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A FORMAL TOTAL SYNTHESIS OF ERYTHROMYCIN A. 2. A CONVERGENT SYNTHESIS OF WOODWARD'S CARBAMATE INTERMEDIATE

Tadashi Nakata,* Mineo Fukui, and Takeshi Oishi*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351-01, Japan

Summary: The key intermediate 1 in Woodward's total synthesis of erythromycin A was synthesized via coupling of the C_1-C_7 and C_8-C_{15} segments.

In the preceding paper, the syntheses of the optically active two segments (+)-2 and (-)-3 having most of chiral centers involved in erythronolide A were reported. In this report, coupling reaction of these two segments and the subsequent elaboration leading to carbamate 1, a key intermediate in Woodward's erythromycin A synthesis, are described.

Aldol strategy is quite promising for this purpose since the reaction between Z-enolate of 2 and aldehyde 3 is presumed to proceed through the transition state I (Fig. 1) where Li cation is coordinating with three oxygen atoms[1,2] resulting in the formation of 7,8-syn-adduct 4 having the C_7-α-OH and C_8-α-Me groups. In fact, $(Me_2PhSi)_2NLi$[1] promoted condensation of these segments in THF at -78°C gave with high stereoselectivity the expected 7,8-syn-8,10-anti-adduct 4[3,4] ($[\alpha]_D^{25}$ +10.4°(c 1.7, $CHCl_3$)) in 75% isolated yield along with a small amount of unseparable mixture of isomers (4%, ca. 4:1). However, all attempts to remove the unneces-

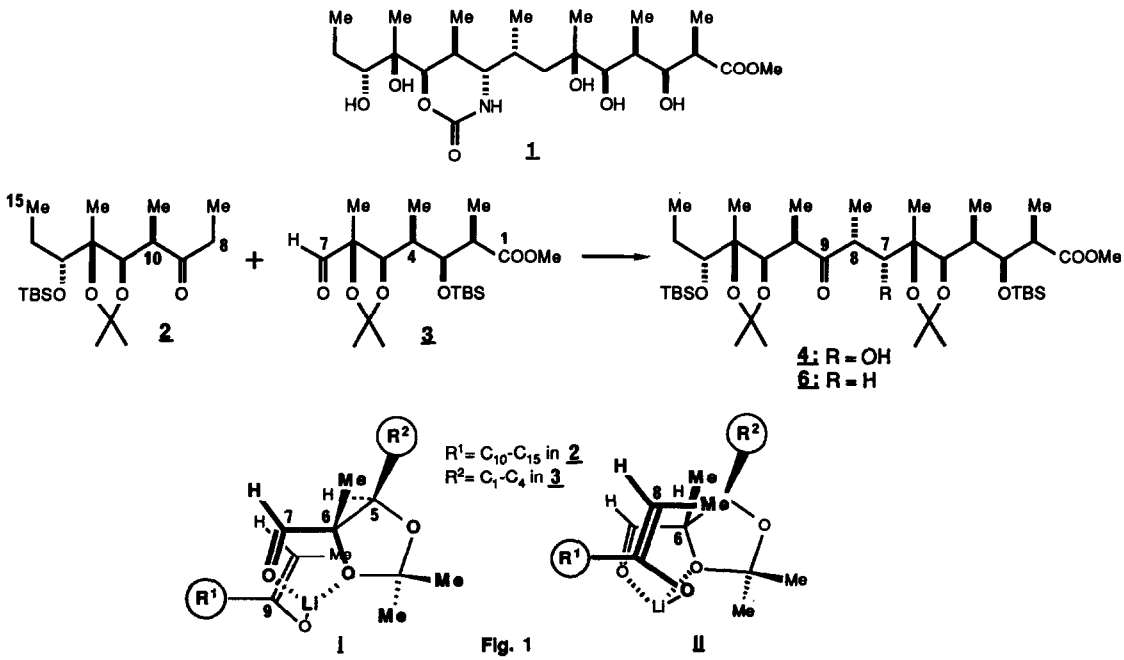
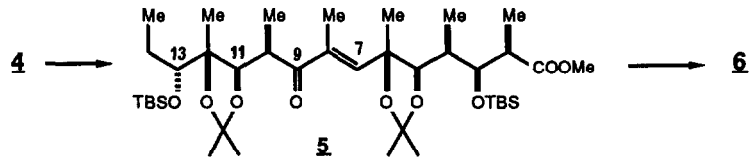


