Chapter 5

Synthetic Strategies towards Erythronolide B and Erythromycin B

Introduction

Due to their fascinating structures and important biological activity, macrolide natural products, especially the erythromycins, have been popular targets for total synthesis and thus, an inspiration for discovering new synthetic methods with wide applications.[1] As synthetic targets, macrolides pose various challenges, such as installing the numerous chiral stereocenters, closing a macrocycle and selectively attaching sugars to the macrolactone. In 1956, R. B. Woodward acknowledged these challenges, stating "Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."[2] Woodward and coworkers eventually addressed the stereochemical issues, identified elements crucial for forming macrocycles, and solved the glycosylation problem in elegant studies culminating in the total synthesis of erythromycin A, published after Woodward's death in 1981.[3]

For more than two decades since Woodward's achievement, synthesizing members of the erythromycin family has been the focus of at least twenty research groups worldwide and thus, hailed as the "most extensive single project in the history of synthetic organic chemistry."[1c] To date, there are three total syntheses of the digylcosides (one of erythromycin A (**1**)[3] and two of erythromycin B (**2**)[4]), and several syntheses of the aglycones, erythronolide A (**3**),[5] erythronolide B (**4**),[6] 6-

deoxyerythronolide B (**5**),[7] and 9-(*S*)-dihydroerythronolide A (**6**)[8] (Figure 1). In addition, researchers have also reported various seco-acids syntheses.[1b]

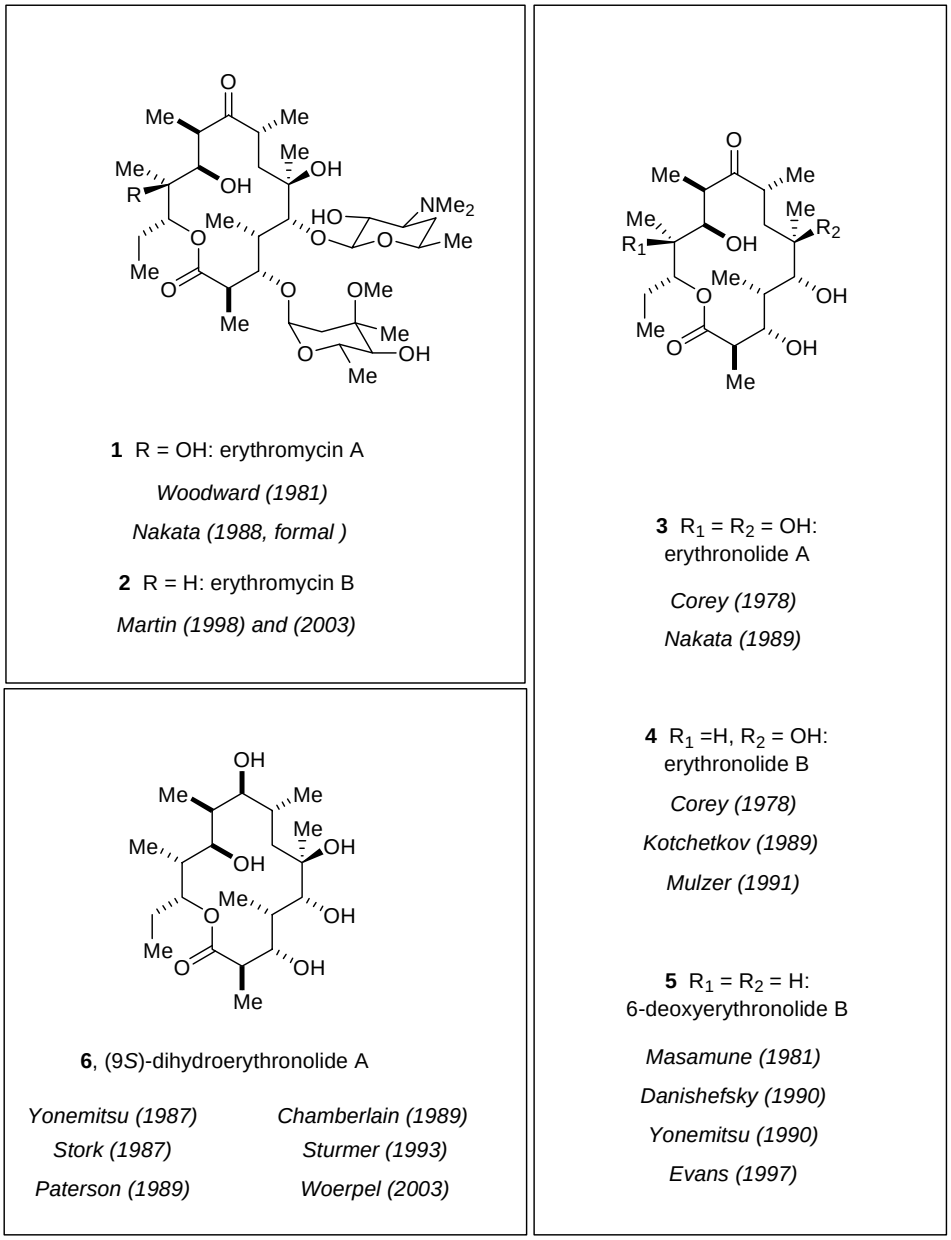


Figure 1. Erythromycin family: popular targets in total synthesis for more than two decades

All these strategies, however, can be classified into three main approaches (defined below) for addressing the polyketide's stereochemical challenges.[1b]

(1) *ring cleavage approach:* involves exploiting a medium ring's conformational bias to stereoselectively form chiral centers on the ring, followed by cleavage of the ring to achieve the desired acyclic architecture;

(2) *carbohydrate approach:* involves manipulating existing stereocenters and functionality from the chiral pool, namely sugars, to form the desired acyclic frameworks;

(3) *acylic approach*: involves using stereoselective methods to form new asymmetric centers in acyclic systems.

