# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF UNNATURAL (–)-ANTIMYCIN $A_3$ AND ITS ANALOG

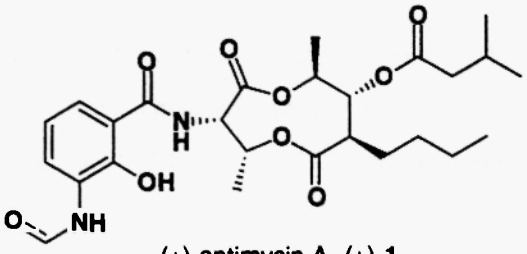
Hitoshi Kondo, Takayuki Oritani and Hiromasa Kiyota*

Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

**Abstract**

Unnatural enantiomer of a dilactone antibiotic (–)-antimycin $A_3$ and its deformylamidodehydroxy analog were synthesized using chelation controlled alkylation as a key step. (–)-Antimycin $A_3$ and its analog hardly showed antimicrobial activity compared with natural antimycin A complex. The formal synthesis of natural (+)-antimycin $A_3$ is also achieved.

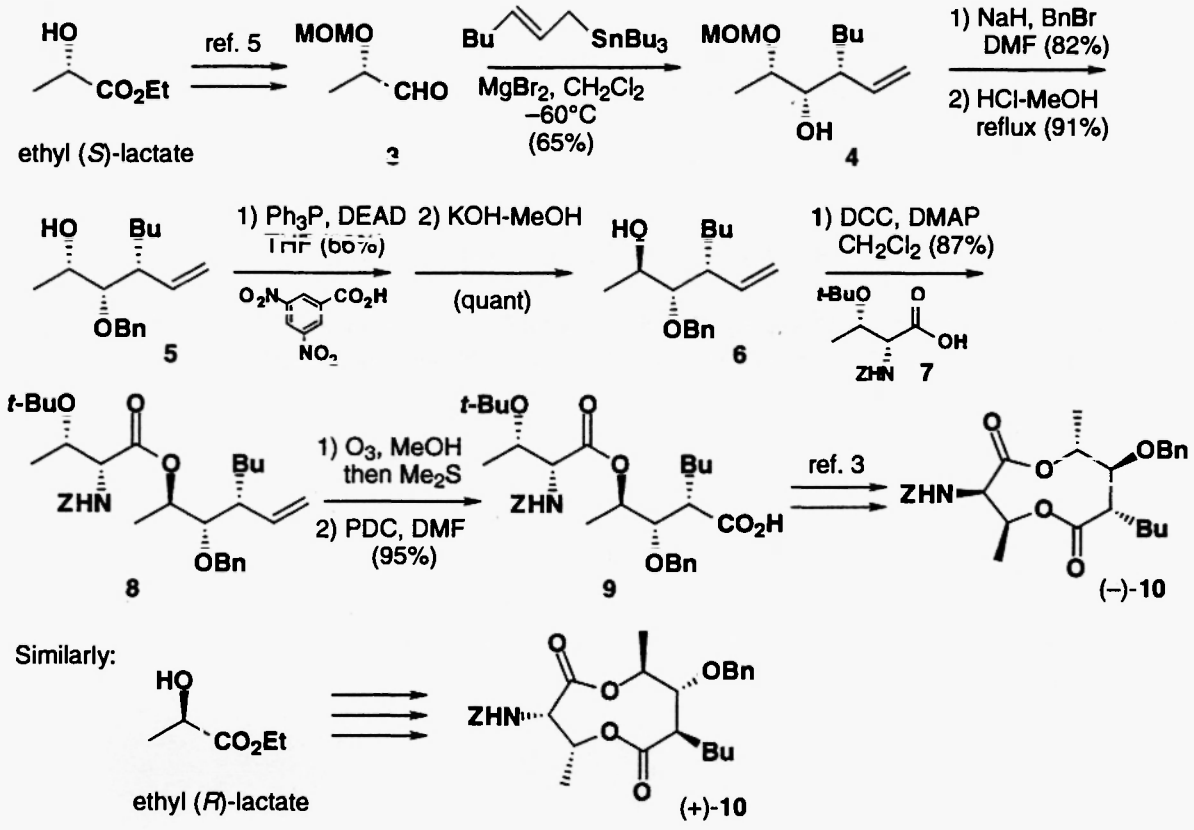
## Introduction



(+)-antimycin $A_3$ (+)-1

A series of antibiotic antimycins have been isolated from various *Streptomyces* species since 1946 (1). The curious dilactone structure and strong biological activities has inspired many scientists to investigate their structure activity relationships, mechanism of action (2) and chemical synthesis (3-5). In our previous communication (6), the inhibition of electron transport of rat liver mitochondria by synthetic unnatural (–)-antimycin $A_3$ (–)-1 and the comparison of the activity between natural (+)-1 and (–)-1 were reported. In this paper, we describe the total synthesis of (–)-1 and its deformylamidodehydroxy analog (–)-2, and the formal synthesis of (+)-1.

