총 설

Stereoselective Routes to Erythronolide A Seco Acid

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Erythronolide A 開發의 光學選擇的인 合成方法

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Abstract : Stereoselective synthetic efforts for erythronolide A seco acid are reviewed from the first discovery of erythromycin A in 1952 up to the end of 1990. The synthetic strategies for construction of ten asymmetric centers embedded in an aglycone of erythramycin A have mostly been realized by the stereoselective preparation of the key fragments followed by coupling them. The synthetic methods employed for the key fragments can be classified into three categorie; a carbohydrate approach, a cyclic approach and an acyclic approach. The coupling has largely been reduced to practice by either aldol-type additions or Wittig olefinations of the key fragments.

요   약

　1952 년에 최초로 erythromycin A 를 분리한 이래, 이의 aglycone(erythronolide)의 開酸을 광학선택적으로 합성하고자 하는 연구결과들을 1990년 말까지 요약하여 소개한다. 이 開酸에 존재하는 10 개의 비대칭 center 들을 구축하기 위한 합성전략은 開酸의 대칭성을 이용, 공통되는 부분을(key fragments) 합성하여 결합하므로써 이루어져 왔다. 이 공통되는 부분을(key fragments) 제조하는 방법들은 크게 세 범위로 나눌수 있다. 첫째, 탄수화합물을 이용하는 방법, 둘째, 중간체로서 고리화합물을 이용하는 방법, 셋째, 비고리화합물에 있어서의 선택성을 이용하는 방법. 이 공통되는 부분을 결합하는 방법으로서는 거의 대부분이 aldol 형태의 결합방법이나 Wittig 형태의 이중결합반응을 이용하는 형식들이 사용되어 왔다.

1. INTRODUCTION

Erythromycin A 1a was first isolated from a strain of *Streptomyces erythraeus* in 1952 as a major compo-nent of the erythromycins which contained two other minor components, erythromycin B 1b and erythrom-ycin C 1c[2]. Erythromycin showed the strongest an-tibacterial activity in vitro among the macrolide anti-

biotics and is most frequently used for chemotherapy of infectious diseases caused by gram-positive bacteria and mycoplasmas. Erythromycin's potent biological activity results from the inhibition of the ribosomaldependent protein synthesis due to tight ribosomal binding of erythromycin[3]. There are six known erythromycins of biosynthetic origin including recently isolated erythromycin F[4], and they are all biologically active.

The structure of erythromycin A was studied by chemical degradation methods[5], which established the 14-membered macrocyclic lactone ring with ten asymmetric centers having two sugars attached at the C-3 and C-5 hydroxy groups of the aglycone. The structure and the stereochemistry of the two sugars were determined by chemical degradation[6], NMR analyses[7], and stereoselective syntheses[8]. An amino sugar, D-desosamine is attached to C-5 and the other non-amino sugar, L-cladinose to the C-3 carbon atom(Fig. 1). Although the stereochemistry of some asymmetric centers of erythromycin A was determined by the degradation study[5], unambiguous assignment was made by X-ray analysis of an erythromycin A hydroiodide dihydrate salt[9]. The absolute stereochemistry of the aglycone, erythronolide A, was established to be $2R, 3S, 4S, 5R, 6R, 8R, 10R, 11R, 12S, 13R$ as shown in Fig. 1. The X-ray analysis also clearly showed the glycosidic linkages to be β for desosamine and α for cladinose, which revised the previous assignment of the β-linkage for cladinose[10].

The biosynthetic pathway of erythromycins was proposed by Martin et al. based on the blocking studies at various sites along the biosynthetic scheme [20]. 6-Deoxyerythronolide B derived from propionate was a common intermediate for all members of erythromycins(A through F). Oxidation of 6-deoxyerythronolide B at C-6 produced erythronolide B, which produced, in turn, erythromycin D 1d after incorporation of two sugars, mycarose at C-3 and desosamine at C-5 through 3-O-mycarosylerythronolide B. Methylation of the hydroxy group of mycarose of
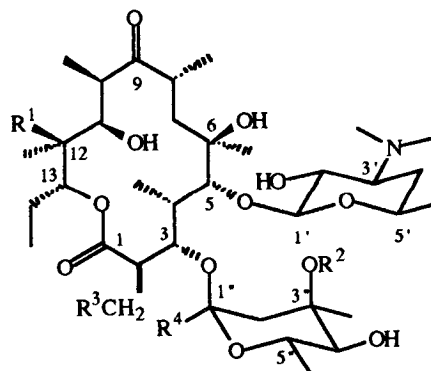
Erythromycins	R^1	R^2	R^3	R^4
A, 1a	OH	CH_3	H	H
B, 1b	H	CH_3	H	H
C, 1c	OH	H	H	H
D, 1d	H	H	H	H
E, 1e	OH	CH_3	OH	H
F, 1f	OH	CH_3	$-O-$	

Fig. 1. Erythromycins A∼F.

1d would produce erythromycin B 1b, while oxidation of 1d at C-12 would produce erythromycin C 1c. Erythromycin A 1a could be obtained from either oxidation of erythromycin B 1b at C-12 or methylation of the alcohol of mycarose of erythromycin C 1c. The proposed scheme was extended to recently isolated erythromycin E 1e via erythromycin F 1f and both of them were metabolites of erythromycin A. Erythromycin is commercially available from Sigma®($ 122.5/ 100 g).

The stereoselective synthesis of erythromycin A as well as the closely related erythromycin B has been one of most challenging synthetic targets because of their formidable stereochemical arrays and functional complexities, as indicated by the often-quoted remark by the late Professor R. B. Woodward, "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers..."[11]. The one and only total synthesis of erythromycin A by Woodward et al.[12] seems to imply the complicated problems in the synthesis of erythromycins with regard

to an efficient construction of the contiguous asymmetric centers. Therefore, these substances have served as a forum for the invention and development of new methods for asymmetric synthesis. As a corollary of these efforts, the powerful and versatile asymmetric aldol reaction methodology has emerged for an efficient construction of the polypropionate backbone present in the the erythronolides as well as other macrolide antibiotics.

In addition to an efficient construction of the ten contiguous stereocenters present in the seco acid of the macrolide, there have been other interests in the synthesis of the macrolide antibiotics: the study of the relationship between the conformation of various seco acid derivatives and their macrolactonization efficacy[13]. It has already been shown by Woodward et al.[12b] that certain structural features such as the S-configuration at C-9 and cyclic protecting groups at C-3/C-5 and C-9/C-11 are required for an efficient lactonization as in 2a(Fig. 2). The 9 S configuration is based on the fact that while the protection of 9 S-dihydroerythronolide 3a was readily achieved, such protection was unobtainable for the 9 R-lactone 3b. It is noteworthy, however, that the protection of alcohols at C-6, C-9, C-11 and C-12 with methoxymethyl group resulted in better yield with the 9 R-seco

acid derivative(15%) than with 9 S-seco acid derivative(10%) although the yield obtained was much lower than that with the cyclic protecting groups of the 9 S-seco acid derivative (70%).