Approaches to Erythronolide B and Erythromycin B

Erythronolide B (**4**) holds a central position in the erythromycin family as a biosynthetic precursor to the other members of this antibiotic clan.[9] Notably, this natural product has been previously synthesized by all three of the main strategies defined above, by three different research groups (Corey,[6a] Kotchetkov,[6b] and Mulzer[6c]). In addition, Martin and coworkers have recently reported a new approach to closely related erythromycin B (**2**).[4] The following discussion aims to summarize key aspects of these four syntheses. In particular, the strategy used to address the stereogenic centers on the C(1) to C(9) fragment of erythronolide B will be stressed to establish appropriate context for our work in this field.

Corey's synthesis

In 1978, E. J. Corey achieved the landmark first total synthesis of erythronolide B (Figure 2).[6a] Corey's plan involves a ring closing lactonization of seco-acid **7** using a general method developed in his lab for forming macrolactones. Treatment of **7** with disulfide **8**, forms an activated ester **9** which cyclizes in refluxing toluene to **10** in 50% yield (Scheme 1). The success of this ring-closing strategy has had a tremendous impact; all subsequent erythromycin syntheses contain the same C-O lactone bond disconnection.[1]

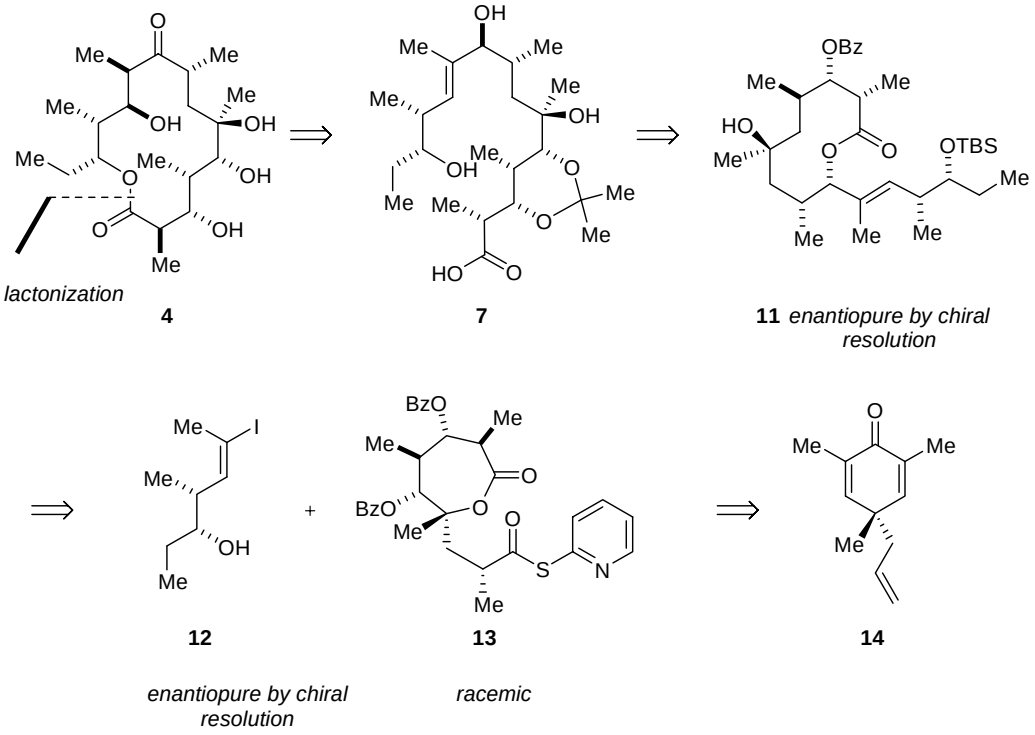
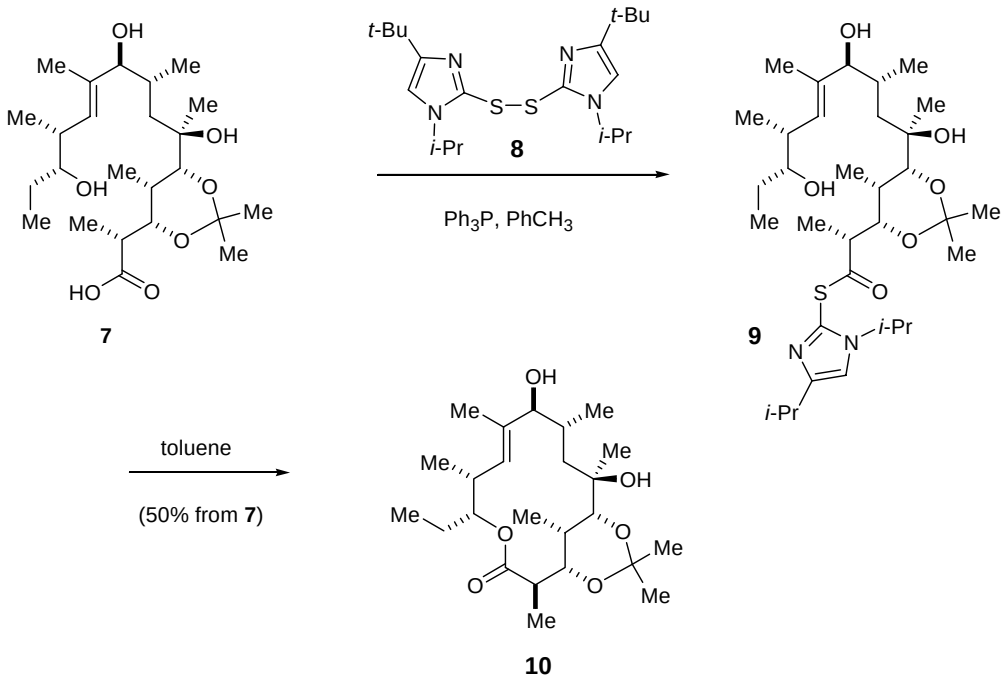


