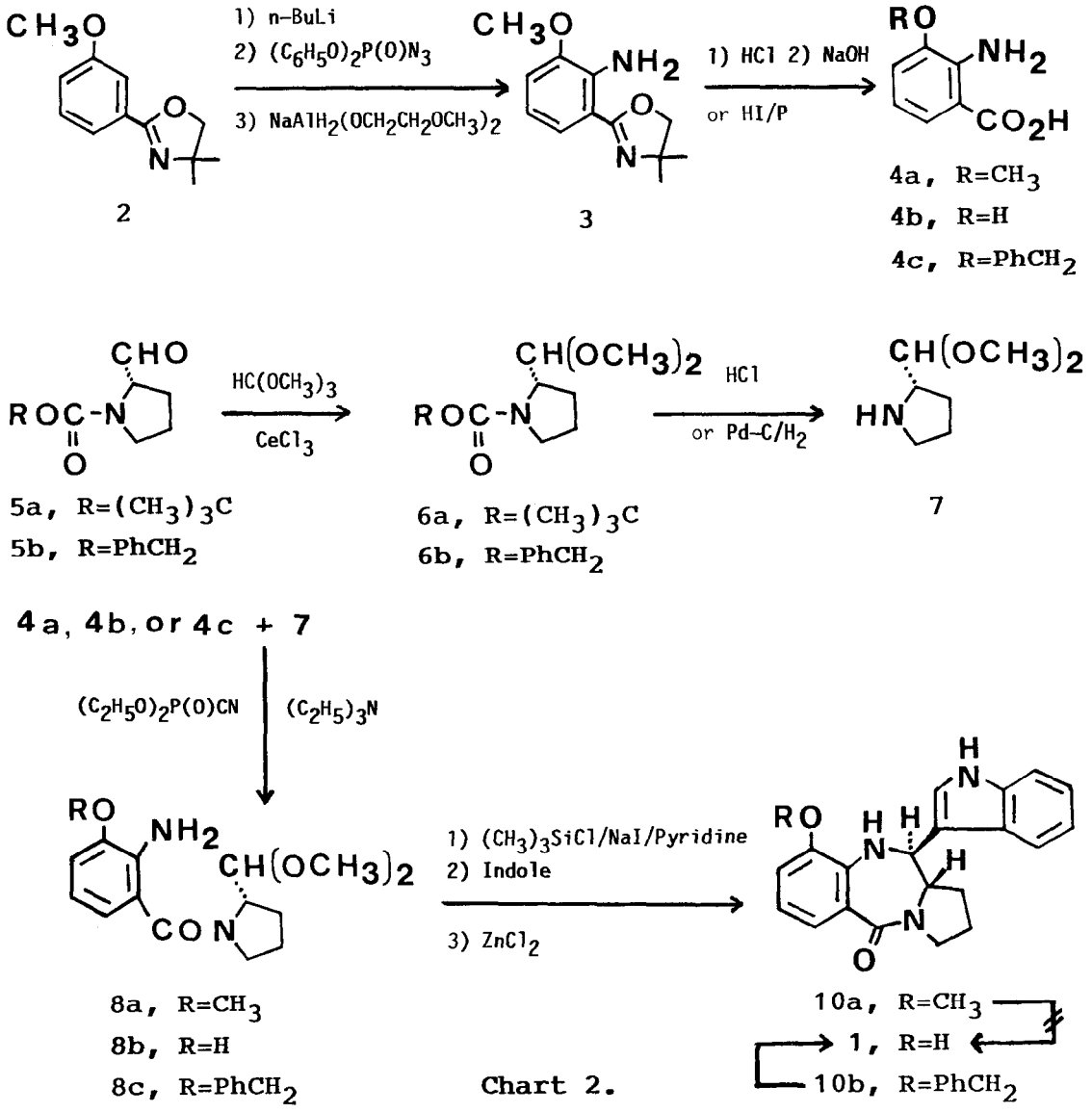

Chart 2.

DEPC method to give the amide **8c** as a pale yellow viscous oil in 77% yield, which underwent the stereoselective Mannich type condensation to furnish O-benzyltilivalline (**10b**), mp 125–126°, $[\alpha]_D^{20}$ +132.5°(c=0.52, MeOH), in 41% yield. Catalytic removal of the benzyl group was easily carried out in a hydrogen atmosphere over 5% palladium-carbon in ethanol to give tilivalline (**1**) in 80% yield.

