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Asymmetric Crotylation Reactions in Synthesis of Polypropionate-Derived Macrolides: Application to Total Synthesis of Oleandolide

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Abstract: Complete details of a convergent asymmetric synthesis of oleandolide (**1**), the aglycon of the macrolide antibiotic oleandomycin, is described. The synthesis has been achieved through the assembly and coupling of the left- and right-hand subunits **12** and **38**, respectively. These subunits were prepared from chiral silane-based asymmetric crotylation reactions to control the stereochemical relationships. The left- and right-hand subunits (C1−C7 and C8−C14) were brought together through a Pd(0)-catalyzed sp^3-sp^2 cross-coupling reaction between the zinc intermediate **40** and vinyl triflate **38** to give **27**. This product was converted to seco acid **42a** and cyclized to lactone **35** under Yamaguchi conditions. This material was then epoxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to install the correct C8 epoxide as a single diastereomer, which after a short deprotection sequence completed the synthesis of oleandolide.

Introduction

Oleandomycin is representative of the 14-membered polypropionate-derived macrolide antibiotics.[1] This natural product contains a number of structurally complex elements, including 10 stereocenters and an unusual exocyclic epoxide at C8 (Figure 1). The compound is produced by the actinomycete *Streptomyces antibioticus* and was originally reported by Sobin et al. in 1955.[2] It was first characterized in 1958 as an epoxide containing a polyhydroxy and polymethyl macrocyclic lactone with two appended sugars, desosamine and L-oleandrose, which permitted partial structure assignment.[3] The complete structure of oleandomycin was established in 1960 by Celmer, Woodward, and co-workers.[4] Its relative configuration was assigned by NMR techniques in 1965 by Celmer[5] and later confirmed by X-ray crystallography of the 11,4″-bis[*O*-(*p*-bromobenzoyl)] derivative by Ogura et al.[6]

Oleandomycin possesses similar breadth of therapeutic activity to the well-known erythromycins. It exhibits activity against Gram-positive and some Gram-negative bacteria, possessing a bacteriostatic rather than a bactericidal action. As a result of its low toxicity and high antibacterial potency, oleandomycin, as well as its phosphate (matromycin) and triacetyloleandomycin (TAO) derivatives, has been used widely in clinical and veterinary areas. Particularly good responses were achieved against Gram-positive bacteria and mycoplasma.[7] Concerning the mechanism of action of these agents, they are believed to inhibit bacterial RNA-dependent protein synthesis by binding to the P site of the bacterial 50S ribosomal subunit, blocking either transpeptidation and/or translocation reactions.[8] These compounds have found nonantibiotic utilities as well. For instance, TAO is currently used in conjunction with a corticosteroid, providing frontline therapy in cases of refractory asthma.[9]

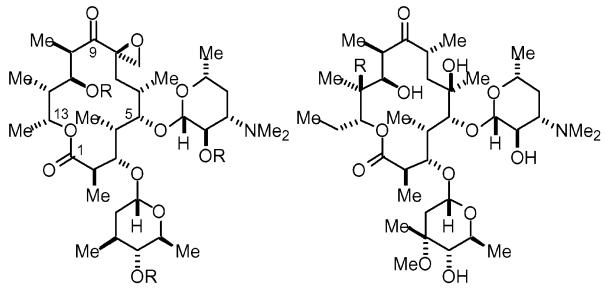

Figure 1. Representative 14-membered macrolides.

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(1) *Macrolide Antibiotics, Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.
(2) Sobin, B. A.; English, R. A.; Celmer, W. D. *Antibiot. Annu.* **1955**, *2*, 827−830.
(3) Els, H.; Celmer, W. D.; Murai, K. *J. Am. Chem. Soc.* **1958**, *80*, 3777−3782.
(4) Hochstein, F. A.; Els, H.; Celmer, W. D.; Shapiro, B. L.; Woodward, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 3225−3227.
(5) Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1797−1799.
(6) Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. *J. Am. Chem. Soc.* **1978**, *100*, 6733−6737.
(7) (a) For a review of macrolides in clinical use, see Nakayama, I. In *Macrolide Antibiotics, Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; pp 261−230. For a review on veterinary practice, see Wilson, R. C. In *Macrolide Antibiotics, Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; pp 301−338.
(8) Corcoran, J. W. In *Macrolide Antibiotics, Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; pp 232−259.
(9) *Drug Evaluations Annual 1995*; Bennett, D. R., Ed.; American Medical Association: Chicago, 1995; p 536.

