Tetrahedron Letters,Vol.29,No.18,pp 2219-2222,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A FORMAL TOTAL SYNTHESIS OF ERYTHROMYCIN A. 1. FACILE AND STEREOSELECTIVE SYNTHESES OF ERYTHRONOLIDE A SEGMENTS BASED ON ACYCLIC STEREOCONTROL

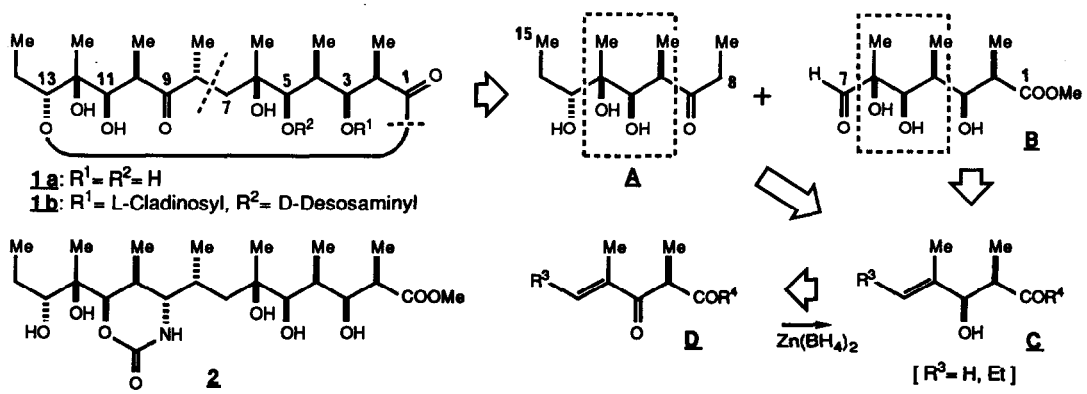
Tadashi Nakata,* Mineo Fukui, and Takeshi Oishi*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351-01, Japan

Summary: Two segments, corresponding to the C_1-C_7 and C_8-C_{15} parts of erythronolide A, were synthesized stereoselectively from the optically active syn-α-methyl-β-hydroxy imides prepared by $Zn(BH_4)_2$ reduction of the corresponding β-keto imides.

Recently, syntheses of erythronolide A (1a) and even erythromycin A (1b) itself have been achieved by several groups.[1] We have also engaged in the synthesis of this unique macrolide antibiotics and now report an efficient synthesis of the key intermediate carbamate 2 in Woodward's total synthesis[1b] of erythromycin A, which constitutes a formal total synthesis of erythromycin A (1b).

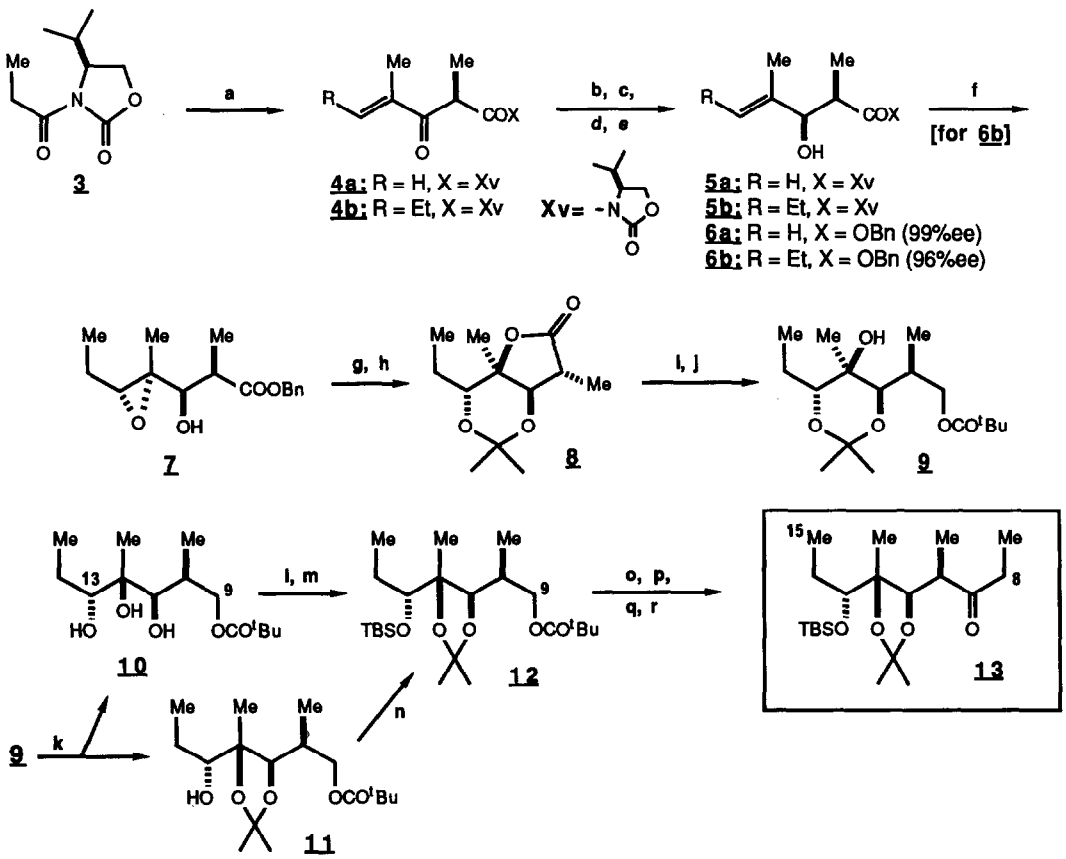
Erythronolide A (1a) can be divided into two segments A and B involving the same array of chiral centers, which means that once the method for the synthesis of A is established, the same sequence of reactions can be applied for the synthesis of B. The strategy of the present synthesis was set up by taking into accounts of the above consideration. The synthetic schemes for A and B have been designed premising to use syn-α-Methyl-β-hydroxy esters C (R^4=OBn) as starting materials, since C have already been synthesized stereoselectively by the reduction of the corresponding β-keto esters D (R^4=OBn) with $Zn(BH_4)_2$.[2] The main drawback of this reductive method that the syntheses of optically active D, and hence C, are difficult was overcome by the remarkable findings by Evans[3] and Yamaguchi[4] that α-methyl-β-keto imides or amides D (R^4=oxazolidone or amine) could be obtained as an optically active form.