Stork and Rychnovsky have found that the stereochemistry of an acetal-protecting group at C-9 and C-11 was critical in the macrolactonization reaction [14]. A seco acid with a9, 11 cyclic ketal 2d and a 9, 11 'A methylacetal' 2c failed to cyclize under Keck' s cyclization condition[15]. Only the 'B methylacetal' 2b underwent an efficient cyclization. An unfavorable 1,3-diaxial interaction between the R[2] group and the C-8 alkyl group seemed responsible for the unsuccessful cyclization as shown in Fig. 3.

Very recently, Yonemitsu et al. succeeded in an extremely efficient macrolactonization utilizing the proper protecting groups as well as a strong activation method for cyclization[13b]. Thus, cyclization of 2e under the modified Yamaguchi macrolactonization conditions(2,4,6-trichlorobenzoic acid mixed anhydride) [16] gave the 9 S-dihydroerythronolide A derivative in 98% yield ! This method made possible an efficient cyclization of macrocycles without resorting to the high dilution technique that had been typically used for the formation of macrolactones from their corresponding acyclic hydroxy acids[17]. Use of the proper

2a, R¹=R³=mesityl, R²=R⁴=H
  b, R¹=R³=R⁴=Me, R²=H
  c, R¹=H, R²=R³=R⁴=Me
  d, R¹=R²=R³=R⁴=Me
  e, R¹=mesityl, R³=3,4-dimethoxyphenyl, R²=R⁴= H

3a, R¹=R³=OH, R²=H
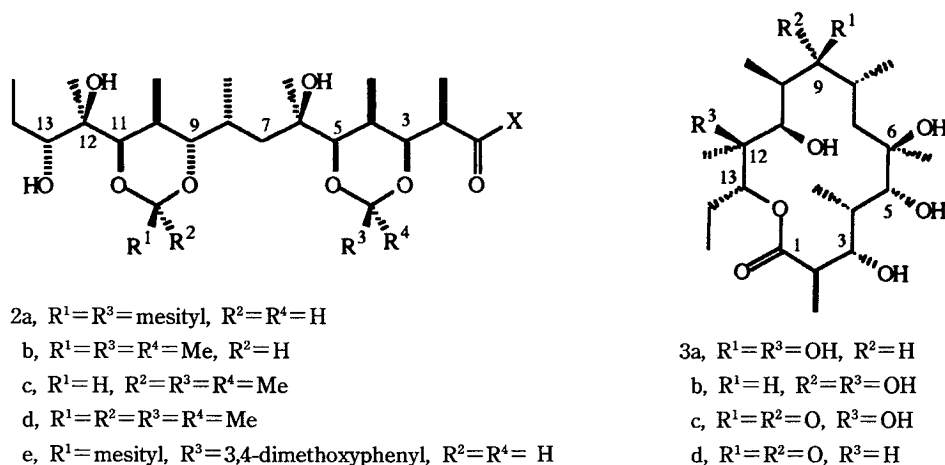 b, R¹=H, R²=R³=OH
  c, R¹=R²=O, R³=OH
  d, R¹=R²=O, R³=H

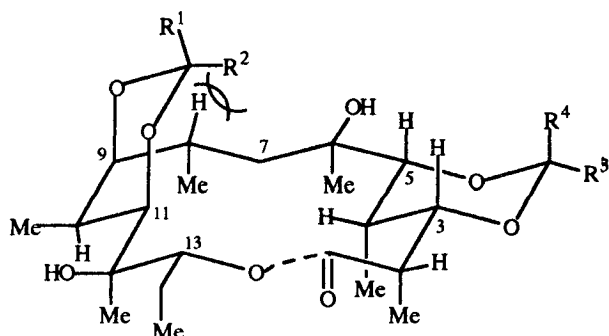Fig. 2. Erythronolide A and its 9-dihydroseco acid derivatives.

Fig. 3. Effect of the stereochemistry of protecting groups on the cyclization.

concentration of the catalyst, 4-dimethylaminopyridine (DMAP) seems to be important because the cyclization of 2a with the similar protecting groups under the Corey's cyclization conditions(thiopyridyl ester) afforded a 3a derivative in 70% yield[12b].

There has also been considerable interest to correlate the rate of lactonization with the conformation of the seco acid, which is determined by the configuration at each asymmetric center[13a]. Such investigations would require a versatile methodology to prepare a series of diastereomers of the seco acid for a systematic study.

2. SYNTHESIS OF ERYTHRONO-LIDE A AND B SECO ACIDS

Synthetic efforts for erythronolide A and B seco acids can be organized into two steps: (1) the synthesis of key fragments(the left-hand and right-hand portions) and (2) coupling of the two fragments into the seco acid chain. The strategies for the synthesis of the key fragments will be described first, and can be further divided according to the main synthetic methods employed to establish the required asymmetric centers as follows:

1. A carbohydrate approach: manipulating the inherent chiral centers of carbohydrate sources.
2. A cyclic approach: utilizing the rigid nature and the reactivity of cyclic intermediates.
3. An acyclic approach: controlling the asymmetric

induction in acyclic molecules with the chiral centers present in themselves(relative asymmetric induction) and/or some other chiral auxiliaries as induction sources(absolute asymmetric induction).

2. 1. Preparation of Key Fragments

2. 1. 1. Carbohydrate Approaches

In 1977, Hanessian and Rancourt recognized the similar pattern of substituents and their stereochemical relationships in the C-1 to C-6 and C-9 to C-15 chains of the erythronolide A seco acid 2 (X=OH, without the protecting groups)[21]. The C-1 to C-6 and C-9 to C-15 chains correspond to L-idose and D-glucose stereochemistry, respectively (Scheme 1). Methyl 2, 3-anhydro-4, 6-O-benzylidene-α-D-allopyranoside 4, readily available from D-glucose, was converted to a mixture of diastereomers 5a and 5b by utilizing the inherent stereochemical bias of 6-membered rings. While the C-9 to C-15 chain was obtained from 5a, inversion at C-5 of 5b was carried out to provide the C-1 to C-6 chain.

Kochetkov et al. also prepared the C-1 to C-6 and C-9 to C-15 segments from levoglucosan(1,6-anhydro-β-D-glucose) 6 (Scheme 2)[22]. The bicyclic nature of levoglucosan was exploited to introduce the methyl groups at C-2 and C-10 with an excellent regio-and stereoselectivity[23]. However, introduction of the other methyl group via Barton's deoxygenation procedure[47] was not selective and gave a 1 : 1 mixture of diastereomers 7 and 8. Each bicyclic acetal 7 and 8, after separation, was transformed into the open-chain dithiane derivatives, 9 and 10, respectively. Epimerization at C-5 of 9 then completed the synthesis of the two key segments.

A related synthesis was realized by Kinoshita et al[24]. Methyl 2,3-anhydro-4,6-benzylidene-α-D-mannopyranoside 11 in Scheme 3, prepared from D-glucose, was converted to bicyclic acetal 12, which acquired the correct stereochemistry at C-4 and C-5 through a rigid trans-fused [4.4.0] bicycle. The diastereofacial difference in the bicyclic compound was used

to direct hydrogenation at an olefin exclusively from the α face, which established the stereochemistry of the methyl group at C-2. The C-10 to C-13 fragment was prepared by successive additions of Grignard reagents to D-ribose derivatives.