Figure 2. Corey's synthesis (thirty steps from **14**, < 0.5% yield)

Scheme 1. Corey's general macrolactonization method

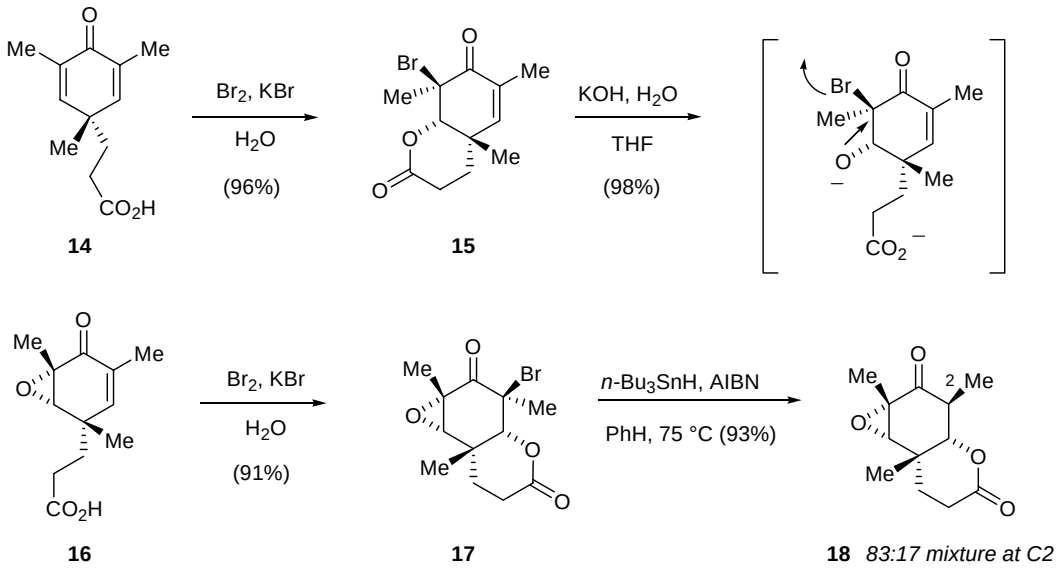


One current drawback of Corey's route involves the chiral resolution of advanced intermediate **11**, by the coupling of enantiopure **12** (which was also obtained by chiral resolution) to a racemic mixture of **13** (Figure 2). As a result of these resolution steps, Corey's synthesis suffers a significant loss in efficiency (> 25%). This historic synthesis of erythronolide B requires thirty transformations from **14**, and has an approximate overall yield of less than 0.5%.

Ring cleavage approach. Corey successfully installs the six chiral centers on the C(1) to C(9) fragment **13** of erythronolide B by a ring cleavage approach (see Schemes 2 and 3). Essential to his strategy is the bromolactonization of symmetrical intermediate **14** to create three stereocenters in a diastereoselective fashion, yielding lactone **15**. Upon saponification to epoxide **16**, a second bromolactonization gives intermediate **17**, creating

two additional stereocenters in the process. The carbon-bromide bond can then be reduced by radical cleavage providing **18** as a 83:17 mixture.

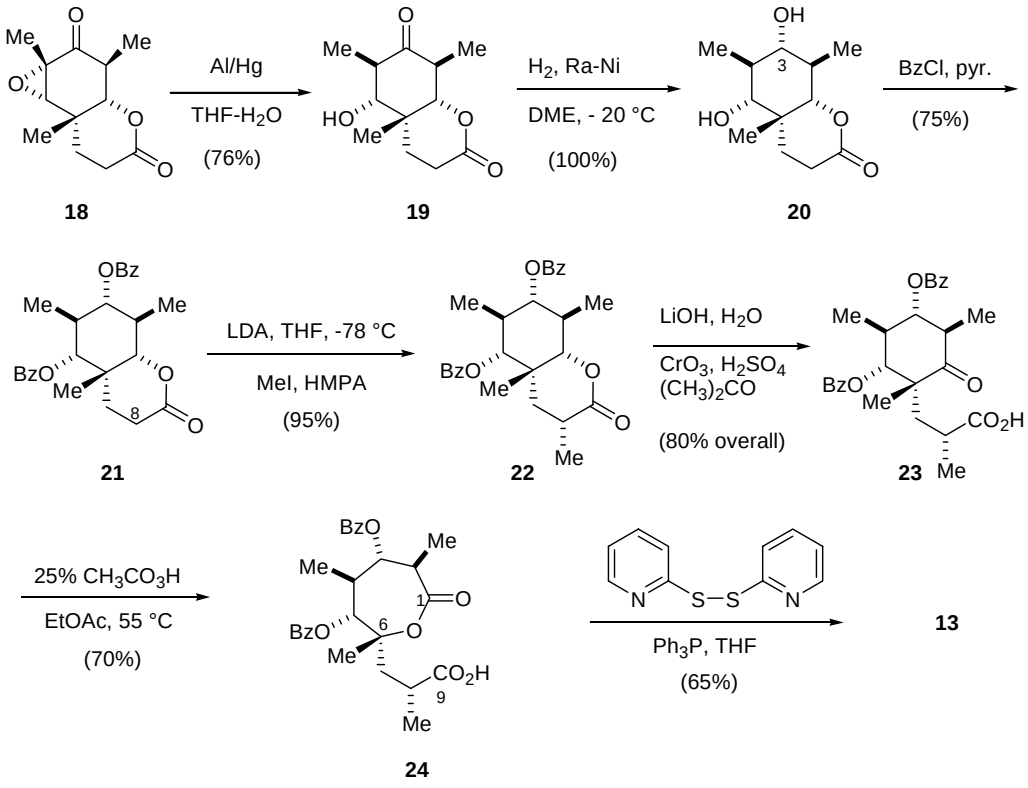
Scheme 2. Corey's ring-cleavage approach to C(1)–C(9) segment of erythronolide B