In this paper, effective syntheses of two segments corresponding to A and B are described[5] and in the accompanying paper, a convergent synthesis of carbamate 2 from the two segments will be reported.



β-Keto imides **4a**[6] (mp 104-5°) and **4b**[6] (mp 40-2°), obtained by applying Evans' method,[3] were reduced with $Zn(BH_4)_2$ in CH_2Cl_2 at -20→-10°C producing β-hydroxy imides **5a**[6] (mp 89-90°) and **5b**[6] (mp 58-9°) with high stereoselectivity (>30:1).[7] After protection of hydroxyl group with ethoxyethyl group,[8] the chiral auxiliary was replaced by benzyloxy group[9] affording, after deprotection of hydroxyl group, the esters **6a**[6] ($[\alpha]_D^{25}$ +18.3°(c 1.62, $CHCl_3$)) and **6b**[6] ($[\alpha]_D^{25}$ +16.5°(c 2.08, $CHCl_3$)) having high optical purity.[10]

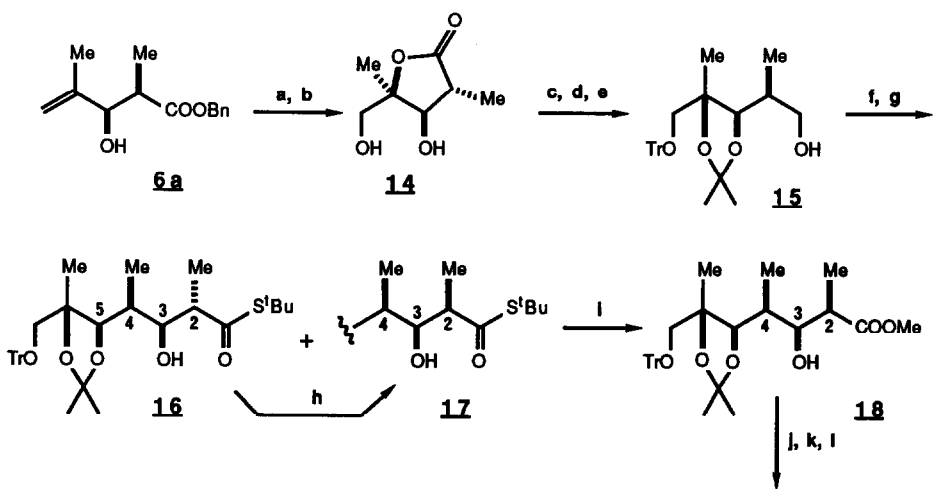
$VO(acac)_2$ catalyzed epoxidation[11] of **6b** proceeded mostly from α-face (13:1) giving α-epoxide **7**. The subsequent hydrogenolysis of benzyl group gave the corresponding carboxylic acid, which attacked the epoxide exclusively from the β-side giving γ-lactone in excellent yield. After the diol group had been protected with acetonide, the resulting lactone **8**[6,12] (mp 65-6°) was successively treated with $LiAlH_4$ and pivaloyl chloride affording **9**. p-TsOH treatment of **9** in 90%-MeOH afforded triol **10**[6] (mp 55-6°, 50% from **8**) together with the