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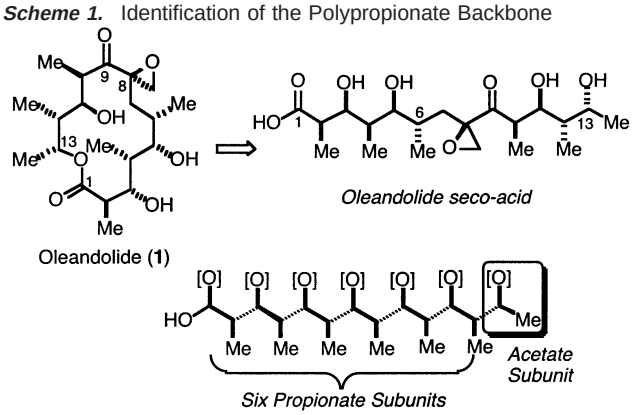
Scheme 1. Identification of the Polypropionate Backbone

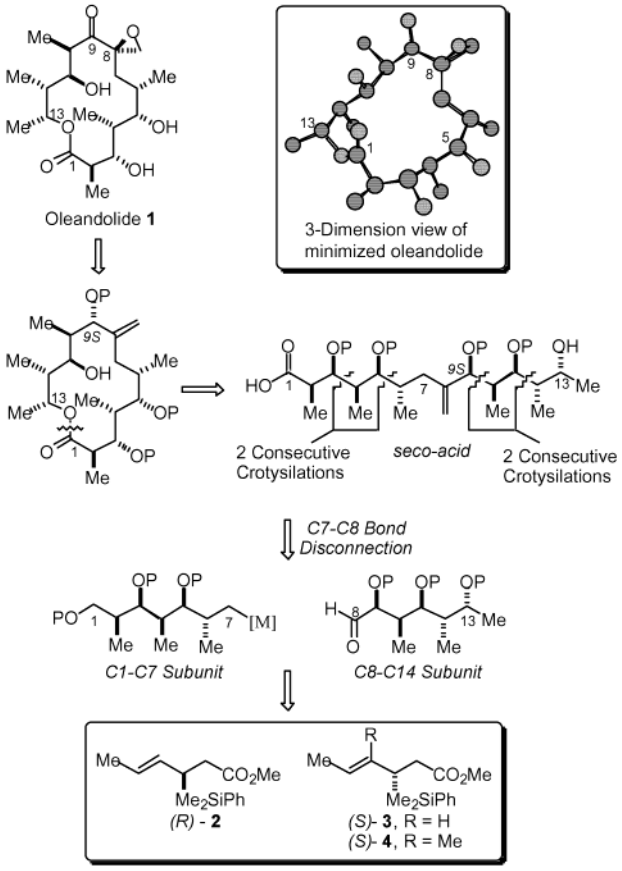


The macrolide antibiotics encompass a biologically active class of molecules sharing the characteristics of a macrocyclic lactone and an amino sugar appendage. Despite the wide variety of stereochemical and oxidation-state permutations represented in these molecules, the aglycon precursors to these compounds are structurally homologous with other polyketide antibiotics, indicative of their common biosynthetic origins.[10] Indeed, each seco acid of the corresponding aglycon precursors bears evidence of the individual propionate, acetate, and occasionally other small carboxylates that are iteratively incorporated into their respective structures during biosynthesis.[11] For instance, the aglycon of oleandomycin, oleandolide (**1**), is a macrocyclic lactone whose polypropionate backbone comprises six propionate subunits and one acetate (Scheme 1). Biosynthetically, these simple building blocks are assembled in an iterative fashion through the enzymatic functions performed by polyketide syntheses and various reductases.[12]

To the chemical community, the stereochemical and functional group complexity of the polypropionate-derived macrolide antibiotics poses a formidable challenge for chemical synthesis. Studies toward the asymmetric synthesis of these natural products have stimulated the development of a host of new reactions and concepts for C−C bond construction in the context of acyclic stereocontrol.[13] To date, four syntheses of oleandolide (**1**) have been reported independently from Tatsuta's,[14] Paterson's,[15] Evans',[16] and our laboratories.[17] The first synthesis of **1** by Tatsuta and co-workers was reported in 1990 and employed a carbohydrate-based approach, and the later two syntheses from Paterson and Evans both relied on chiral enolate-based bond construction technology to establish the stereochemical relationships. In 1988 Tatsuta accomplished the bisglycosidation of oleandolide (**1**) to provide the natural product oleandomycin,

(10) (a) Hopwood, D. A.; Sherman, D. H. *Annu. Rev. Genet.* **1990**, *24*, 37−66. (b) Hutchinson, C. R.; Fujii, I. *Annu. Rev. Microbiol.* **1995**, *49*, 201−238.
(11) Woodward, R. B. *Angew. Chem.* **1956**, *68*, 13−20.
(12) (a) Cortes, J.; Haydock, S. F.; Roberts, G. A.; Bevitt, D. J.; Leadlay, P. F. *Nature* **1990**, *348*, 176−178. (b) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675−679. (c) Malpartida, F.; Hopwood, D. A. *Nature* **1984**, *309*, 462−464.
(13) (a) For a review of synthetic efforts in this field see Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624. (b) Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1452−1454. (c) *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukas, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2.
(14) Tatsuta, K.; Ishiyama, T.; Tajima, S.; Xoguchi, Y.; Gunji, H. *Tetrahedron Lett.* **1990**, *31*, 709−712.
(15) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287−11314.
(16) Evans, D. A.; Kim, A. N.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921−5942.
(17) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229−9230.