Yonemitsu et al. prepared both the C-1 to C-5 and C-7 to C-15 fragments of erythronolide A from D-glu-cose (Scheme 4)[25]. Starting from diacetone D-glu-cose, the stereochemistry at both C-10 and C-11 of 14 was established by hydrogenation from the less hindered face of the [3.3.0] bicycle. Both hydroxy groups at C-12 and C-13 of 15 were then introduced simultaneously through a stereoselective osmylation of the Z-olefin. Interestingly, the observed sense of
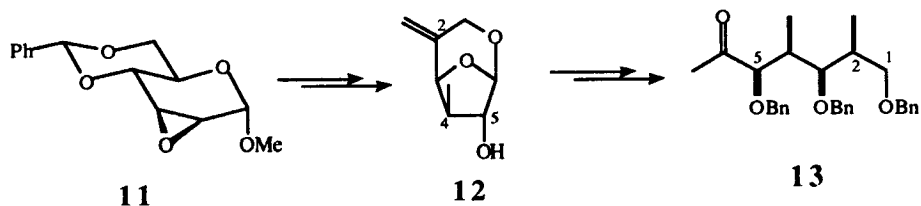
Scheme 1. The Synthesis of the C-1 to C-6 and C-9 to C-15 Fragments of Erythronolide A by Hanessian and Rancourt.

5a, R^1 = Me, R^2 = OMe
b, R^1 = OMe, R^2 = Me
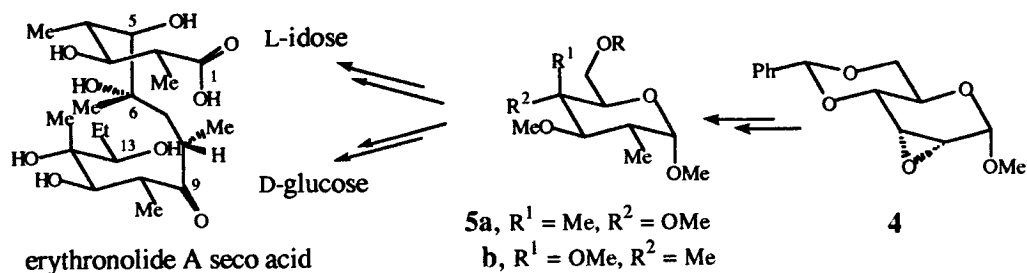
Scheme 2. The Synthesis of the C-1 to C-6 and C-9 to C-15 Fragments of Erythronolide B by Kochetkov et al.
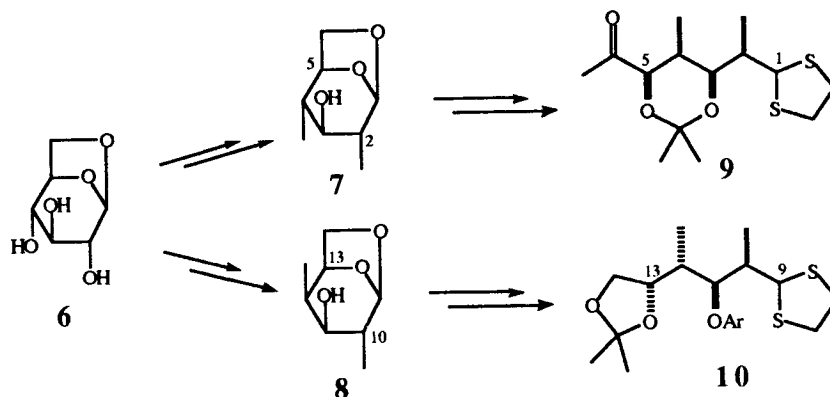
Scheme 3. The Synthesis of the C-1 to C-6 Fragment of Erythronolide A by Kinoshita et al.

asymmetric induction corresponded to the exceptions previously noted by Kishi et al. for Z-olefins[48]. Subsequent epoxidation at C-8 and C-9 with m-chloroperoxybenzoic acid and the selective epoxide opening with sodium cyanoborohydride in the presence of a Lewis acid afforded the left-hand fragment 16[26].

Wakamatsu et al. reported the synthesis of the two chiral segments of 6-deoxyerythronolide B by converting levoglucosan 6 to the acyclic chain, which is reminiscent of the methodology described by Kochetkov et al.(see Scheme 2). It is noteworthy that the ring opening of the terminal allylic epoxide of 17 with sodium cyanoborohydride in the presence of a Lewis acid resulted in the retention of stereochemistry at C-10 of 18 (Scheme 5).

2. 1. 2. Cyclic Approaches

In their first total synthesis of erythronolide A and B, Corey et al. utilized the cis-fused [4. 4. 0] bicyclic systems 20 for the stereoselective synthesis of the common intermediate 21 (Scheme 6)[28]. Two consecutive iodolactonizations of trienone 19 were used to set up three chiral centers at C-2, C-4 and C-5 of 21. Hydrogenation of a cis-fused bicyclic system 20 occurred stereoselectively to give the α-alcohol at C-3, and following methylation afforded the thermodynamically more stable product with the desired stereochemistry at C-8 of 21. Bayer-Villager oxidation of 21 inserted a hydroxy group at C-6 of the C-1 to C-9 intermediate with retention of stereochemistry. The C-10 to C-15 fragment was derived from the regioselective opening of epoxide 22 followed by hydrozirconation of a derivative of 23 to form the E-vinyl

iodide 24.

Woodward et al. also took advantage of the hidden symmetry in erythronolide A, and used the rigid dithiadecalin 25 to provide the common intermediate 26 for the two key moieties 27 and 28 (Scheme 7)[12]. The dithiadecalin 25 was derived from dehydration of the corresponding aldol adduct of 36% ee that was obtained from racemic starting materials with D-proline as catalyst. The homochiral 25 was obtained by crystallization. Both reduction and hydroxylation of 25 occurred stereoselectively from a less hindered side to afford four contiguous asymmetric centers of 26. A salient feature of this approach is to recognize the dithiadecalin system as an efficient asymmetric control as well as a methyl equivalent. This approach is reminiscent of the earlier synthesis of the juvenile hormone by Masamune et al[29].