14 **15** **16** **17** **18** *83:17 mixture at C2*

The epoxide **18** is reductively opened by aluminum amalgam to form a hydroxyl ketone **19** (Scheme 3). Importantly, the diastereoselective hydrogenation of ketone **19** installs the requisite C(3) hydroxyl stereocenter. After protection of **20** with benzoyl chloride, critical introduction of the C(8)-methyl stereocenter was achieved by alkylation of **21** with methyl iodide to provide **22**. Jones oxidation of **22** provides ketone **23**—properly functionalized to undergo ring cleavage. A Bayer-villager oxidation of the carobocyclic ring or **23** enables *ring cleavage* to lactone **24**, installing the key C(6) tertiary alcohol stereocenter. Esterification of **24** provides **13** which contains the key stereocenters in the C(1)–C(9) segment, and is activated for coupling to iodide **12** (see Figure 2).

Scheme 3. Corey's ring-cleavage to install the C(6) stereocenter



Kotchetkov's synthesis

In 1974, Miljkovic *et al.* proposed using sugars as the basic building blocks for the synthesis of polyketides.[10] Five years later, Hannessian realized this idea by synthesizing a seco-acid of erythronolide A from glucose.[11] Aside from a different protecting group plan, Kotchetkov essentially mimics Hannesian's scheme to make erythronolide B (Figure 3). Based on Woodward's seco-acid cyclization precedence,[3] Kotchetkov prepared the seco-acid **25** containing the presumably critical 3,5;9,11-bis(cyclo)acetal protecting groups. (Indeed, with the Corey-Nicolaou double activation method, **25** lactonizes to form the corresponding macrolactone in 50% yield.) The key

fragments in Kotchetkov's synthesis, sulfoxide **26** and ketone **27** were both derived from levoglucosan **28**.