Scheme 2. Retrosynthetic Analysis of Oleandolide



and thus a synthesis of **1** constitutes a formal total synthesis of oleandomycin.[18] We elected to pursue the synthesis of oleandolide to expand the scope and the utility of the double-stereodifferentiating crotylation methodology recently developed in our laboratory.[19] It was our intention to design a highly convergent and efficient pathway that could address the selective installation of the stereogenic centers utilizing our chiral organosilane reagents.[20] The use of these reagents, which bear C-centered chirality, represents a mechanistically different approach from the chiral enolate and enolate surrogate methodology often used in the preparation of stereochemically complex molecules.

Results and Discussion

Synthesis Plan. Our retrosynthetic analysis of oleandolide (**1**) is outlined in Scheme 2. Opening of the lactone results in the generation of an acyclic C1−C14 seco acid. Studies on the related macrolide antibiotic erythromycin have shown that the stereochemistry at C9 is critical in determining the efficiency of macrolactonization reactions used to close the 14-membered ring: changing the configuration at C9 has a pronounced effect on the conformations available to the seco acid and hence on the success of the macrolactonization.[13] Although the C9

(18) Tatsuta, K.; Kobayashi, W.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975−3978.
(19) (a) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475−12476. (b) Panek, J. S.; Cirillo, P. F. *J. Org. Chem. Soc.* **1993**, *58*, 294−296. (c) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809−811. (d) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727−8730.
(20) For a review, see Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.

stereocenter would eventually be lost through oxidation to a ketone, this center, bearing an *S* configuration, has proved instrumental in achieving efficient conversion in the macrocyclization.[15,16] Consequently, the C9 stereocenter was installed as 9*S* configuration prior to macrocycle formation.

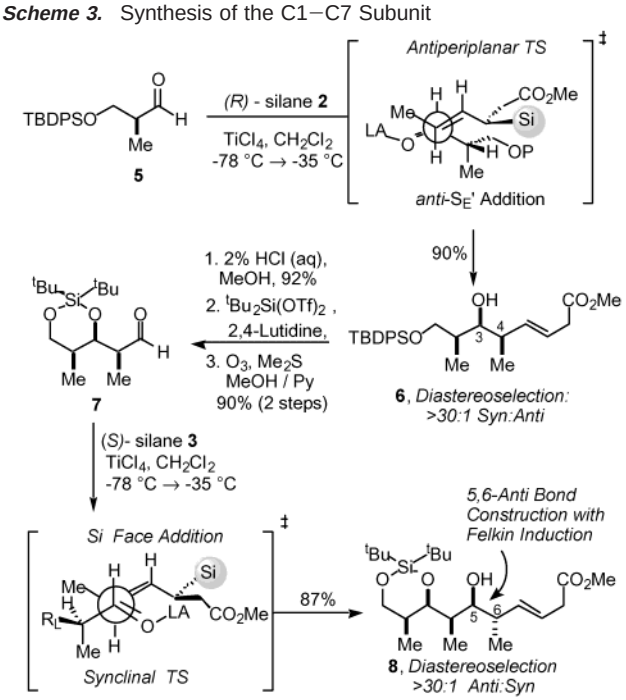
The exocyclic epoxide at C8 is a unique structual feature of oleandolide not found in any of the other known macrolide antibiotics; accordingly, it was envisaged that this sensitive functionality might be introduced after the macrocyclization. We reasoned that the *re* (α) face (bottom) of the exocyclic olefin might become sterically hindered and resistant to electrophilic addition if the allylic (*9S*)-hydroxy is protected by a large protecting group. Conventional epoxidation with *m*-CPBA should provide the desired diastereoisomer by delivering the electrophile predominantly from the *si* (*β*) face of the exocyclic alkene. Accordingly, the 9*S* configuration may play a crucial role not only in efficient macrolactonization but also in the late-stage substrate-controlled epoxidation. Planning a highly convergent synthesis, C−C bond disconnection of seco acid at C7−C8 would divide the molecule into two advanced subunits of similar complexity. The crucial carbon bond formation was based on a nucleophilic addition of an alkylmetal intermediate to the C8 aldehyde of the C8−C14 subunit. The required C8 olefin, precursor to the epoxide, will be installed by a phosphorus-based olefination methodology of the corresponding ketone.

Having defined a fragment coupling strategy, we focused on the stereoselective installation of stereogenic centers in the C1−C14 acyclic polypropionate backbone. The array of alternating methyl and oxygen groups on the carbon backbone suggested to us that eight of the stereocenters of oleandolide might be constructed through four double stereodifferentiating crotylation using three different chiral silanes.[21] The remaining stereocenter (C13-hydroxy) will be established by a heteroatom-directed hydride reduction of the corresponding *β*-hydroxy ketone. The Lewis acid promoted asymmetric crotylation between these chiral organosilanes and the requisite chiral aldehydes will be conducted for the introduction of the required stereogenic centers.