## Results and Discussion

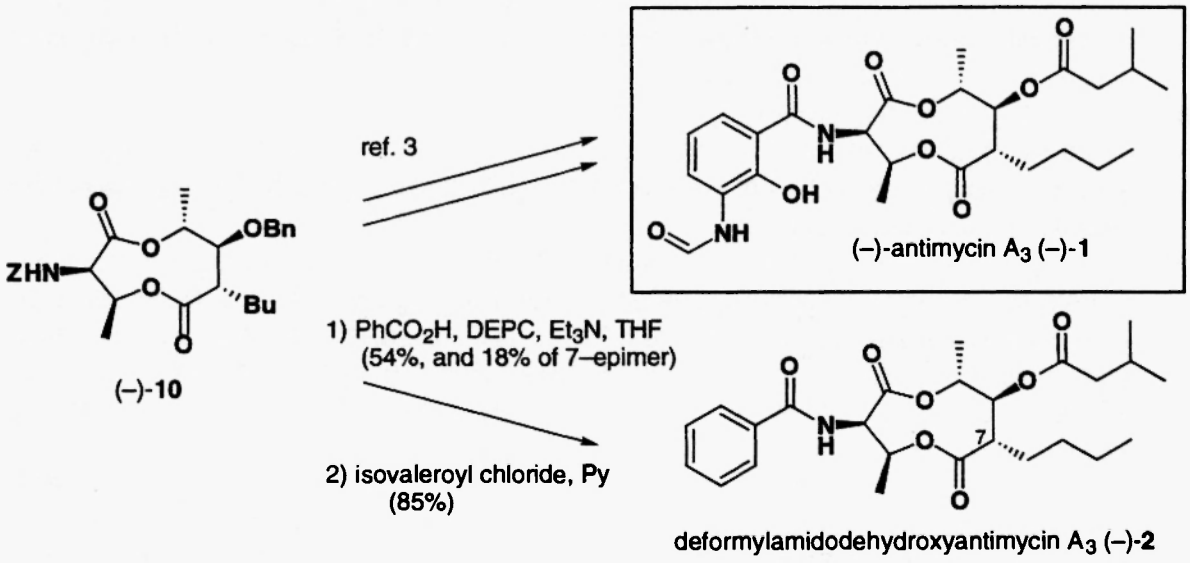



Scheme 1. Formal synthesis of (+)- and (–)-antimycin $A_3$

Scheme 1 shows the construction of dilactone skeleton of antimycin $A_3$. Aldehyde **3** (5) derived from ethyl (*S*)-lactate was treated with allylic stannyl compound under chelation control ($MgBr_2$) to give all-*syn* product **4** (7,8). The ratio of **4** to other diastereomers was 95:5 (65% and 3.4% isolated yields, respectively). This selectivity decreased in the case of the corresponding THP and EE ethers (*ca.* 85:15) instead of MOM. The hydroxyl group of **4** was protected as benzyl ether and the MOM ether was cleaved to afford 5. The formed hydroxyl group of 5 was substituted with 3,5-dinitrobenzoic acid by Mitsunobu condition, and the resulting DNB ester was hydrolyzed to give 6. The hydroxy group of 5 was completely inverted. Then threonine residue **7** (9) was coupled with **6** to afford **8** in 87% yield. Direct introduction of **7** to **5** by Mitsunobu reaction failed in low yield of the desired product. The double bond of **8** was cleaved to give Kinoshita's intermediate 9 (3). This compound 9 was converted to dilactone (–)-**1 0** (10). In addition, natural enantiomer (+)-**1 0** was also prepared from ethyl (*R*)-lactate by the same procedure as described for (–)-**1 0** (**10**). (–)-**1 0** was

converted to the unnatural enantiomer, (–)-antimycin $A_3$ (–)-**1** according to Kinoshita's procedure (3, 11), and also to deformylamidodehydroxyantimycin $A_3$ (–)-**2** (12) (Scheme 2).

Antifungal activity of (–)-**1** and (–)-**2** was investigated. Compared with natural antimycin mixture, unnatural compounds, (–)-**1** and (–)-**2**, scarcely inhibited the growth of *Saccharomyces cereviciae*. This follows our previous findings (6), that is, the configuration of the dilactone ring system plays important rolls in expressing the activities of antimycins.




Scheme 2. Synthesis of (–)-antimycin $A_3$ and its analog.

## Conclusion

In conclusion, the formal syntheses of (+)-antimycin $A_3$ (+)-**1** and the total synthesis of (–)-**1** and its deformylamidodehydroxy analog (–)-**2** were achieved. The total yield of Kinoshita's intermediate **9** from the lactate derivative **3** was 26% in 8 steps. Our synthesis was superior to the previous ones in view of the availability of the starting material and the selectivity of the key tin catalyzed alkylation reaction. The unnatural enantiomers (–)-**1** and (–)-**2** scarcely inhibited the growth of *Saccharomyces cereviciae*.