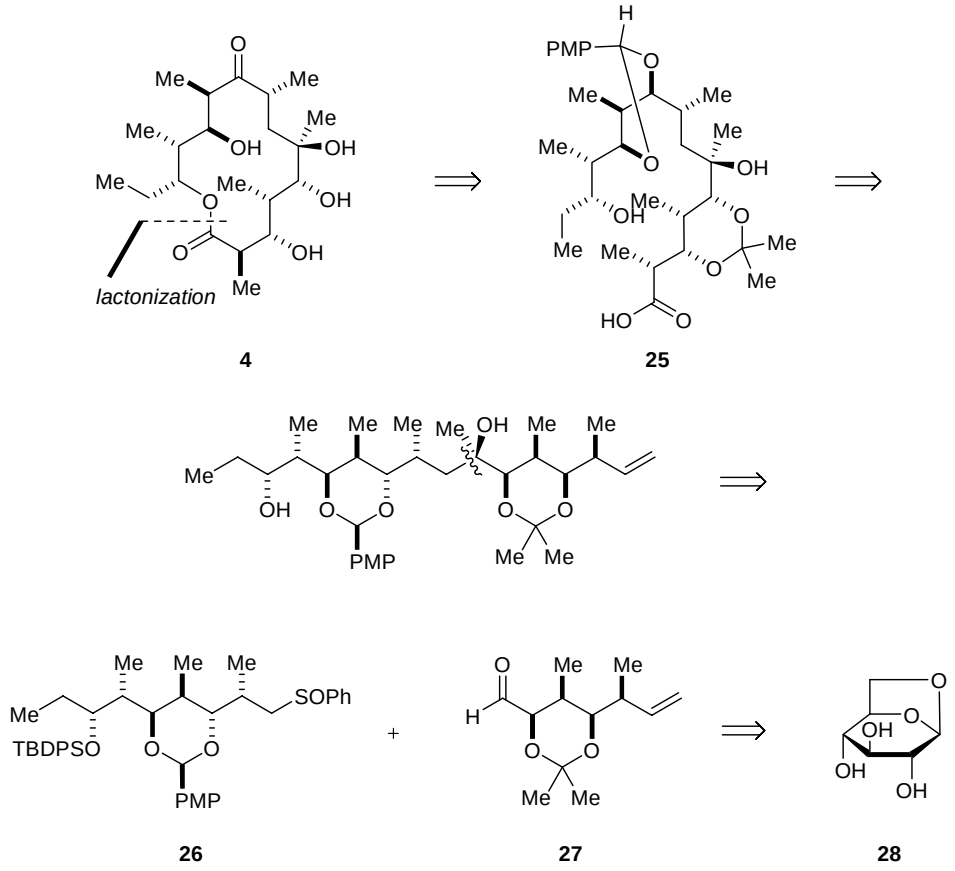
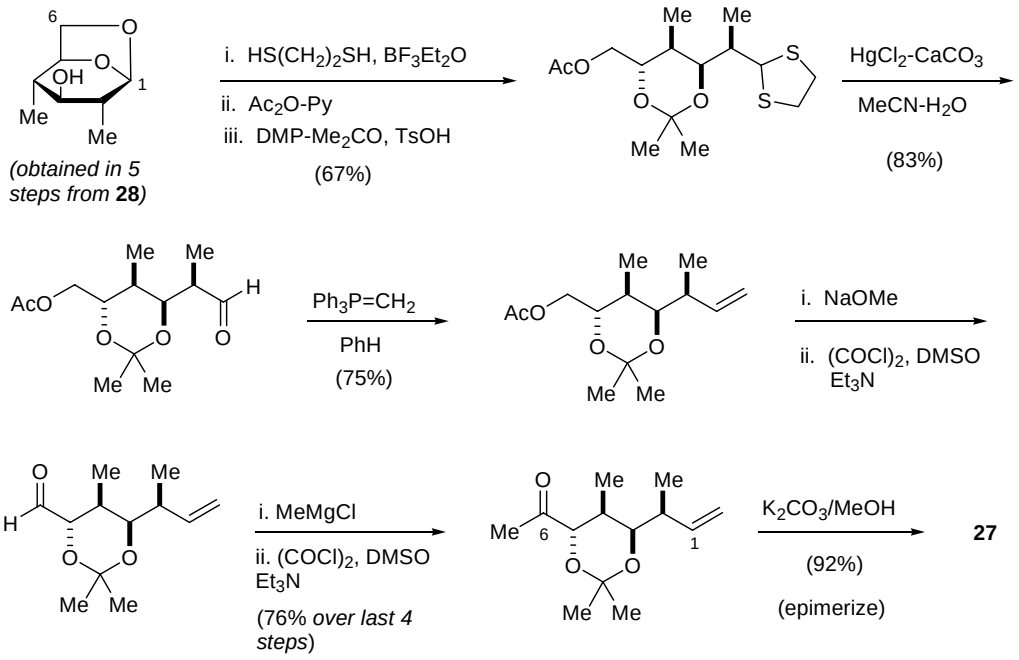


Figure 3. Kotchetkov's synthesis (thirty-six steps from **28**)

Sugar approach. Unfortunately, using levoglucosan as the chiral source necessitates many protecting group and functional group manipulations which diminishes the efficiency of this route. For example, Scheme 4 outlines the sixteen functional group and protecting group interchanges required for elaborating the sugar **28** to the C(1)–C(6) segment **27** of erythronolide B. In spite of starting with chiral building blocks which already contain most of the required asymmetric centers, Kotchetkov's

synthesis requires thirty-six transformations from **28**. Furthermore, a sugar approach hampers the design of flexible syntheses, and as such limits access to clinical analogues.

Scheme 4. Kotchetkov's derivitization of levoglucason to C(1) to C(6) fragment **27**



Mulzer's Synthesis

In 1991, Mulzer and coworkers completed the total synthesis of erythronolide B in twenty-five linear steps from *(R)*-2,3-*O*-isopropylideneglyceraldehyde **29**, in an approximate overall yield of 0.8% (Figure 4).[6c] Mulzer speculated that reducing the number of tetrahedral centers on the seco-acid, especially in the region surrounding C(9), could aid cyclization. Indeed, the 8,9 anhydro seco acid **30** smoothly formed macrolactone **31**, under Yamaguchi's conditions (> 85% yield). The key coupling in this route involves the Cram-chelate[12] selective addition of the allyl sulfide anion **32** to ketone **33** installing the requisite C(6) tertiary alcohol center (96% yield, 88:12 dr). Fragments **32** and **33** were both derived from **29**.