Synthesis of the C1−C7 Subunit. By employment of chiral organosilanes, the majority of the stereochemical relationships were introduced with high levels of selectivity. The synthesis of the C1−C7 subunit utilized two asymmetric crotylation reactions for the introduction of the C3−C4 and C5−C6 stereogenic centers. The construction began with an asymmetric crotylation between the α-methyl aldehyde **5** and silane reagent (*R*)-**2**,[21a] generating the 3,4-syn homoallylic alcohol **6** in 90% yield (dr > 30:1 *syn*:*anti*; Scheme 3). This syn-selective crotylation is consistent with an anti-S_E' mechanism.[19a,20] The use of Lewis acids such as $TiCl_4$ (1.2 equiv), in combination with a silicon-based protecting-group strategy, prevents chelate formation and helps direct the (*R*)-silane approach to the *si* face of the aldehyde, where the aldehyde adopts the preferred Felkin rotamer.

Homoallylic alcohol **6** was converted to aldehyde **7** in a three-step sequence: (i) desilylation with 2% aqueous HCl/MeOH at room temperature afforded the corresponding diol, and (ii) protection of the resulting diol with $^tBu_2Si(OTf)_2$ (1.1 equiv)

Scheme 3. Synthesis of the C1−C7 Subunit



and 2,6-lutidine in CH_2Cl_2 at −78 °C, followed by (iii) ozonolysis of the *E* double bond, successfully afforded **7** in 81% overall yield (Scheme 3). In the presence of $TiCl_4$, the condensation between aldehyde **7** and (*S*)-silane **3** produced the anti homoallylic alcohol **8** (dr > 30:1 5,6-anti/5,6-syn) with excellent levels of Felkin induction. In this double stereodifferentiating crotylation reaction, the formation of compound **8** can be rationalized by addition of silane **3** to the *si* face of the aldehyde **7** via the normally favored Felkin orientation in the transition state. The configuration of the silane, and the stereoelectronic preference for anti S_E' addition, determines the facial selectivity of the silane reagent, which is translated into the stereochemistry of the C5 methyl substituent of the product.

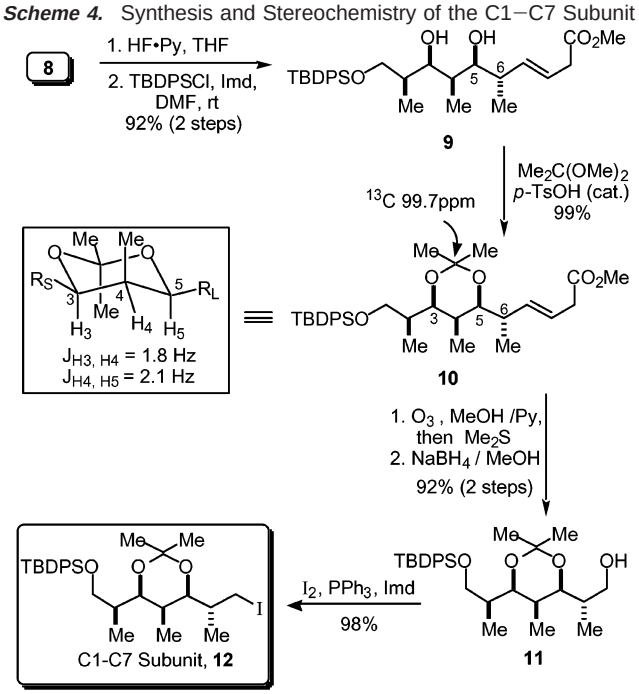
Compound **8** was converted to diol **9** in two steps: deprotection of the 1,3-diol (HF·Py) followed by selective protection of the primary hydroxyl as its *tert*-butyldiphenylsilyl (TBDPS) ether gave diol **9** in 92% overall yield. Acetonide formation between the C3−C5 diol of **9** provided acetonide **10** in nearly quantitative yield (Scheme 4). Analysis of the three-bond coupling constants correlating C_3-C_4 and C_4-C_5 in the ^1H NMR spectrum of acetonide **10** revealed small vicinal coupling values ($J_{H3,H4} = 1.8$ Hz, $J_{H4,H5} = 2.1$ Hz), which is consistent with syn stereochemistry between C3−C4 and C4−C5 stereogenic centers.

Further evidence for this assignment was obtained from the ^{13}C NMR chemical shifts of ketal and methyl groups of the acetonide carbons of **10** (99.7, 30.0, and 19.5 ppm respectively), which are in excellent agreement with the values commonly observed for *syn*-1,3-diol acetonides (methyl groups resonating at 19 and 30 ppm). The NMR experiment indicated a lack of resonance in the regions expected for an *anti*-1,3-diol acetonide (25.0 ppm).[22] Synthesis of the C1−C7 subunit **12** was completed

(21) (a) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78−88. (b) Jain, N. F.; Cirillo, P. F.; Schaus, J. V.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8723−8726.

(22) Rychnovsky and Evans have independently reported reliable ^{13}C NMR correlation experiments where ppm values of the quaternary carbon atom of acetonides can be correlated to 1,3-syn or 1,3-anti stereochemical relationships. (a) Rychnovsky, S. D.; Roger, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515 (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7103.