Stork et al. recognized the structurally and stereochemically identical fragments 32 and 33 of a 9R-seco acid derivative with an exception that asymmetric centers at the C-2 and C-8 were antipodal (Scheme 8)[30a]. Hydroxy-directed epoxidation of (1 S, 2 S)-(+)-2-methyl-3-cyclopenten-1-ol gave epoxide 29 as a single isomer. After the regioselective epoxide opening, the conjugate addition of lithium dimethyl cuprate to the cyclopentenone intermediate was controlled by a bulky silyl protecting group (TBS, tert-bytyl-dimethylsilyl) to furnish 30. An additional chiral center at C-5 of 32 was established through epimerization. The opposite stereochemistry at C-8 of 33 was acquired with hydrogenation of the cyclopentenone derived from 30 to give 31. Here again, the bulky silyl protecting group played an important role in controlling the
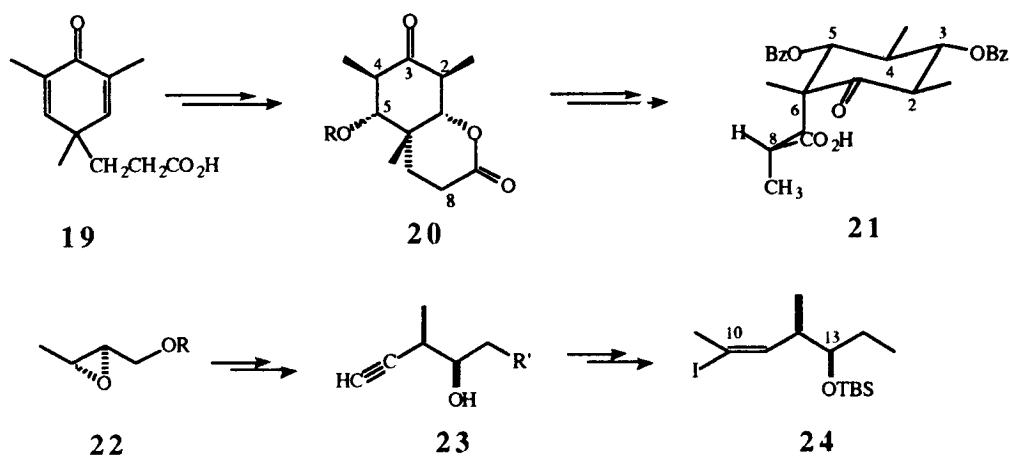
Scheme 4. The Synthesis of the C-7 to C-15 Fragment of Erythronolide A by Yonemitsu et al.

14   **15**   **16**
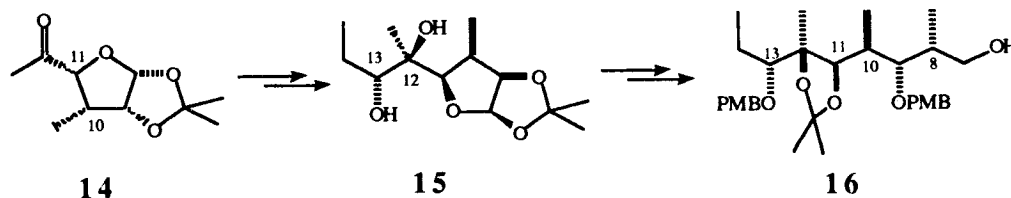
Scheme 5. The Synthesis of the C-9 to C-15 Fragment of Erythronolide B by Wakamatsu et al.

$^tBuC(O)O$ ⋯ OBn OH **17** → NaCNBH₃ / BF₃·Et₂O → $^tBuC(O)O$ 13 OBn OH 10 OH **18**
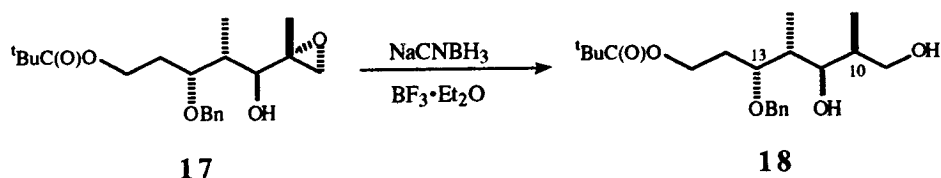
Scheme 6. The Synthesis of the C-1 to C-9 and C-10 to C-15 Fragments of Erythronolide B by Corey et al.

CH₂CH₂CO₂H **19**   RO 4 3 2 5 8 O O **20**   BzO 5 4 3 OBz 6 8 H CO₂H CH₃ **21**

OR 22   HC≡ R' OH **23**   I 10 13 OTBS **24**

asymmetric induction. Two successive aldoltype additions then completed the left-hand fragment 33. As was pointed out, inversion of the stereochemistry at C-9 would be required for the efficient macrolactonization.

Stock and Rychnovsky elaborated their efforts for the synthesis of 9 S-dihydroerythronolide A based on an iterative butenolide construction (Scheme 9)[30 b]. Dihydroxyfuranone 34[50] was manipulated into butenolide 35. Hydrogenation of the latter was controlled by a bulky substituent at C-11 to afford stereoselectively two additional asymmetric centers present in lactone 36. Another cycle of the butenolide elaboration led to the C-7 to C-15 fragment 38 with the desired 9 S-configuration.

Vedejs et al. prepared the C-1 to C-9 segment of erythronolide A during the course of their study to

identify conformational factors of medium- and large-ring alkenes (Scheme 10)[31]. The starting compound 40 (R=OH) was obtained with high selectivity by hydroboration of 39 followed by the oxidative workup. Subsequent three-carbon ring expansion of 40 afforded 41 with the E-olefin geometry. Osmium tetroxide oxidation of 41 gave 42 as a single isomer having the same stereochemistry of the C-2 to C-6 portion of erythro nolide A.