## References

(1) B. R. Dunshee, C. Leben, G. K. Keitt and F. M. Strong, J. Am. Chem. Soc. 71, 2436 (1946). K. Nakayama, F. Okamoto and Y. Harada, J. Antibiot. ser. A. 9, 63 (1956). K. Watanabe, T. Tanaka, K. Fukuhara, N. Miyairi, H. Yonehara and H. Umezawa, J. Antibiot. ser. A. 10, 39 (1957). G. M. Tener, F. M. Bumpus, B. R. Dunshee and F. M. Strong, J. Am. Chem. Soc. 75, 1100 (1953). W. Liu and F. M. Strong, J. Am. Chem. Soc. 81, 4387 (1959). E. E. van Tamelen, J. P. Dickie, M. E. Loomans, R. S.

Dewey and F. M. Strong, J. Am. Chem. Soc. 83, 1639 (1961).

(2) E. C. Slater, Biochimica et Biophysica Acta 301,129 (1973). R. E. Lennon, Advances in Applied Microbiology 16, 55 (1973).

(3) M. Kinoshita, S. Aburaki, M. Wada and S. Umezawa, Bull. Chem. Soc. Jpn. 46, 1279 (1973). S. Aburaki and M. Kinoshita, Bull. Chem. Soc. Jpn. 52, 198 (1979).

(4) T. Nakata, M. Fukui and T. Oishi, Tetrahedron Lett. 24, 2657 (1983).

(5) H. H. Wasserman and R. J. Gambale, J. Am. Chem. Soc. 107, 1423 (1985).

(6) H. Miyoshi, H. Kondo, T. Oritani, I. Saitoh and H. Iwamura, FEBS Lett. 292, 61 (1991).

(7) G. E. Keck and E. P. Boden, Tetrahedron Lett. 25, 1879 (1984).

(8) Mulzer *et al.* reported the highly stereoselective synthesis of all *anti* isomer of **4** derivative by using the corresponding allylic chromium(II) reagent (Hiyama reaction): J. Mulzer, T. Schulze, A. Strecker and W. Denzer, J. Org. Chem. 53, 4098 (1988).

(9) E. Schröder, Liebigs Ann. Chem. 670, 127 (1963).

(10) (–)-**1 0**: mp 117.0-119.0℃, $[\alpha]_D^{22}$ –53° (*c* = 0.54, $CHCl_3$) and (+)-**1 0**: mp 119.0-120.0℃, $[\alpha]_D^{22}$ +47° (*c* = 0.45, $CHCl_3$) {ref. (3) for (+)-**1 0**: 118.5-119.5℃, $[\alpha]_D^{22}$ +53℃ (*c* = 0.73, $CHCl_3$)}. The spectral data were identical with those reported (3).

(11) (–)-**1**: mp 173.5-174.5℃ (petroleum ether-ether), $[\alpha]_D^{22}$ –74° (*c* = 0.47, $CHCl_3$) {ref. (3): 174.0-174.5℃, $[\alpha]_D^{24}$ +80℃ (*c* = 1.0, $CHCl_3$)}. HR-EIMS: calcd. for $C_{25}H_{36}O_9N_2$, 520.2421; found, 520.2420.

(12) (–)-**2**: colorless needles, mp 183-185℃, $[\alpha]_D^{22}$ –100° (*c* = 0.20, $CHCl_3$). IR (KBr) ν max $cm^{-1}$: 3340, 1750, 1735, 1645, 1530, 1370, 1185, 1165. $^1$H-NMR δ (400 MHz, $CDCl_3$): 0.86 (3H, t, *J* = 7.0 Hz), 0.99 (6H, d, *J* = 6.4 Hz), 1.29 (3H, d, *J* = 6.0 Hz), 1.33 (3H, d, *J* = 7.1 Hz), 2.14 (1H, m), 2.25 (2H, m), 2.50 (1H, m), 4.97 (1H, dq, *J* = 5.8, 9.6 Hz), 5.10 (1H, dd, *J* = 9.8, 9.8 Hz), 5.34 (1H, dd, *J* = 7.7, 7.7 Hz), 5.75 (1H, dq, *J* = 7.3, 7.3 Hz), 6.85 (1H, d, *J* = 7.6 Hz), 7.3-7.6 (3H, m), 7.8-7.9 (2H, m). $^{13}$C-NMR δ (100 MHz): 13.8, 15.1, 17.9, 22.4, 22.5, 25.5, 28.3, 29.2, 43.3, 50.2, 54.1, 71.5, 74.5, 75.6, 127.1, 128.8, 132.2, 133.3, 166.9, 170.7, 171.7, 173.1. EIMS (m/z): 462 [$(M+1)^+$, 3%], 417 (42), 377 (20), 316 (20), 257 (35), 206 (28) 161 (100), 105 (100). HR-EIMS: calcd. for $C_{26}H_{35}O_7N$, 461.2411; found, 461.2413.

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