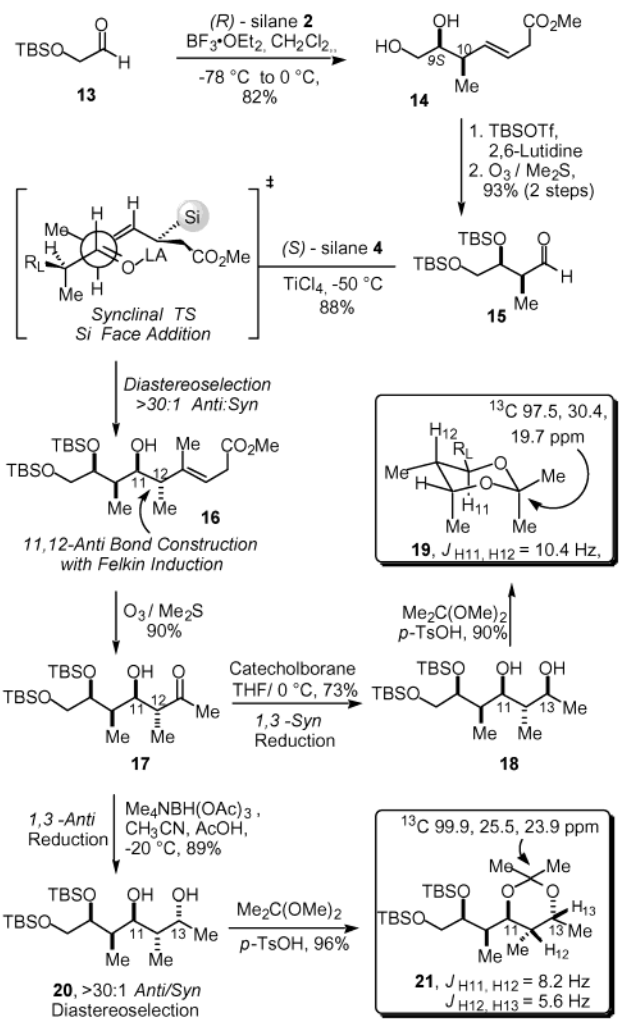
Scheme 4. Synthesis and Stereochemistry of the C1−C7 Subunit



by oxidative cleavage [O_3/dimethyl sulfide (DMS)] of the *E* double of **10**, followed by reduction of the crude aldehyde ($NaBH_4$), which gave primary alcohol **11** in 92% yield. Subsequent treatment of this material with PPh_3/I_2/imidazole[23] produced the primary alkyl iodide **12**, completing the C1−C7 subunit.

Synthesis of the C8−C14 Subunit. The synthesis of this subunit began with the syn-selective crotylation of α-silyloxy acetaldehyde **13** with silane (*R*)-**2**. This BF_3•OEt_2-promoted reaction gave diol **14** with high levels of selectivity and installed the C9 stereocenter (Scheme 5).[24] Deprotection of the primary *tert*-butyldimethylsilyl ether occurred while the reaction was warmed from −78 to 0 °C,[25] which led to the isolation of diol **14** in 80−82% yield. This diol was protected as its di-TBS ether; subsequent oxidative cleavage of the double bond (O_3/Me_2S) afforded α-methyl aldehyde **15** in 93% yield. This material was used in a second double stereodifferentiating crotylation reaction with *β*-methyl-substituted silane (*S*)-**4**.[21b] Use of a $TiCl_4$-promoted reaction (CH_2Cl_2 at −50 °C) produced the 11,12-*anti*-homoallylic alcohol **16** (88% yield; dr > 30:1 anti/syn) with Felkin induction.[19a] The use of chiral silane **4** permitted the introduction of a trans-trisubstituted olefin, which was cleaved under standard ozonolysis conditions to afford the *β*-hydroxyketone **17**. To confirm the anti stereochemistry between the newly installed methyl and hydroxyl groups in compound **16**, the *β*-hydroxyketone **17** was converted to acetonide **19** in two steps: (i) directed reduction utilizing catecholborane[26] gave syn diol **18**, followed by (ii) conversion of the diol **18** to acetonide **19** by use of 2,2-dimethoxypropane with a catalytic amount of *p*-TsOH. Analysis of the ^1H NMR spectrum of this acetonide revealed a large vicinal coupling

Scheme 5. Synthesis of the C8−C14 Subunit



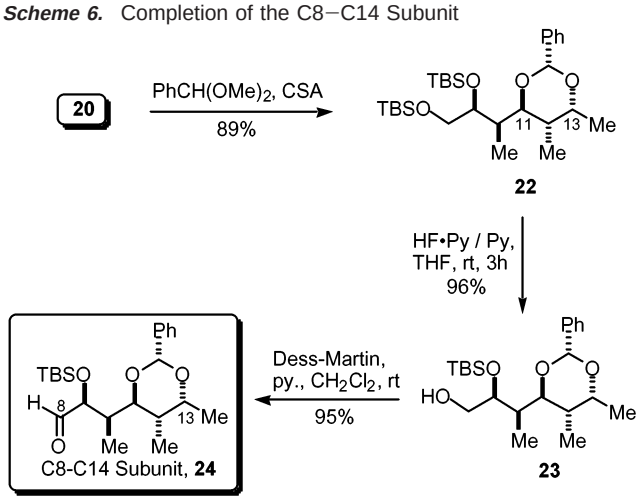
constant (J = 10.4 Hz) between H_{11} and H_{12}, which confirmed the anti relationship between C11−C12 stereocenters. The ^{13}C chemical shifts of the acetonide carbons of **19** are 97.5, 30.4, and 19.7 ppm, indicative of a *syn*-diol-derived acetonide.[22]