Fig. 1

sary hydroxyl group at C_7 was unsuccessful.[6] Thus, although the desired C_8-α-Me group was successfully introduced by the aldol condensation, **4** was converted into enone **5**[3] ($[\alpha]_D^{25}$ +7.7° (c 1.32, $CHCl_3$)) in 2 steps: 1. MsCl, DMAP/Pyr., RT.; 2. K_2CO_3/MeOH, RT. (84% from **4**) and its catalytic hydrogenation was examined. When enone **5** was hydrogenated in EtOH using 10%-Pt on C as a catalyst, **6** having the C_8-α-Me group[7] was obtained after SiO_2 chromatography in 91% yield with remarkably high stereoselectivity (35:1).



A plausible explanation is as follows. The preferred conformers of enone **5** may be illustrated as **5a** and **5b** having s-trans and s-cis geometries from the NMR data.[8] On catalytic hydrogenation, the active site of catalyst surface may initially coordinate with the s-cis enone **5b**[9] preferentially giving the transition state **5c**, then hydrogen attacks from the β-side giving the α-Me derivative **6** since the α-side is highly hindered by the bulky X [-CH(Et)OTBS] group. 1,4-Hydrogen addition should also take place since formation of enol **7**[10] having the partial structure shown in Fig. 2[11] was observed by TLC monitoring during hydrogenation.[12] Protonation to the enol in **7** again takes place from the less hindered β-side producing **6**.

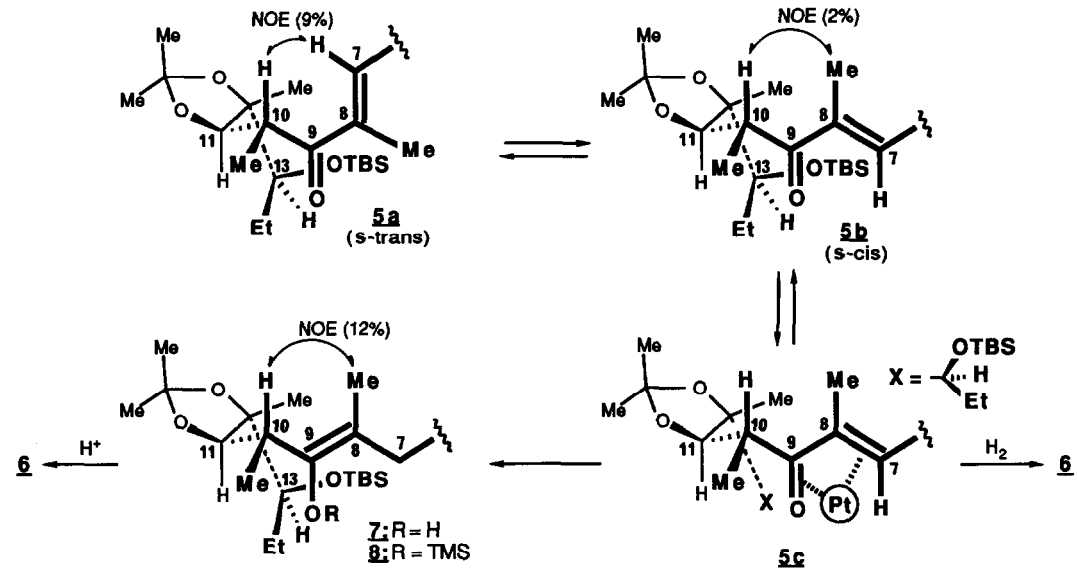
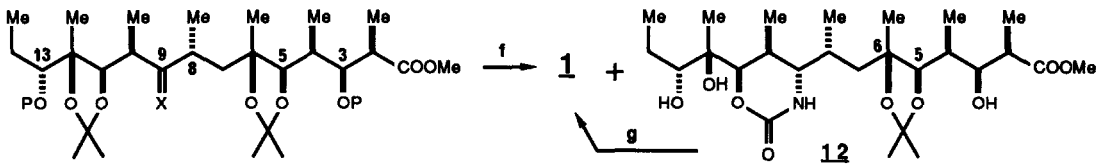