Reagents and conditions: a. 1) LDA/THF,-78°C; 2) R-CH=C(Me)-COCl(reverse addition),-78°C(**4a**: 53%; **4b**: 90%); b. $Zn(BH_4)_2/CH_2Cl_2$,-20→-10°C(**5a**: 69%; **5b**: 81%); c. $EtOCH{=}CH_2$,PPTS/CH_2Cl_2,RT.; d. $PhCH_2OLi$/THF,-20→0°C; e. PPTS/EtOH,50°C(**6a**: 78% for 3 steps; **6b**: 47% for 3 steps); f. t-BuOOH,$VO(acac)_2$/toluene,-20→0°C; g. H_2,10%Pd-C/MeOH,RT.; h. $Me_2C(OMe)_2$,CSA/CH_2Cl_2,RT. (84% for 3 steps); i. $LiAlH_4$/ether,0°C; j. t-BuCOCl/Pyr.,RT.; k. TsOH/aq.MeOH,RT.,3 days(**10**: 50% for 3 steps; **11**: 40% for 3 steps); l. TBS-Cl,imidazole/DMF,RT.(92%); m. $Me_2C(OMe)_2$,CSA/CH_2Cl_2(100%); n. TBS-OTf,2,6-lutidine/CH_2Cl_2,RT.(96%); o. KOH/MeOH-ether,RT.(100%); p. DMSO-$(COCl)_2$,Et_3N/CH_2Cl_2,-78°C; q. EtMgBr/ether,0°C; r. PDC,MS-4A/CH_2Cl_2,RT.(89% for 3 steps).

rearranged five-membered acetonide **11**[6] (an oil, 40% from **8**). The fully protected **12** was obtained from **11** by simple silylation. **12** could also be synthesized by a regioselective silylation of C_{13}-OH[13] of **10** followed by five-membered acetonide formation. Synthesis of a left half segment **13**[6] ($[\alpha]_D^{25}$ +30.5°(c 1.50, $CHCl_3$)), corresponding to the C_8–C_{15} part of erythronolide A, was accomplished by 4 steps from **12**: 1. hydrolysis of pivaloyl ester; 2. Swern oxidation[14a]; 3. addition of EtMgBr; and 4. PDC oxidation into ethyl ketone.

Then, the synthesis of the right half segment **19** was investigated. Lactone-diol **14**[6] (mp 106–7°, $[\alpha]_D^{25}$ +26.8°(c 1.28, $CHCl_3$); lit.,[15] mp 106–106.5°, $[\alpha]_D^{26}$ +26.8°(c 0.91, $CHCl_3$)), prepared from **6a** in a similar manner as described in the synthesis of the left half segment was mono-protected by trityl group and then reduced with $LiBH_4$ in refluxing THF. The resulting triol was treated with PPTS-$CuSO_4$ in acetone giving the five-membered acetonide **15**[6] selectively. The primary alcohol in **15** was converted into aldehyde by Swern oxidation[14a] and condensed with t-butylthio ester[1b] gave 2,3-anti-adduct **16**[6] (mp 176–7°) as the main product together with a small amount of 2,3-syn-adduct **17**. This procedure is practically useful because the products having the desired 3,4-syn configuration are formed exclusively. 2,3-anti-Product **16** can then be isomerized into the 2,3-syn-derivative **17** by kinetically controlled protonation.[1b] Sodium methoxide treatment of **17** gave the desired 2,3,4-all-syn-compound **18**[6,16] (mp 88–9°) in excellent combined yield (64% from **15**, 4 steps). Synthesis of a right half segment **19**[6] ($[\alpha]_D^{25}$ -12.2°(c 1.25, $CHCl_3$)) from **18** was achieved by the following simple operations: 1. silylation of C_3-OH; 2. removal of trityl group by hydrogenolysis; and 3. Swern oxidation using trifluoroacetic anhydride.[14b]

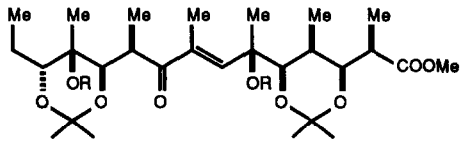


Reagents and conditions: a. t-BuOOH, $VO(acac)_2$/toluene, -20→0°C; b. H_2, 10%Pd-C/MeOH, RT.(83% for 2 steps); c. Tr-Cl, DMAP/Pyr., 50°C; d. $LiBH_4$/THF, reflux; e. PPTS, $CuSO_4$/acetone, RT.(68% for 3 steps); f. DMSO-$(COCl)_2$, Et_3N/CH_2Cl_2, -78°C; g. EtCOSt-Bu, LDA/THF, -100°C(**16**: 75% for 2 steps; **17**: 13% for 2 steps); h. t-BuLi, TMEDA/THF, -100°C then AcOH, -100°C(94%, **16**:**17**=1:9); i. NaOMe/MeOH, RT.(84%); j. TBS-OTf, 2,6-lutidine/CH_2Cl_2, RT.(100%); k. 20%$Pd(OH)_2$-C/MeOH, RT.(89%); l. DMSO-$(CF_3CO)_2O$, Et_3N/CH_2Cl_2, -78°C(90%).

