

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

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Summary: The key intermediate **1** in Woodward's total synthesis of erythromycin A was synthesized via coupling of the C₁-C₇ and C₈-C₁₅ 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 **2**-enolate of **2** and aldehyde **3** is presumed to proceed through the transition state **I** (Fig. 1) where Li⁺ is coordinating with three oxygen atoms^{1,2} resulting in the formation of 7,8-*syn*-adduct **4** having the C₇- α -OH and C₈- α -Me groups. In fact, (Me₂PhSi)₂NLi¹ 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} ([α]_D²⁵ +10.4° (c 1.7, CHCl₃)) 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-

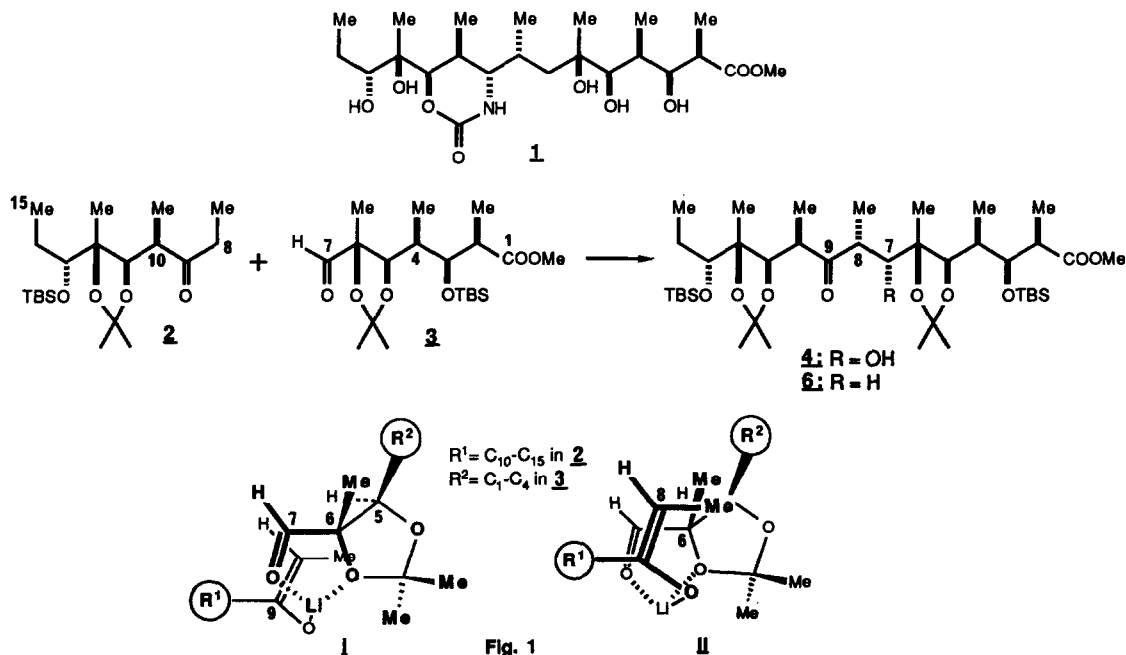
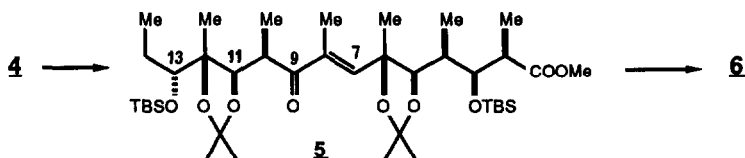


Fig. 1

sary hydroxyl group at C₇ was unsuccessful.⁶ Thus, although the desired C₈- α -Me group was successfully introduced by the aldol condensation, **4** was converted into enone **5**³ ($[\alpha]_D^{25} +7.7^\circ$ (c 1.32, CHCl₃)) in 2 steps: 1. MsCl, DMAP/Pyr., RT.; 2. K₂CO₃/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 C₈- α -Me group⁷ was obtained after SiO₂ 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. 2¹¹ 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**.