The new Mannich type condensation developed above requires both chlorotrimethylsilane-sodium iodide-pyridine and zinc chloride in addition to indole. Hence, the reaction might proceed as follows. Trimethylsilylation of the amino group in **8** followed by activation with zinc chloride gives **A**, which furnishes **B**, as shown in Chart 3. Elimination of methoxy-trimethylsilane from B affords the imine which will be activated with zinc chloride to give **C**.

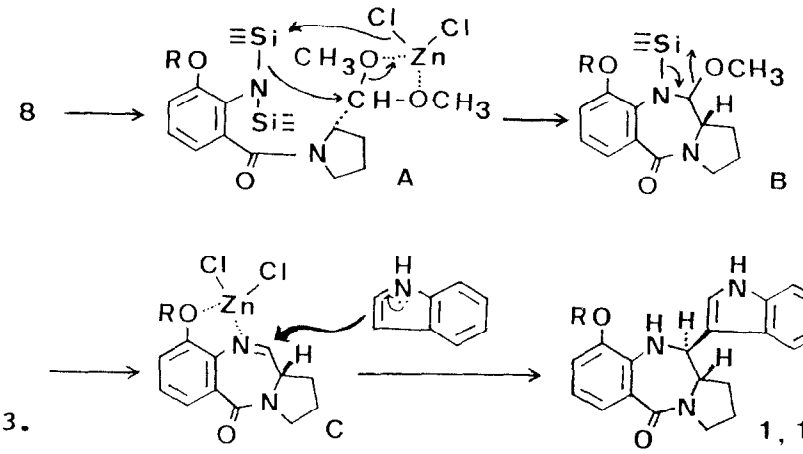

Chart 3.

Nucleophilic attack of indole to **C** from the less hindered top face produces the tilivallines.

A particularly interesting feature of this synthesis of tilivalline is an overall efficiency suitable for large scale production and the complete stereoselectivity of the Mannich type cyclization of **8**. Furthermore, the above synthesis includes generally useful processes developed by our own group: (1) regioselective amination of arenes using DPPA as $^{+}NH_2$ synthon,[6] (2) conversion of α-amino acids to α-amino aldehydes without racemization,[7] (3) racemization-free acetal formation from α-amino aldehydes, (4) the amide bond formation using DEPC,[9] and (5) the new Mannich type condensation.

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References and Notes

1. For Part 64, see S. Kato, Y. Hamada, and T. Shioiri, Tetrahedron Lett., **27**, 2653 (1986).
2. Present address : Sagami Chemical Research Center, Nishi-ohnuma, Sagamihara, Kanagawa 229, Japan.
3. N. Mohr and H. Budzikiewicz, Tetrahedron, **38**, 147 (1982).
4. For reviews, see L.H. Hurley, J. Antibiot., **30**, 349 (1977); L.H. Hurley and D.E. Thurston, Pharm. Res., 52 (1984).
5. A.I. Meyers and W.B. Avila, J. Org. Chem., **46**, 3881 (1981).
6. S. Mori, T. Aoyama, and T. Shioiri, Tetrahedron Lett., **25**, 429 (1984); S. Mori, T. Aoyama, and T. Shioiri, Chem. Pharm. Bull., **34**, 1524 (1986).
7. Y. Hamada and T. Shioiri, Chem. Pharm. Bull., **30**, 1921 (1982).
8. J.-L. Luche and A.L. Gemal, J. Chem. Soc., Chem. Comm., 977 (1978); A.L. Gemal and J.-L. Luche, J. Org. Chem., **44**, 4187 (1979).
9. For a review, see T. Shioiri, J. Synth. Org. Chem. Japan, **37**, 856 (1979).
10. N. Mohr, Ph. D. thesis (University of Köln), 1980.
11. Iodotrimethylsilane was also not effective for this conversion; see reference 3.
12. Tilivalline (**1**) has been reported[3,10] to show mp 168° and $[\alpha]_D^{25}$ +126.8°(MeOH). When a methanolic solution of the synthetic **1** was concentrated and the residue was solidified with diethyl ether, **1** formed a colorless amorphous solid, mp 169-171° (moistened from 138°). $[\alpha]_D^{25}$ +197°(c=0.98, MeOH), which was recrystallized from aqueous methanol to give yellow prisms, mp 242-245°, $[\alpha]_D^{27}$ +234°(c=0.57, MeOH).
13. L. Cleaver, S. Nimgirawath, E. Ritchie, and W.C. Taylor, Aust. J. Chem., **29**, 2003 (1976).

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