REFERENCES AND NOTES

1) a) E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, and J. R. Falck, J. Am. Chem. Soc., **101**, 7131 (1979); b) R. B. Woodward, et al., J. Am. Chem. Soc., **103**, 3210, 3213, and 3215 (1981); c) B. Bernet, P. M. Bishop, M. Caron, T. Kawamata, B. L. Roy, L. Ruest, G. Sauve, P. Soucy, and P. Deslongchamps, Can. J. Chem., **63**, 2810, 2814, and 2818 (1985); d) M. Kinoshita, M. Arai, K. Tomooka, and M. Nakata, Tetrahedron Lett., **27**, 1811 (1986); M. Kinoshita, M. Arai, N. Ohsawa, and M. Nakata, ibid., **27**, 1815 (1986); e) G. Stork and S. D. Rychnovsky, J. Am. Chem. Soc., **109**, 1565 (1987); f) H. Tone, T. Nishi, Y. Oikawa, M. Hikota, and O. Yonemitsu, Tetrahedron Lett., **28**, 4569 (1987).

2) T. Nakata and T. Oishi, Tetrahedron Lett., **21**, 1641 (1980). We have also succeeded in a synthesis of erythronolide A seco-acid derivative i as a racemic form from racemic C (R^4=OBn), see: T. Nakata, Y. Tani, and T. Oishi, The 4th International Conference on Organic Synthesis (IUPAC) at Tokyo, Aug. **1982**, Abstracts of Papers, p. 78; T. Oishi and T. Nakata, Acc. Chem. Res., **17**, 338 (1984).



i (R = Bn)

3) D. A. Evans, M. D. Ennis, T. Le, N. Mandel, and G. Mandel, J. Am. Chem. Soc., **106**, 1154 (1984).

4) Y. Ito, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., **25**, 6015 (1984).

5) A part of this work was presented at the 106th Annual Meeting of the Pharmaceutical Society of Japan at Chiba, April **1986**, Abstracts of Papers, p. 402.

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

7) cf. T. Nakata, S. Nagao, and T. Oishi, Tetrahedron Lett., **25**, 6465 (1985).

8) Without protection of a hydroxyl group, a considerable extent of racemization of the resulting β-hydroxy benzylester was observed, which would be caused by alcoxide mediated retro-aldol reaction followed by recondensation.

9) D. A. Evans, M. D. Ennis, and D. J. Mathre, J. Am. Chem. Soc., **104**, 1737 (1982).

10) The enantiomeric purities were determined via the Mosher ester technique, see: J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., **34**, 2543 (1969).

11) K. B. Sharpless and R. C. Michaelson, J. Am. Chem. Soc., **95**, 6136 (1973).

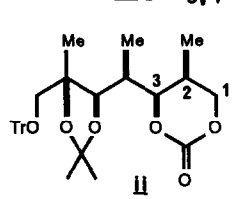
12) One recrystallization from hexane gave optically pure 8. Optical purity was checked by 400MHz ^{1}H-NMR spectrum of the (+)-MTPA ester of C_9-OH derived from 12 (>99%ee).

13) The numberings are based on that of 1 for convenience.

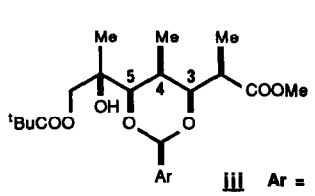
14) a) A. J. Mancuso, S. -L. Huang, and D. Swern, J. Org. Chem., **43**, 2480 (1978); b) S. -L. Huang, K. Omura, and D. Swern, Synthesis, 297 (1978).

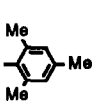
15) P. A. McCarthy, Tetrahedron Lett., **23**, 4199 (1982). The synthesis of the racemate of 14 (mp 64-5°) has been accomplished by us in the same method as described here. This work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan at Tokyo, April **1980**, Abstracts of Papers, p. 123.

16) Stereochemistry of the compound 18 was confirmed by conversion of 18 into cyclic compounds ii ($J_{2,3}$= 2.8 Hz) and iii ($J_{3,4}$=$J_{4,5}$= 2.1 Hz).



ii



iii Ar = 

(Received in Japan 12 February 1988)