Deslongchamps et al. synthesized the whole skeleton of erythronolide A seco acid using the stereoelectronic as well as steric preferences of the 1,7-dioxaspiro [5.5] undecane system such as 45 (Scheme 11) [32]. The ketal 43 was prepared as a single isomer by stereoelectronically preferred addition of optically pure TMS-protected (R)-5-hexyn-3-ol to a racemic δ-valerolactone derivative. The correct stereochemistry
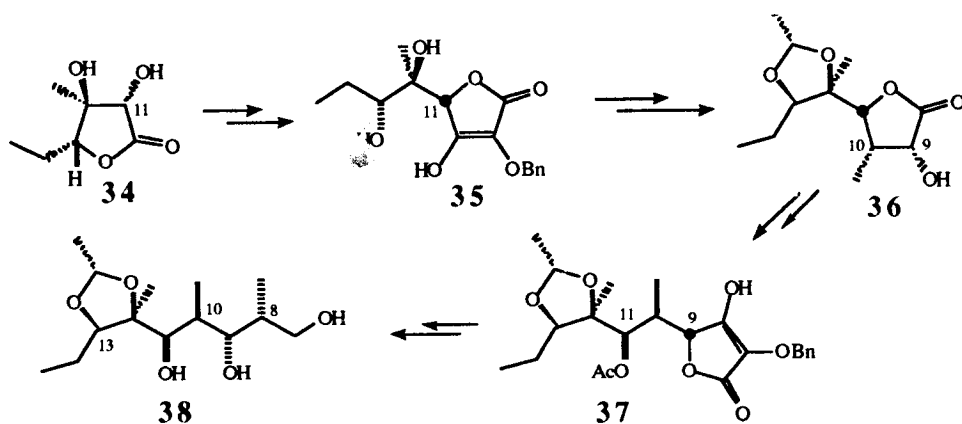
Scheme 7. The Synthesis of the C-3 to C-8 and C-9 to C-15 Segments of Erythronolide A by Woodward et al.
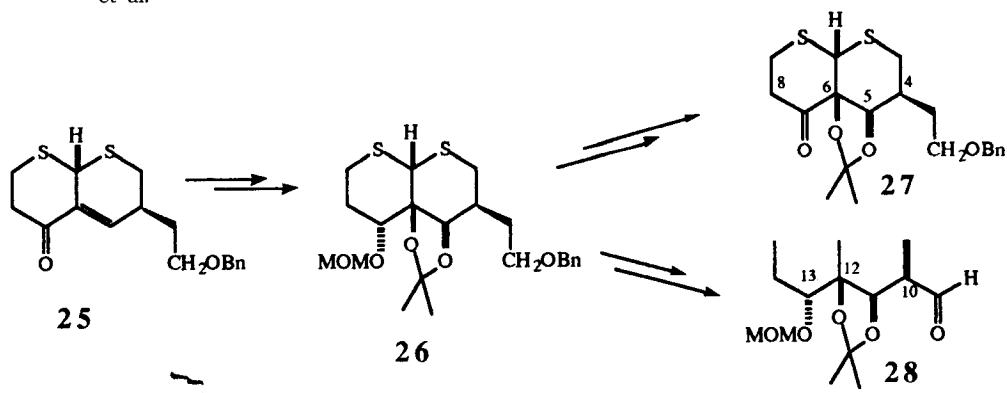
Scheme 8. The Synthesis of the C-1 to C-6 and C-7 to C-15 Segments of Erythronolide A by Stork et al.
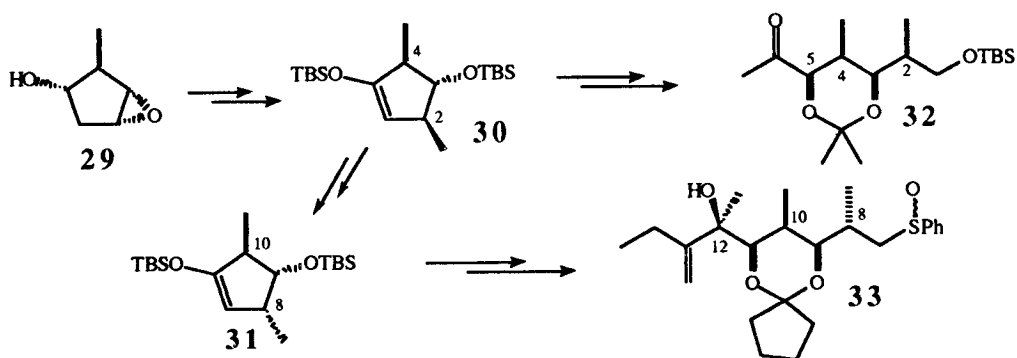
Scheme 9. The Synthesis of the C-7 to C-15 Chain of Erythronolide A by Stork and Rychnovsky.

at C-8 of 44 was established by equilibriation of the epimeric mixture derived from the cyclization of the hydrogenated 43. An allylic oxidation at C-12 of 44 followed by the stereoselective 1,4-addition to the resulting cyclohexenone intermediate introduced the methyl group at C-10. Subsequent quenching of the resulting enolate installed the hydroxy group at C-11, and addition of the Grignard reagent gave the desired chiral center at C-12 of 45. Four-carbon extension at C-5 completed the synthesis of the seco acid.

More recently, Martin et al. reported the synthesis of the C-1 to C-10 and C-11 to C-15 fragments in their synthesis of an erythronolide B seco acid derivative (Scheme 12)[33]. The homochiral furan 46 derived from an Evans aldol condensation[51,52] was treated with bromine in aqueous acetonitrile to give an intermediate, dihydroxy enedione, which underwent acid-catalyzed cyclization to give the bicyclic ketal 47. Two methyl groups were sequentially added to 47 from the less hindered face to afford 48 with high selectivity, which had the C-3 to C-10 backbone of erythronolide A and B. The remaining chiral centers at C-2 and C-3 were introduced by a Lewis-acid mediated aldol reaciton giving 49 as a major product (ca. 4 : 1). The C-11 to C-15 fragment was also prepared by an Evans aldol reaction with propionaldehyde.

2. 1. 3. Acyclic Approaches

1) Aldol reactions. Masamune et al. employed the homochiral α-alkoxy ketone 51, prepared from mandelic acid, to synthesize the C-1 to C-10 and C-11

to C-15 fragments of 6-deoxyerythronolide B (Scheme 13)[34]. Condensation of the optically pure aldehyde 50 with the boron enolate of S-proceeded with high selectivity to give an aldol adduct, which was then converted to the Prelóg-Djerassi lactonic acid 52 (R =OH). Another aldol reaction of the aldehyde of 52 (R=H) with the boron enolate of S-51 provided 53 with all the required substituents as well as stereochemistry of the right-hand fragment.

Paterson et al. efficiently prepared the C-1 to C-5 and C-7 to C-11 fragments of erythronolide A utilizing the Evans aldol methodology (Scheme 14)[35]. The aldol condensation of the racemic aldehyde 54 with the boron enolate of the Evans oxazolidinone[51 b] produced a ca. 1 : 1 mixture of diastereomers 55. The diastereomeric mixture was converted to hydroxylactones 56, which were readily separated into 56a and 56b. This represented an improved synthesis of the same hydroxylactones used by Stork et al., the intermediates derived from 30 and 31, respectively (see Scheme 8).

Heathcock et al. utilized the reagents 60 and 61, which were developed in their laboratory for the stereoselective aldol reactions[36]. Condensation of the racemic aldehyde 57 with a lithium enolate of racemic 60 produced a syn-syn diastereomer 58 in a ratio of 15 : 1 (Scheme 15)[37]. Another aldol condensation of the aldehyde derived from 58 with racemic 61 gave an anti-syn(between the newly generated centers, C-6/C-5 and C-5/C-4, respectively) diastereomer 59 with moderate selectivity (85 : 15). The racemic major al-
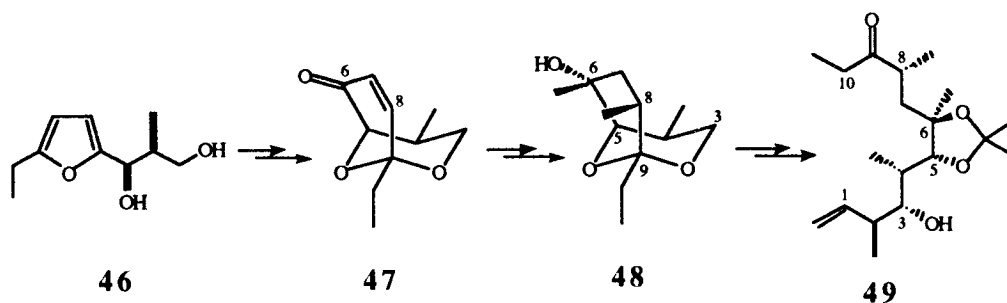
Scheme 10. The Synthesis of the C-1 to C-9 Fragment of Erythronolide A by Vedejs et al.