The desired *anti*-diol **20** was obtained by a heteroatom-directed hydride reduction of *β*-hydroxyketone **17** with $Me_4NBH(OAc)_3$.[27] This directed reduction afforded the *anti*-1,3-diol **20** in 89% yield as a single diastereomer. The C11−C13 anti stereochemical relationship of diol **20** was verified by analysis of the ^{13}C NMR spectrum of the corresponding acetonide **21**. The chemical shifts of the two acetonide methyl groups were observed at 25.5 and 23.9 ppm, in agreement with values commonly observed for an *anti*-1,3-diol acetonide (25.0 ppm).[22]

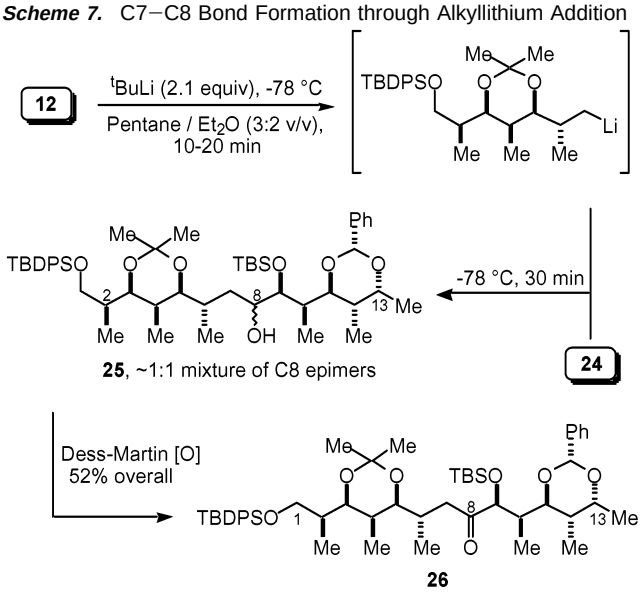
With the installation of all the requisite stereogenic centers of the C8−C14 subunit, we elected to protect the C11,C13 *anti*-diol as its benzylidene acetal to achieve an orthogonal protection (Scheme 6). Accordingly, a thermodynamically controlled acetalization of the C11,C13 *anti*-diol **20** with benzaldehyde dimethyl acetal in the presence of a catalytic amount of CSA gave, after 12 h, compound **22** as a single stereoisomer. The primary TBS silyl ether was selectively deprotected with HF•Py/pyridine/tetrahydrofuran (THF) [1:2:5 v/v/v; room temperature, 3 h, 96% yield], and the resulting primary alcohol **23**

(23) Corey, E. J.; Pyne, S. G.; Su, W. G. *Tetrahedron Lett.* **1983**, *24*, 4883−4886.
(24) The 9*S* isomer has been shown to be crucial in the success of the macrocyclization reaction; see refs 15 and 16 for further discussion.
(25) Due to the low reactivity profile of this reaction, a higher reaction temperature was required to drive the reaction into completion.
(26) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190−5192.
(27) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

Scheme 6. Completion of the C8−C14 Subunit



Scheme 7. C7−C8 Bond Formation through Alkyllithium Addition



was converted to chiral aldehyde **24** by oxidation with the Dess−Martin reagent,[28] completing the synthesis of the C8−C14 subunit.

C7−C8 Bond Formation. With the C1−C7 and C8−C14 subunits in hand, the stage was set to explore conditions to merge the two subunits. Our first experiments centered on the direct addition of an organometallic species derived from iodide **12** to aldehyde **24**. This option would construct the C7−C8 carbon bond while convergently providing the fully functionalized C1−C14 polypropionate backbone of the macrolide. Preliminary experiments revealed that simple nucleophiles, alkyllithium (MeLi), or Grignard reagents (EtMgBr, *n*-BuMgCl) cleanly added to substrate **24** at low temperature. However, attempts to convert **12** into such species were unsuccessful. The organolithium derived from **12** by halogen−metal exchange with ^{t}BuLi (2.0 equiv) was itself short-lived and operationally difficult to handle.[29] A diethyl ether or THF solution of the organolithium intermediate could be maintained at low temperature and added to aldehyde **24**, although low yields (15−20%) of the product were observed. Attempts to transmetalate the organolithium derived from **12** with $MgBr_2$, CuCN, or $CeCl_3$ prior to addition of aldehyde **24** led to poor isolated yields, formation of byproducts, or decomposition of the starting aldehyde.