Fig. 2

Ketone **6** was reduced with $Zn(BH_4)_2$ in ether (0°C→RT.) providing C_9-β-OH derivative **9** (40:1, 95% yield).[13] Conversion of the C_9-β-OH into C_9-α-N_3 was achieved by 2 steps (mesylation; LiN_3 treatment),[14] giving **10** (mp 116-7°, $[\alpha]_D^{25}$ +2.6°(c 2.0, $CHCl_3$)).[3] Carbamate **11** (Ar=p-NO_2-Ph) was obtained in 3 steps from **10** (desilylation by n-Bu_4NF; reduction of azide

into amino group; and carbamate formation). Hydrolysis of the two acetonide groups was effected by treating **11** with 48%-HF/CH_3CN (1:9) at RT. for 2-3h.[15] Addition of Et_3N induced the cyclic carbamate formation producing the desired carbamate **1**[3] (mp 166-7°, recrystallized from acetone, 49% from **11**; lit.,[14] mp 164.5-165.5°) together with its $C_{5,6}$-acetonide **12** (22%), which could be converted into **1** by using the same hydrolysis conditions as noted above (46% yield, 63% conversion). IR and NMR (500MHz) spectra of our synthetic compound **1** were found to be identical[16] with those of the authentic sample prepared by Woodward et al.[14]



a, b → **9**: X = α-H, β-OH; P = TBS
c, d, e → **10**: X = α-N_3, β-H; P = TBS
11: X = α-$NHCO_2Ar$, β-H; P = H

Reagents and conditions: a. MsCl, DMAP/Pyr., RT. (98%); b. LiN_3/HMPA, 60°(84%); c. n-Bu_4NF/THF, RT. (90%); d. H_2, PtO_2/THF, RT.; e. ClCOOAr, aq. $NaHCO_3$/CH_2Cl_2, RT. (93% for 2 steps); f. 48%-HF/CH_3CN(1:9), RT., then Et_3N, RT.; g. 48%-HF/CH_3CN(1:9), RT.

REFERENCES AND NOTES

1) S. Masamune, J. W. Ellingboe, and W. Choy, J. Am. Chem. Soc., **104**, 5526 (1982) and references cited therein. Also see: S. Masamune and W. Choy, Aldrichimica Acta, **15**, 47 (1982); S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, Angew. Chem. Int. Ed. Engl., **24**, 1 (1985).

2) The other transition state **ii** (Fig. 1) leading to the 7,8-syn-adduct having C_7-β-OH and C_8-β-Me can be ignored since an approach of the lithium enolate of **2** from the upper side of the aldehyde in **3** is severely resisted by the C_6-Me group.

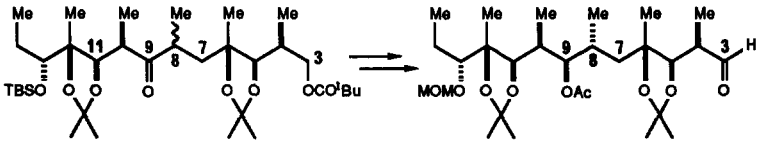
3) The structure of each new compound was confirmed by IR, ^{1}H-NMR (400 or 500MHz) spectra, and elemental analysis (C, H, and N).

4) Although syn-relationship between the $C_{7,8}$ substituents is evident from the small coupling constant ($J_{7,8}$=3.7 Hz),[5] their absolute configurations (C_7-α-OH, C_8-α-Me) were assigned by taking into account of the transition state geometry. See discussions noted in ref. 2. Direct evidences to support these assignments were provided by a physico-chemical study of a model system, which will be reported elsewhere.

5) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, J. Am. Chem. Soc., **95**, 3310 (1973); "Stereochemistry" Vol. 1, A. Gaudemer, M. Golfier, A. Mandelbaum, and R. Parthasarathy, "Determination of Configurations by Spectrometric Methods", Ed. by H. B. Kagan, Georg Thieme Publishers, Stuttgart, 1977, p. 69.

6) Reactivity of the hydroxyl group at C_7 to electrophiles was remarkably weak. Only acetylation and mesylation in the presence of DMAP proceeded.

7) The α-configuration of C_8-Me of **6** was deduced from the results of the model experiments. In model experiments, a mixture of **13a** and **13b** was obtained by hydrogenation of the corresponding enone in a ratio of 18:1. The main product was converted into **14**, whose IR and NMR (90MHz) spectra were found to be identical with the reported spectral data of the authentic sample prepared by Woodward et al.,[14] establishing the α-configuration of the C_8-Me group of the catalytic hydrogenation product **13a**. The authors are grateful to Dr. Takeshi Shimizu of this Institute for recording 90MHz-NMR spectrum of the compound **14**.