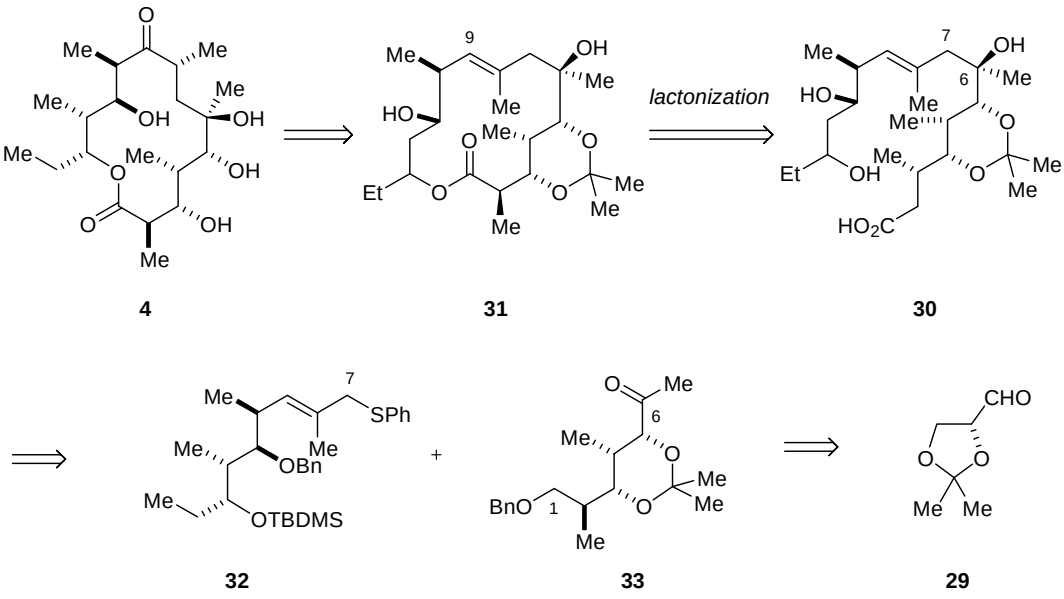
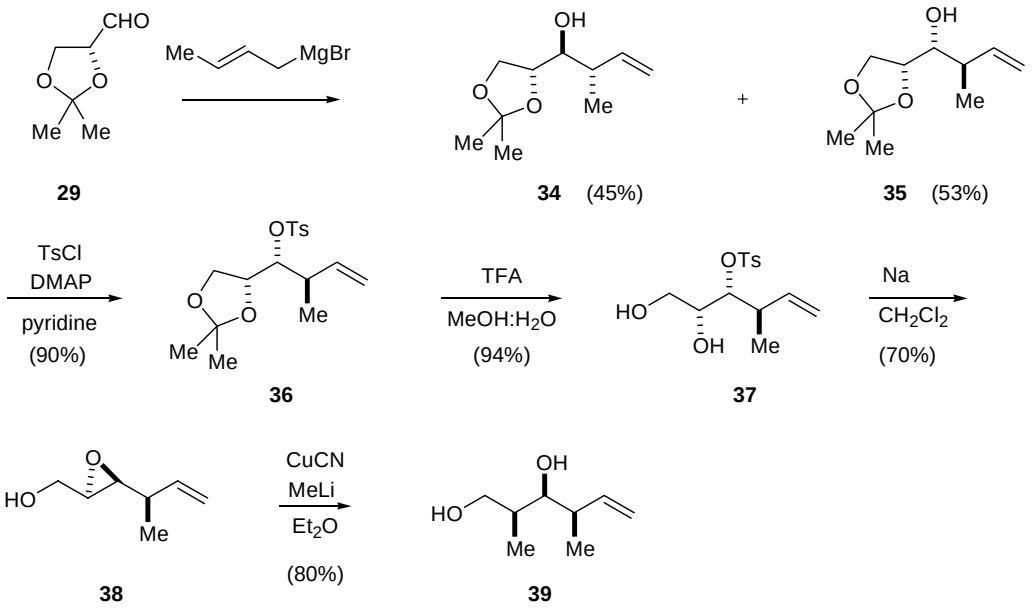


Figure 4. Mulzer synthesis (twenty-five steps from **29**, 0.8% yield)

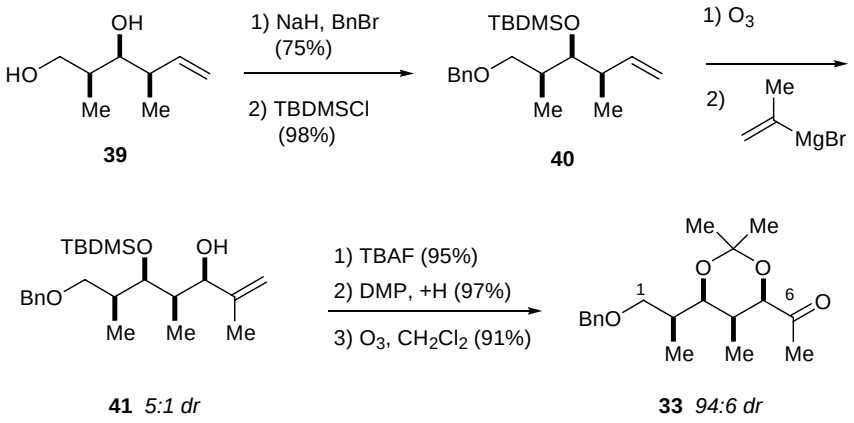
Acyclic approach. As shown in Scheme 5, Mulzer's synthesis of the C(1)–C(6) fragment **33** involves allylation of aldehyde **29** to produce a mixture of **34** and **35** in 45% and 55% yield, respectively.[13] The alcohol **34** was then transformed via intermediates **36**, and **37** to epoxy alcohol **38**, which upon treatment with Lipshutz' methylcuprate regiospecifically furnished the 1,3-diol **39** in about 40% yield overall.[14] (Notably, alcohol **35** also obtained from the allyation of aldehyde **29** was transformed to sulfoxide **32**).

Scheme 5. Mulzer's acyclic approach to C(1)–C(6) fragment of erythronolide B



As shown in Scheme 6, compound **39** was then monbenzylated at the primary position, and silylated to give **40**, which was subjected to ozonolysis to form an aldehyde that was treated with isopropenylmagnesium bromide. The silyl group suppresses a 1,3-chelate mechanism, enabling a Felkin-Anh pathway to occur and form **41** as a 5:1 mixture of diastereomers. Subsequent deprotection, acetonide protection and ozonolysis yields **33,** which can be epimerized at C(6) to enrich the diasteromeric ratio to 94:6.