39   **40**   **41**   **42**
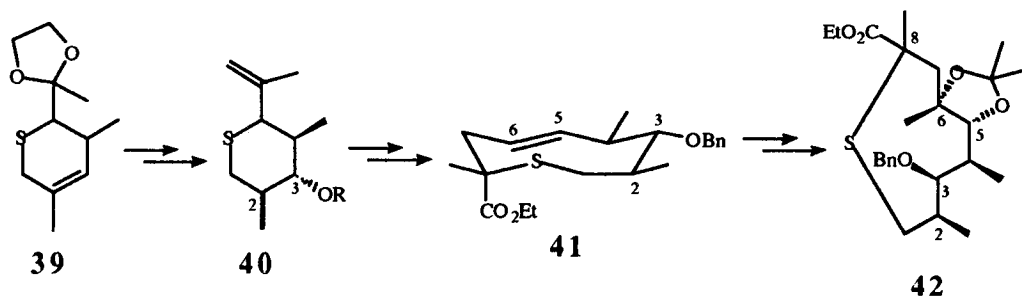
Scheme 11. The Synthesis of the C-5 to C-13 Fragment of Erythronolide A by Deslongchamps et al.
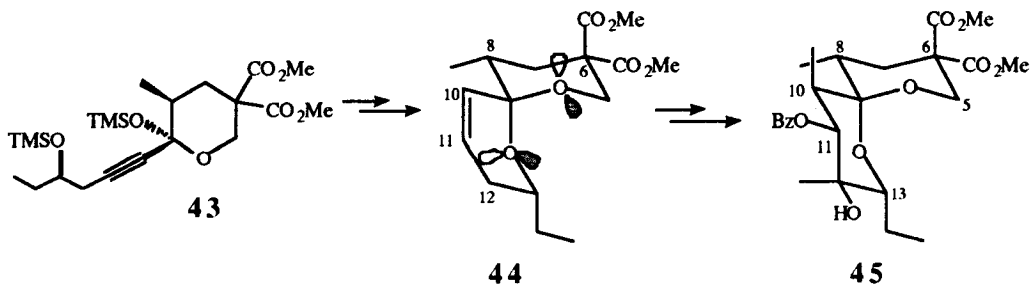
Scheme 12. The Synthesis of the C-1 to C-10 Fragment of Erythronolide B by Martin et al.

dol adduct 59 was then resolved into each enantiomer. The major portion of the C-8 to C-15 moiety was established with the aldol reaction of the optically pure aldehyde 62 with 61.

2) Epoxidation and Selective Opening of Epoxides. Sato et al. prepared the C-1 to C-7 segment of 6-deoxyerythronolide B by the use of *syn*-and *anti*-β-methyl-γ-rimethylsilyl homoallylic alcohols, 67 and 68, respectively (Scheme 16)[38]. Condensation of the optically pure aldehyde 63 with a lithium enolate of 2,6-di-*tert*-butyl-4-methylphenyl propionat yielded exclusively the *anti*(C-5/C-6)-*syn*(C-5/C-4) diastereomer 64[39]. Epoxidation of 64 with *tert*-butyl hydroperoxide[53] gave 65 as a single product. Regioselective opening of the epoxide of 65 with the Grignard reagent produced exclusively 66, which tcorresponded to the right-hand segment of 6-deoxyerythronolide B.

Mulzer et al. reported the synthesis of the C-1 to C-7 fragment of erythronolide B as an elaboration

of the 2-methyl-1,3-diol subunit for the synthesis of propionate-derived natural products such as the macrolide antibiotics (Scheme 17)[40,41]. Regioselective opening of 69 with a high-order cuprate[42] followed by manipulation of the vinyl group gave 70 having a propionate moiety with a suitable appendage. Both hydroxy groups at C-5 and C-6 of 71 were then introduced with catalytic osmylation in a ratio of 21 to give 71 as a major product.

Nakata et al. synthesized the C-1 to C-7 and C-8 to C-15 fragments of erythronolide A (Scheme 18) [43]. The alcohol 72 was prepared in an enantiomerically pure form using an Evans oxazolidinone and the selective reduction of the resulting β-keto imide. Vanadiumcatalyzed epoxidation[53] of 72 proceeded with a good selectivity (13 : 1) giving α-epoxide 73. Subsequent hydrogenolysis resulted in inversion at a tertiary carbon to give 74, which corresponded to the C-3 to C-7 (R=H) and the C-9 to C-15 (R=Et)
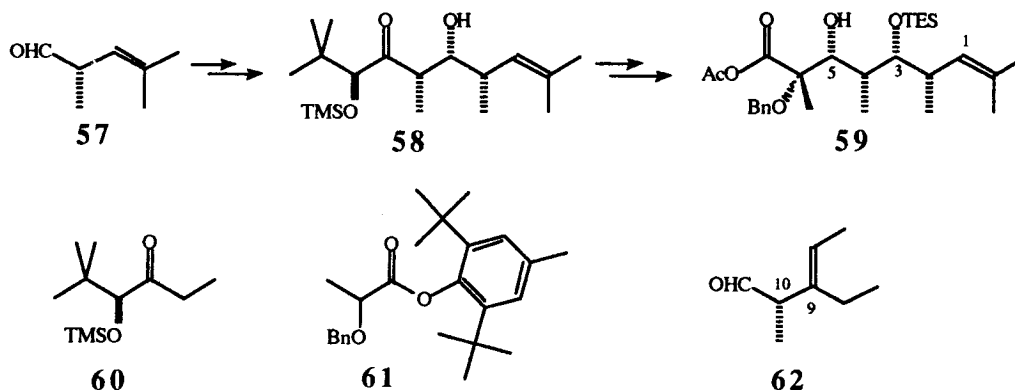
Scheme 13. The Synthesis of the C-1 to C-9 Portion of 6-Deoxyerythronolide B by Masamune et al.
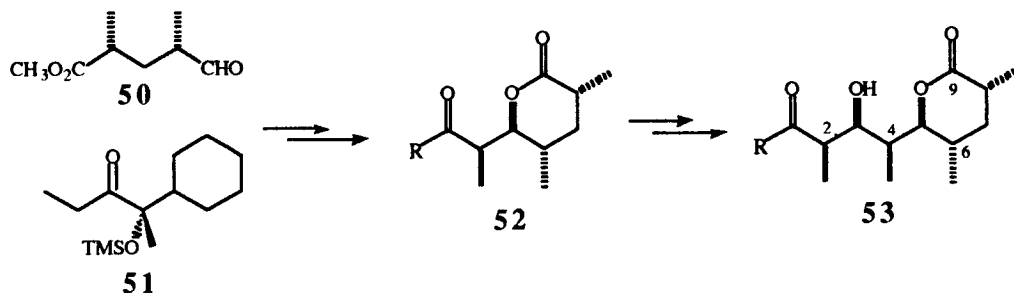
Scheme 14. The Synthesis of the C-1 to C-5 and C-7 to C-11 Portions of Erythronolide A by Paterson et al.
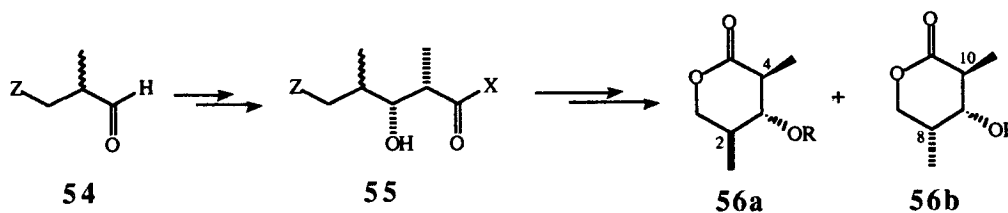
Scheme 15. The Synthesis of the C-1 to C-7 and C-8 to C-15 Moieties of Erythronolide A by Heathcock et al.

segments.