13a,b [a: C_8-α-Me; b: C_8-β-Me] 14

8) The signal of C_7-H appears at the lower field (δ 6.62) eliminating the presence of the cis enone structure. Enhancement of C_7-H (9%) and C_8-Me (2%) signals was observed upon irradiation of C_{10}-H showing that C_{10}-H is located in the same plane with the enone system. A large coupling constant between C_{10}-H and C_{11}-H ($J_{10,11}$=9.3 Hz) shows that C_{10}-H is anti-coplaner with C_{11}-H. The authors are grateful to Ms. Tamiko Chijimatsu for NOE experiments of 5 and 8.

9) The conformer s-trans 5a may be converted into s-cis 5b as s-cis 5b is transformed to 5c and thus all of 5a is eventually converted into 5c.

10) When the crude hydrogenation product was treated with TMS-OTf in the presence of 2,6-lutidine in CH_2Cl_2, TMS-enol ether 8 was obtained in addition to ketone 6 (the ratio of 8 to 6 is ca. 1:1). 8 is not produced by the same conditions from ketone 6. In model experiments, the enol (one isomer) was also produced along with a mixture of ketones 13a,b by the hydrogenation of the corresponding enone. In this case, the enol remained unchanged during measurements of IR and NMR spectra [IR($CHCl_3$): 3300, 1670, 890 cm^{-1}; NMR ($CDCl_3$, 400MHz): δ 7.67 (s, disappears by D_2O addition, OH), 4.01 (d, J=9.8 Hz, C_{11}-H), 1.77 and 2.50 (each d, J=14.7 Hz, C_7-CH_2), 1.65 (s, C_8-Me)].

11) A large enhancement of C_8-Me signal (12%) in 8 was observed upon irradiation of C_{10}-H. A large coupling constant between C_{10}-H and C_{11}-H ($J_{10,11}$=8.8 Hz) was also observed.

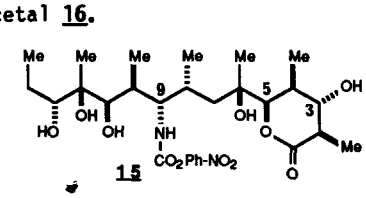
12) Exclusive formation of trans TMS-enol ether 8 may support the intermediacy of the s-cis-transition state 5c.

13) The reduction should proceed through the zinc-mediated chelated transition state involving the C_9- and C_{11}-oxygen atoms. It is noteworthy that the excellent selectivity (40:1) was obtained even in the reduction of the ketone not conjugated with an unsaturated group. In the previous experiments, excellent results were obtained only in the reduction of the conjugated ketones in the corresponding systems, see: T. Nakata, Y. Tani, M. Hatozaki, and T. Oishi, Chem. Pharm. Bull., 32, 1411 (1984); T. Oishi and T. Nakata, Acc. Chem. Res., 17, 338 (1984).

14) R. B. Woodward et al., J. Am. Chem. Soc., 103, 3210, 3213, and 3215 (1981).

15) Woodward's conditions (NH_2OH·HCl, KH_2PO_4/aq. MeOH, reflux) used in the hydrolysis of acetonides in the related compound (C_{13}-OMOM derivative) gave only unidentified products in our case. This decomposition may be induced by an attack of free alcohol at C_{13} on the spacially closely located active carbamate group (see Fig. 2) at the early stage of the reaction. Moreover, formation of δ-lactone 15 should be avoided. Thus, 48%-HF in CH_3CN, a rather weak acid, was used and the reaction was stopped when formation of 15 began to take place. δ-Lactone 15 has been reported to be an exclusive product under the usual acid hydrolysis conditions. See a footnote of ref. 14.

16) The structure 1 was also confirmed by comparing IR and NMR (500MHz) spectra of a cyclic acetal 16 derived from 1 with those of the authentic sample. The authors are grateful to Professor P. Deslongchamps for providing authentic samples of cyclic carbamate 1 and its $C_{3,5}$-acetal 16.



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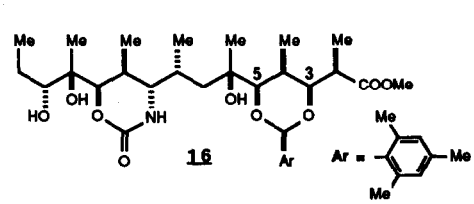

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