Scheme 6. Felkin selective allylation to install the C(5) hydroxyl stereocenter



39 **40** **41** *5:1 dr* **33** *94:6 dr*

Martin's synthesis of erythromycin B

In 2003, Martin and coworkers reported their second-generation approach to erythromycin B which involves twenty-seven transformations and an approximate overall yield of 0.8% from furan-aldehyde **42** (Figure 5). For the first time in a macrolide synthesis, the sugar residue is appended *prior* to the macrolactonization step. Under Yamaguchi's protocol, **43** cyclizes to form the corresponding macrocycle in excellent yield (85%). Two key disconnections, a crotyllation and an aldol transformation, reveal alehdyde **44**, **45**, and the C(3) to C(9) fragment **46**.

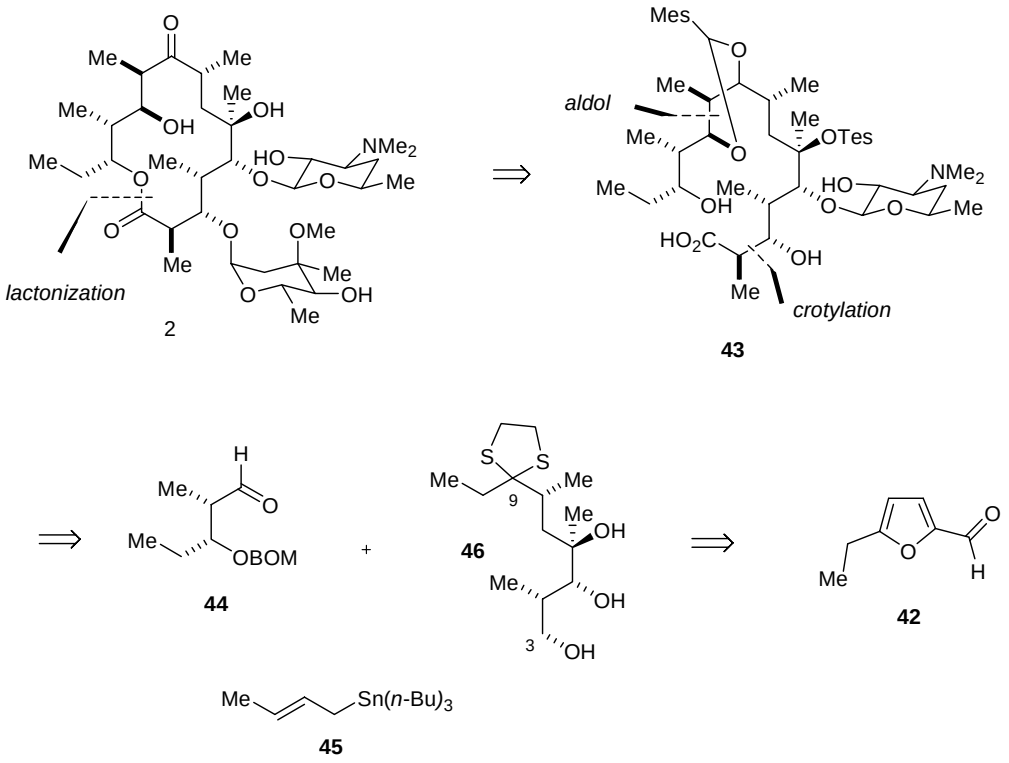
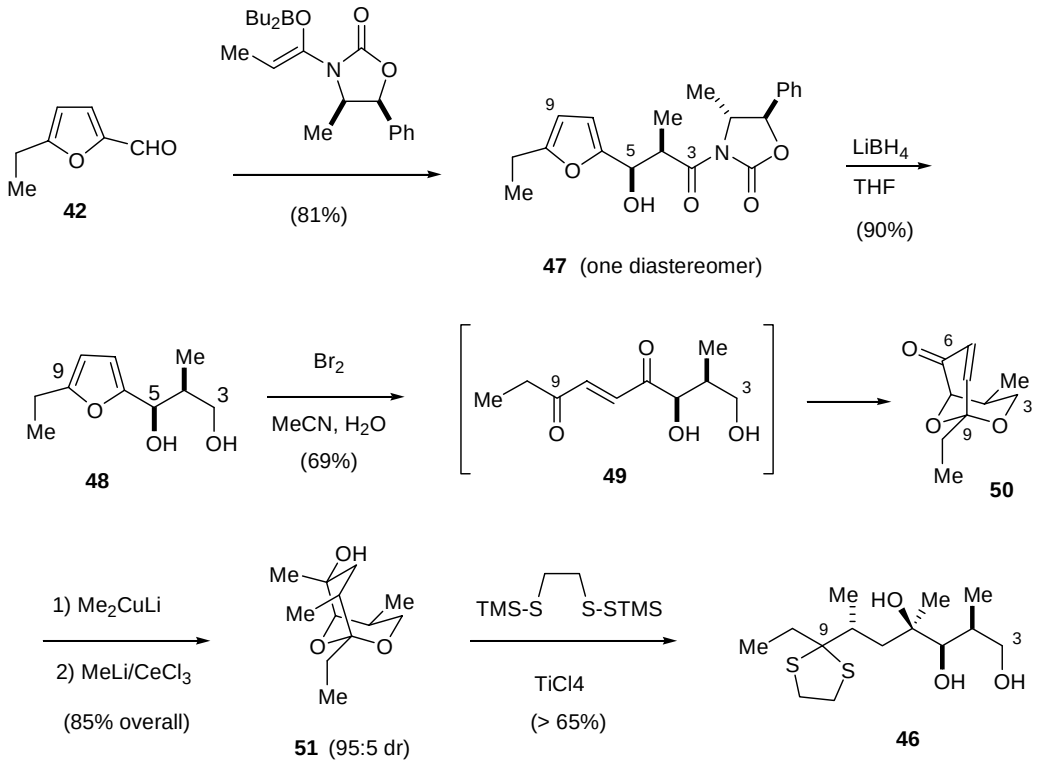