After considerable effort, we found that in the solvent system of Bailey and Punzalan[30] (pentane/diethyl ether, 3:2 v/v), the derived alkyllithium intermediate of **12** condensed with aldehyde **24** at −78 °C and gave **25** as a mixture of diastereomeric alcohols in 50−60% modest yield. This mixture of secondary alcohols **25** was oxidized to the ketone by use of the Dess−Martin reagent, providing **26** in 52% yield (two steps from aldehyde **24**; Scheme 7). Having prepared the C1−C14 carbon backbone of the natural product, further elaboration to the seco acid was next pursued.

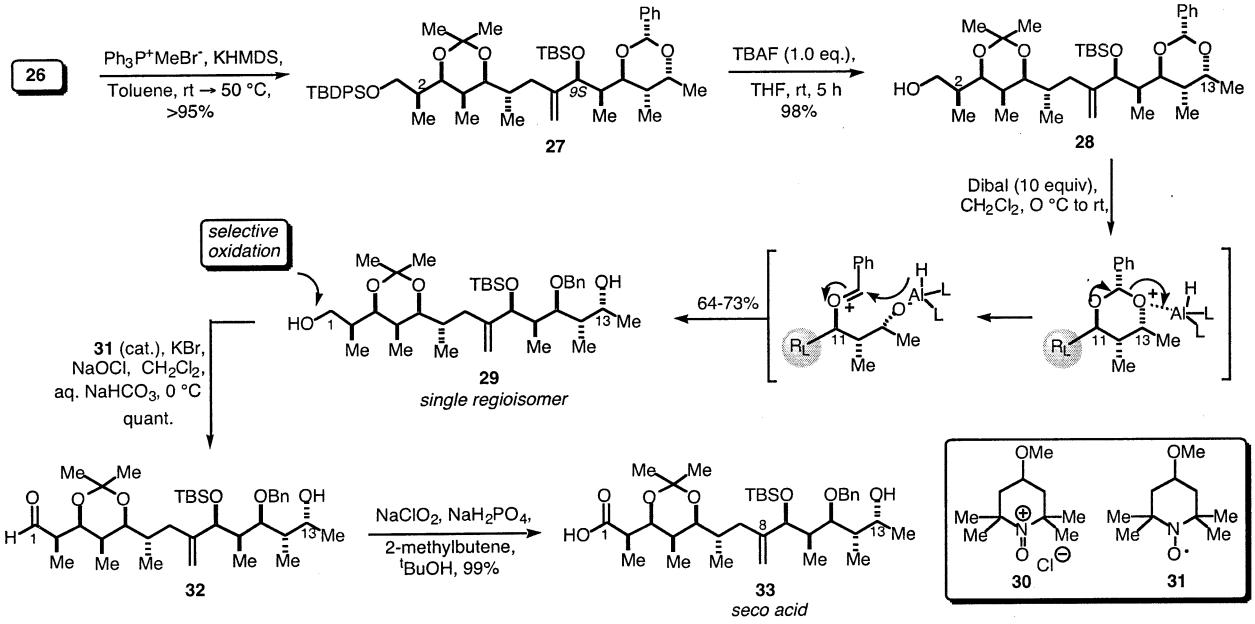
Synthesis of the Seco Acid. Olefination of ketone **26** was undertaken to establish the C8 terminal olefin that would serve as the precursor to the epoxide. Accordingly, Wittig olefination with triphenylphosphonium methylide ($Ph_3P{=}CH_2$) cleanly produced the desired alkene **27** in 95% yield (Scheme 8). Transformation of the C1-alcohol to a carboxylic acid required selective removal of the primary TBDPS protecting group in the presence of the secondary TBS ether at C9, which presented potential problems given the complexity and acid liability of the molecule.[31,32] Gratifyingly, the TBDPS group could be cleanly removed by 1.0 equiv of tetrabutylammonium fluoride (TBAF) and provided the primary alcohol **28** in 98% yield with the C9 TBS ether left intact. In the next important reaction sequence, the benzylidene acetal of **28** was opened regioselectively in the presence of excess diisobutylaluminum hydride (DIBAL)[33] to afford diol **29** in ∼70% yield, which liberated the C13 secondary hydroxy.

The conversion of diol **29** to seco acid **33** necessarily required the selective oxidation of the C1-hydroxy to a carboxylic acid in the presence of the secondary C13 OH group. Recent literature precedent had indicated that the use of hindered chlorooxoammonium salts should be ideal for this process.[34] The use of stoichiometric oxoammonium chloride salt **30** for selective oxidation of compound **29** resulted in a complicated mixture of products. However, in situ generation of the unstable salt derived from 4-methoxy-2,2,6,6,tetramethylpiperidine-1-oxyl (4-methoxy-TEMPO) **31** by a catalytic process proved to be efficient and produced the desired hydroxy aldehyde **32** in quantitative yield.[35] This material was further oxidized by sodium chlorite to deliver the seco acid **33** in 99% yield.[36]