Yonemitsu et al. improved their synthesis of the C-1 to C-5 and C-9 to C-15 segments of erythronolide A (see Scheme 4). The homochiral epoxy allylic alcohol 75, derived from the Sharpless asymmetric epoxidation[54], was converted with a good selectivity (8.7 : 1) to give alcohol 76 in the presence of a Lewis

acid(Scheme 19)[126]. Another allylic epoxidation with MCPBA proceeded with a poor selectivity (3 : 2) to afford epoxide 77. Epoxide opening of the latter compound with a borane· THF complex was very regioselective to give diol 78 as a single isomer. The C-1 to C-5 segment was also prepared using a similar sequence although the epoxide opening was not as

selective as with the epoxide 77.

3) Pericyclic reactions. Danishefsky et al. obtained the C-1 to C-9 portion of 6-deoxyerythronolide B by the cyclocondensation of silyloxydienes such as 79 with aldehydes (Scheme 20)[44]. The Lewis-acid(BF$_3$ · OEt$_2$) catalyzed cycloaddition of silyloxydiene 79 [45] with commercially available racemic aldehyde 80 produced a *threo* isomer 81 as a major product of a 4.3 : 1 mixture of diastereomers. The dihydro-γ-pyrone 81 was then converted into the Prelog-Dje-rassi lactone 52 (X=OH). The aldehyde derivative (X=H) of the latter was subjected to another cycloaddition with the diene 79 in the presence of a different

Lewis acid (ZnCl$_2$) to yield the *erythro* isomers in a ration of ca. 3 : 2. The major *erythro* isomer 82, the Cram product, corresponded to the C-1 to C-9 portion of the aglycone.

Burke et al. successfully applied an Ireland-Clasien rearrangement to construct the contiguous stereocenters of each segment(Schem 21)[46]. The protected lactate was transformed into dioxanones 83a and 83b through a series of selective addition of the Grignard reagents. The dioxanones 83 underwent [3.3] sigmatropic rearrangement to give the fully functionalized tetrahydropyran templates 84 and 85 from 83a and 83b, respectively. Subsequent ring cleavage of dihyd-
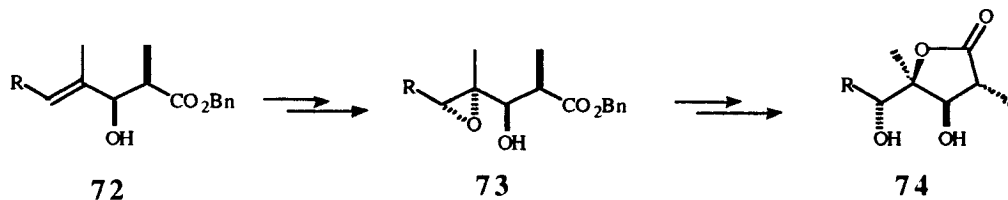
Scheme 16. The Synthesis of the C-1 to C-7 Segment of 6-Deoxyerythronolide B by Sato et al.
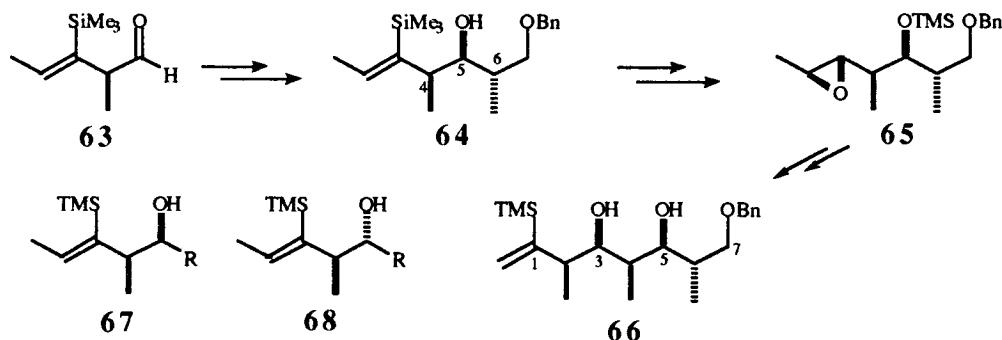
Scheme 17. The Synthesis of the C-1 to C-7 Moiety of Erythronolide B by Mulzer et al.
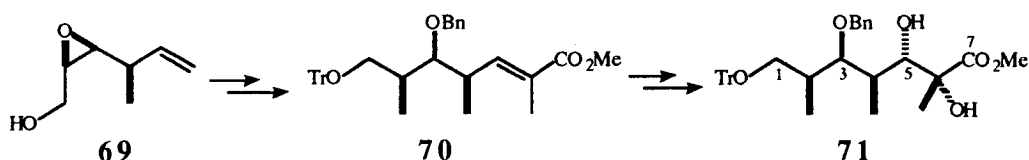
Scheme 18. The Synthesis of the C-3 to C-7 and C-9 to C-15 Fragments of Erythronolide A by Nakata et al.

rofurans 84 and 85 led to both the C-1 to C-6 and C-7 to C-15 segments after a series of transformations.

4) Allylic asymmetric induction. Cha et al. efficiently generated four contiguous stereogenic centers of 89 by exploiting the stereocontrol by an allylic oxygen substituent (Scheme 22)[51]. The homochiral ε-hydroxy-Z, E-diene ester 88 was prepared by the asymmetric reduction[55] of ε-keto-Z, E-diene ester that was obtained in only two steps from 5-hydroxy-4-methylbutenolide. Dihydroxylation with osmium tetroxide was very regio-and stereoselective to give the dihydroxybutenolide in a ratio of ≥ 15 : 1. The fourth stereogenic center in 89 was created by the stereoselective hydrogenation using the bulky substituent in the butenolide ring[56] after the protection of the diol functionality with an acetonide group. The γ-butyrolactone 89 was manipulated into the two key fragments 90 and 91 of erythronolide A, respectively [1].

2. 2. Coupling Strategies

Coupling reactions of the two key fragments can be classified into three reaction types: the nucleophilic addition of one fragment to a carbonyl group of the other fragment, the Wittig reaction between two fragments and others. Each reaction type is further divided depending on the sites of coupling of the key fragments.