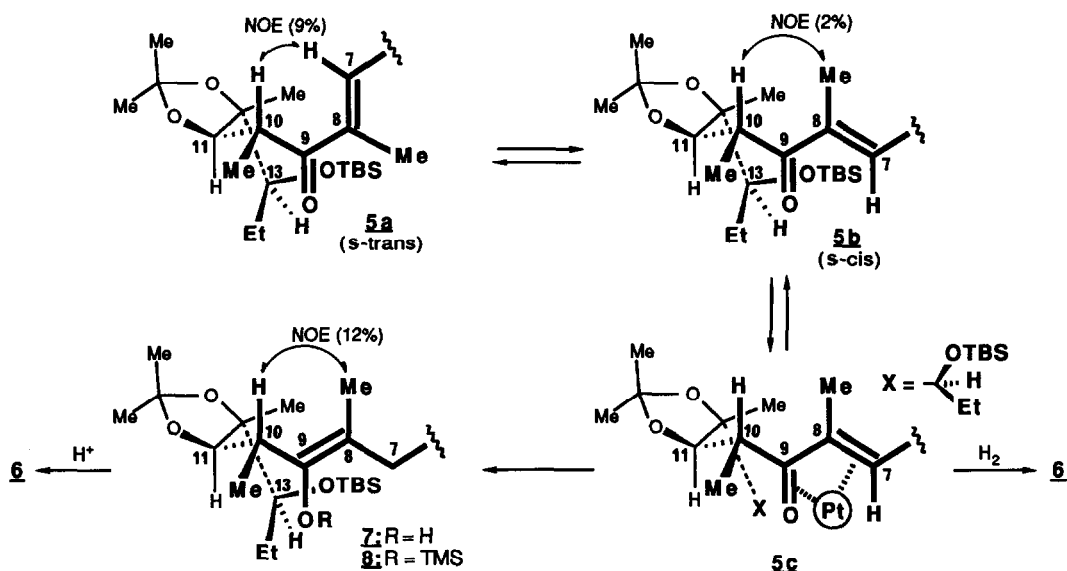
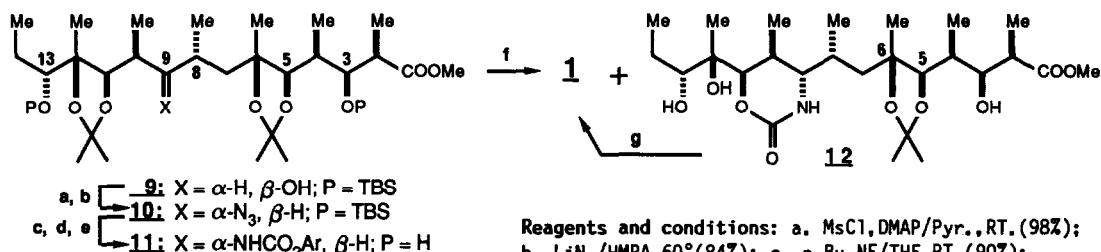


Fig. 2

Ketone **6** was reduced with Zn(BH₄)₂ in ether (0°C-RT.) providing C₉- β -OH derivative **9** (40:1, 95% yield).¹³ Conversion of the C₉- β -OH into C₉- α -N₃ was achieved by 2 steps (mesylation; LiN₃ treatment),¹⁴ giving **10** (mp 116-7°, $[\alpha]_D^{25} +2.6^\circ$ (c 2.0, CHCl₃)).³ Carbamate **11** (Ar=p-NO₂-Ph) was obtained in 3 steps from **10** (desilylation by n-Bu₄NF; reduction of azide

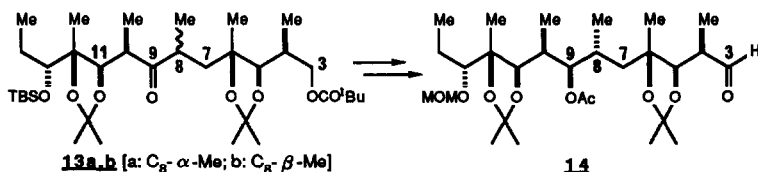
into amino group; and carbamate formation). Hydrolysis of the two acetonide groups was effected by treating **11** with 48% $\text{HF}/\text{CH}_3\text{CN}$ (1:9) at RT. for 2-3h.¹⁵ Addition of Et_3N induced the cyclic carbamate formation producing the desired carbamate **13** (mp 166-7°, recrystallized 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 identical¹⁶ with those of the authentic sample prepared by Woodward et al.¹⁴



Reagents and conditions: a. MsCl , DMAP/Pyr., RT. (98%); b. LiN_3/HMPA , 60° (84%); c. $n\text{-Bu}_4\text{NF}/\text{THF}$, RT. (90%); d. H_2 , PtO_2/THF , RT.; e. ClCOOAr , aq. $\text{NaHCO}_3/\text{CH}_2\text{Cl}_2$, RT. (93% for 2 steps); f. 48% $\text{HF}/\text{CH}_3\text{CN}$ (1:9), RT., then Et_3N , RT.; g. 48% $\text{HF}/\text{CH}_3\text{CN}$ (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 C₇- β -OH and C₈- 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 C₆-Me group.
- 3) The structure of each new compound was confirmed by IR, ¹H-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 (C₇- α -OH, C₈- 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 C₇ to electrophiles was remarkably weak. Only acetylation and mesylation in the presence of DMAP proceeded.
- 7) The α -configuration of C₈-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 C₈-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**.



- 8) The signal of C₇-H appears at the lower field (δ 6.62) eliminating the presence of the cis enone structure. Enhancement of C₇-H (9%) and C₈-Me (2%) signals was observed upon irradiation of C₁₀-H showing that C₁₀-H is located in the same plane with the enone system. A large coupling constant between C₁₀-H and C₁₁-H ($J_{10,11}$ =9.3 Hz) shows that C₁₀-H is anti-coplanar with C₁₁-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 CH₂Cl₂, 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(CHCl₃): 3300, 1670, 890 cm⁻¹; NMR (CDCl₃, 400MHz): δ 7.67 (s, disappears by D₂O addition, OH), 4.01 (d, J =9.8 Hz, C₁₁-H), 1.77 and 2.50 (each d, J =14.7 Hz, C₇-CH₂), 1.65 (s, C₈-Me)].
- 11) A large enhancement of C₈-Me signal (12%) in **8** was observed upon irradiation of C₁₀-H. A large coupling constant between C₁₀-H and C₁₁-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 C₉- and C₁₁-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 (NH₂OH·HCl, KH₂PO₄/aq. MeOH, reflux) used in the hydrolysis of acetonides in the related compound (C₁₃-OMOM derivative) gave only unidentified products in our case. This decomposition may be induced by an attack of free alcohol at C₁₃ on the spatially 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 CH₃CN, 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**.