Figure 5. Martin's synthesis (twenty-seven steps from **42**, 0.8% yield)

Synthesis of the C(3)–C(9) fragment. Martin developed an elegant six-step synthesis of the C(3) to C(9) fragment **46**, starting from the known aldehyde **42**, which was prepared by a Vilsmeier-Haack formylation of 2-ethylfuran.[15] As shown in Scheme 7, aldehyde **42** was subjected to a diastereoselective Evan's aldol protocol to provide **47** in 81% yield as one diastereomer. Reductive removal of the auxiliary with lithium borohydride affords **48** in 90% yield. Oxidation of diol **48** with bromine, forms an intermediate dihydroxy enedione **49** which *in situ* undergoes acid-catalyzed bicycloketalization to provide **50** in 69% yield. Importantly, the conformation of this bicycle enables highly stereoselective 1,4-addition of lithium dimethylcuprate, followed by stereoselective 1,2-addition of methyl lithium to furnish **51** in 85% overall yield.

Treatment of **51** with an ethanedithiol protecting group opens the bicycle, affording the acyclic C(3)–C(9) backbone **46**.

Scheme 7. Martin's approach to the C(3)–C(9) segment of erythromycin



Concluding Remarks

Arguably, the most effective strategy for addressing stereochemistry in the erythromycins rely on the *acyclic* approach, applying, namely, aldol or allylation reactions *iteratively*.[16] In contrast to the *sugar* or *ring-cleavage* strategies, applying stereoselective bond forming methods also enable the development of more convergent and flexible synthetic routes. Remarkably, the Claisen rearrangement,[17] has not been exploited in the synthesis of the erythromycin family, *despite* its efficacy for constructing

stereocenters on acyclic architectures. The next chapter presents our contributions to the field of macrolide antibiotic synthesis through a novel synthesis of erythronolide B based on our tandem acyl-Claisen rearrangement.[18]

References

(1) For comprehensive reviews on macrolide synthesis, see: (a) *Macrolide Antibiotics* (Ed.: S. Omura), Academic Press, Orlando, FL, **1984**. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (c) Mulzer, J. *Angew. Chem.-Int. Edit. Engl.* **1991**, *30*, 1452–1454.

(2) Woodward, R. B. In *Perspectives in Organic Chemistry*, Todd, A., Ed., Intersciene Publishers: New York 1956, p. 155.

(3) For the total synthesis of erythromycin A, see: Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Auyeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H. J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Babu, T. V. R.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N. C. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213.

(4) For the total syntheses of erythromycin B, see: (a) Hergenrother, P. J.; Hodgson, A.; Judd, A. S.; Lee, W. C.; Martin, S. F. *Angew. Chem.-Int. Edit.* **2003**, *42*, 3278–3281. (b) Martin, S. F.; Hida, T.; Kym, P. R.; Loft, M.; Hodgson, A. *J. Am. Chem. Soc.* **1997**, *119*, 3193–3194.

(5) For total syntheses of erythronolide A, see: (a) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613–4628. (b) Nakata, M.; Arai, M.;

Tomooka, K.; Ohsawa, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618–2635. (c) Corey, E. J.; Kim, S.; Yoo, S. E.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620–4622.

(6) For total syntheses of erythronolide B, see: (a) Corey, E. J.; Kim, S.; Yoo, S. E.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620–4622. (b) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S. *Tetrahedron Lett.* **1981**, *22*, 4315–4318. (c) Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910–923.

(7) For total syntheses of 6-deoxyerythronolide A, see: (a) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636–1648. (b) Evans, D. A.; Kim, A. S. *Tetrahedron Lett.* **1997**, *38*, 53–56. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921–5942.

(8) For syntheses of dihydroerythronolide A, see: (a) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565–1567. (b) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569–4572. (c) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463–7466. (d) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247–6256. (e) Sturmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem.-Int. Edit. Engl.* **1993**, *32*, 101–103. (f) Peng, Z. H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018–6019.

(9) See Chapter 4 for discussion of the biosynthesis of the erythromycins and references therein.

(10) Miljkovi.M; Gligorij.M; Satoh, T.; Miljkovi.D *J. Org. Chem.* **1974**, *39*, 1379–1384.

(11) Hanessian, S.; Rancourt, G. *Can. J. Chem.-Rev. Can. Chim.* **1977**, *55*, 1111–1113.

(12) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.

(13) Mulzer, J.; Delasalle, P.; Freissler, A. *Liebigs Annalen Der Chemie* **1986**, 1152–1171.

(14) Mulzer, J.; Autenriethansorge, L.; Kirstein, H.; Matsuoka, T.; Munch, W. *J. Org. Chem.* **1987**, *52*, 3784–3789.

(15) Martin, S. F.; Lee, W. C.; Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674–4688.

(16) For an excellent use of aldol chemistry in macrolide synthesis, see Evan's synthesis of oleandymycin and 6-deoxyerythronolide b (18 linear steps), reference 7c.

(17) See Chapter 1 for discussion of the Claisen rearrangement, and reference therein.

(18) See Chapter 3 for discussion of the tandem acyl-Claisen rearrangement.