A. Aldol-Type Addition
   1) The ketone enolate at C-10 and the aldehyde at C-11[22e,33,34b].
   2) The ketone enolate at C-8 and the aldehyde at C-9[1,12a].
   3) The ketone enolate at C-8 and the aldehyde at C-7[43b].
   4) The sulfoxide anion[22d,30a] or magnesium anion[14] at C-7 and the ketone at C-6.
   5) The sulfoxide anion at C-7 and the aldehyde

Scheme 19. The Improved Synthesis of the C-9 to C-15 Segment of Erythronolide A by Yonemitsu et al.
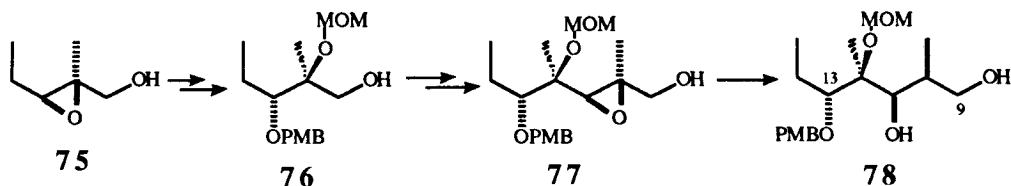
Scheme 20. The Synthesis of the C-1 to C-10 Portion of 6-Deoxyerythronolide B by Danishefsky et al.
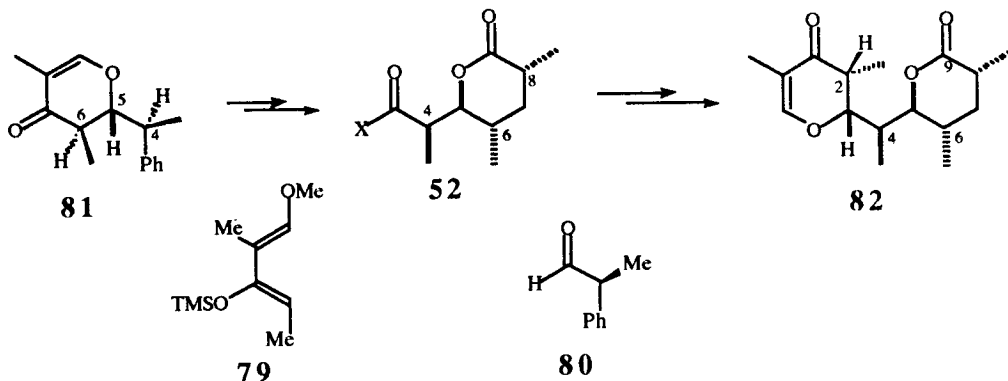
Scheme 21. The Synthesis of the C-1 to C-6 and C-7 to C-15 Segments of Erythronolide A and B by Burke et al.

Scheme 22. The Synthesis of the C-3 to C-8 and C-9 to C-15 Fragments of Erythronolide A by Cha et al.

at C-6[26a,d].

6) The sulfonyl anion at C-5 and the aldehyde at C-6[13b].

7) The vinyl anion at C-8 and the aldehyde at C-9[13a].

8) The vinyl anion at C-10 and the aldehyde at C-9[24c].
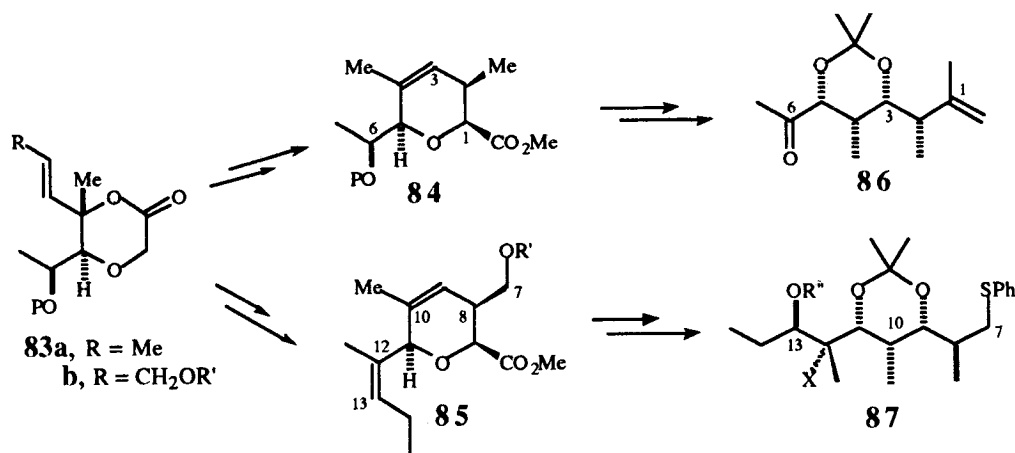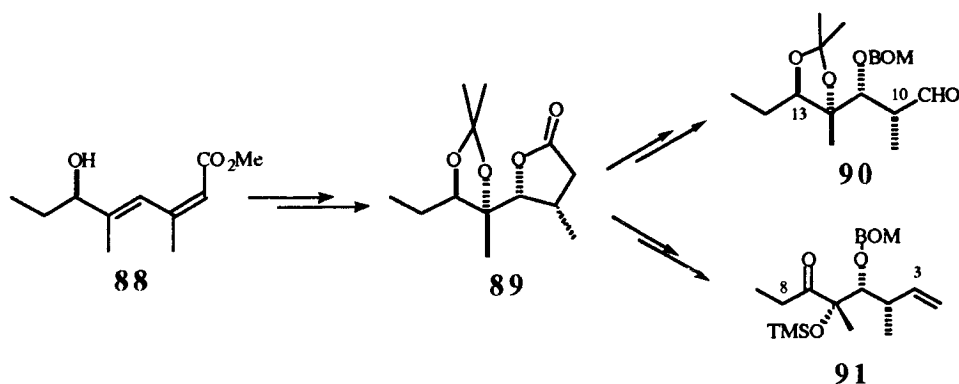
9) The vinyl anion at C-10 and the thioester at C-9[28b,c].

B. The Wittig Olefination

1) The phosphonate at C-6 and the aldehyde at C-7[26c,35b].

2) The phosphonate at C-7 and the aldehyde at

C-8[21b].

C. Others[32a]

3. SUMMARY

The stereoselective synthesis of erythromycin A has attracted a considerable attention of synthetic organic chemists due to its plethora of asymmetric centers as well as its biological activity. In addition, formation of a macrocyclic ring has been challenging because of the unfavorable entropy factor. The synthetic efforts for the ten asymmetric centers embedded in an aglycone of erythromycin A have mostly

been realized by the stereoselective preparation of the key fragments followed by the coupling of them. The synthetic strategies employed for the key fragments can be classified according to the main methodology used as follows.

1. A carbohydrate approach: manipulating the inherent chiral centers of carbohydrate sources.
2. A cyclic approach: utilizing the rigid nature and the reactivity of cyclic intermediates.
3. An acyclic approach: controlling the asymmetric induction in acyclic molecules with the chiral centers present in themselves (relative asymmetric induction) and/or some other chiral auxiliaries as induction sources (absolute asymmetric induction).

The coupling has largely been reduced to practice by either the aldol-type additions or the Wittig olefinations of the key fragments.

Formation of the macrolactone ring had mainly depended upon high dilution techniques. Recently, however, there have been several studies of the effect of the conformartion of various seco acid derivatives on the macrolactonization efficacy. The 14-membered aglycone has effectively been formed without resorting to the high dilution methods choosing the proper conformations and cyclic protecting groups of the erythronolide A seco acid.

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