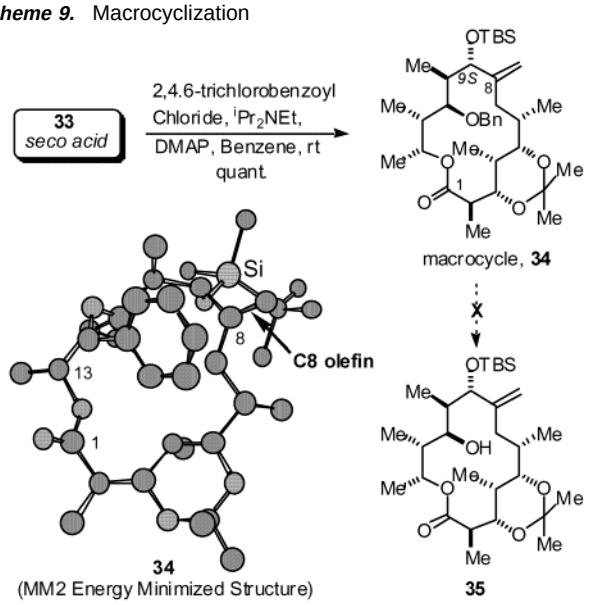
Cyclization and Elaboration of the Macrocycle. Macrolactonization of the (9*S*)-TBS ether **33** was effected under modified Yamaguchi conditions[37] to afford macrolide **34** in

(28) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(29) For a review on the halogen−lithium exchange using ^{t}BuLi, see Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1−23.
(30) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5400−5406.
(31) For an excellent review on selective deprotection of silyl ethers, see Nelson, T. D.; Crouch, R. D. *Synthesis*, **1996**, 1031−1069.
(32) For review on protecting-group strategies in organic synthesis, see Schelhaas, M.; Waldmann H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2056−2083.
(33) (a) Yamamoto, H.; Maruoka, K. *Tetrahedron* **1988**, *44*, 5001−5032. (b) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1596.
(34) For recent review, see DeNooy, A. E. J.; Basemer A. C.; VanBekkum, H. *Synthesis* **1996**, 1153−1174.
(35) (a) Anelli, P. L.; Biffi, C.; Montanarie, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (b) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856−6872.
(36) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574−5576.
(37) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367−6370. (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9.

Scheme 8. Preparation of Seco Acid



Scheme 9. Macrocyclization



quantitative yield (Scheme 9). This cyclization was performed as a two-step, one-pot procedure whereby an intermediate mixed anhydride was formed from 2,4,6-trichlorobenzoyl chloride before treatment with excess *N*,*N*-dimethyl-4-aminopyridine (DMAP).[37] This highly efficient cyclization may be attributed to the preferential closure of the seco acid in which the large C-9*S* substituent ultimately can achieve the thermodynamically more stable pseudoequatorial position on the macrocycle **34**.[38]

With the assembly of the macrocycle complete, the synthesis was nearing the stage for introduction of the last stereogenic center, the C8 exocyclic epoxide. Depicted as one of the low-energy conformers of **34**, the *re* (bottom) face of C8 olefin is illustrated as being blocked by the C9-OTBS group, whereas the *si* (top) face was obstructed by the C11-benzyl ether (Scheme 9).[39] Higher energy conformations (up to 8 kJ mol^{-1} above the ground state) showed a similar local conformation about the C8 olefin. Furthermore, attempts to introduce the C8-epoxide on **34** prior the C11-benzyl group removal proved unsuccessful.[40] The results of those experiments indicated that, to obtain a stereoselective epoxidation, the C11 benzyl group of macrocycle **34** needed to be removed in order to expose the *si* face of the C8 olefin. Unfortunately, all attempts at the debenzylation of macrocycle **34** failed. The presence of the C8 double bond in **34** precluded the use of standard hydrogenolysis conditions for benzyl ether deprotection; while debenzylation via a dissolving metal reduction (Li or Na/liquid NH_3, THF, −78 °C) reduced the lactone. Furthermore, by use of Freeman's lithium di-*tert*-butylbiphenyl radical anion (LDBB) reagent[41] in THF at −78 °C, the desired alcohol **35** was obtained in modest yields ranging between 20% and 30%.

At this stage of the synthesis, it became apparent that although a convergent, stereoselective synthesis of the macrolide **34** had been developed, the elaboration of this intermediate to complete the synthesis of oleandolide was likely to be difficult resulting from late-stage protecting-group manipulations. In addition, modest yield obtained during the fragment coupling [**12** + **24** → **25**] and the benzyl ether removal [**34** → **35**] placed us in a difficult position to complete the synthesis in seamless manner. Accordingly, we concluded that a more effective fragment coupling protocol and protecting-group strategy was necessary to achieve an efficient synthesis of oleandolide.

Revised Retrosynthetic Analysis. In the revised approach, the crucial C7−C8 bond formation relied on a Pd(0)-catalyzed sp^3−sp^2 cross-coupling reaction between an alkylmetal species and a vinyl triflate fragment (Scheme 10). The new approach retains the same C1−C7 subunit **12**, and the vinyl triflate **38** would be readily accessible from aldehyde **24**.

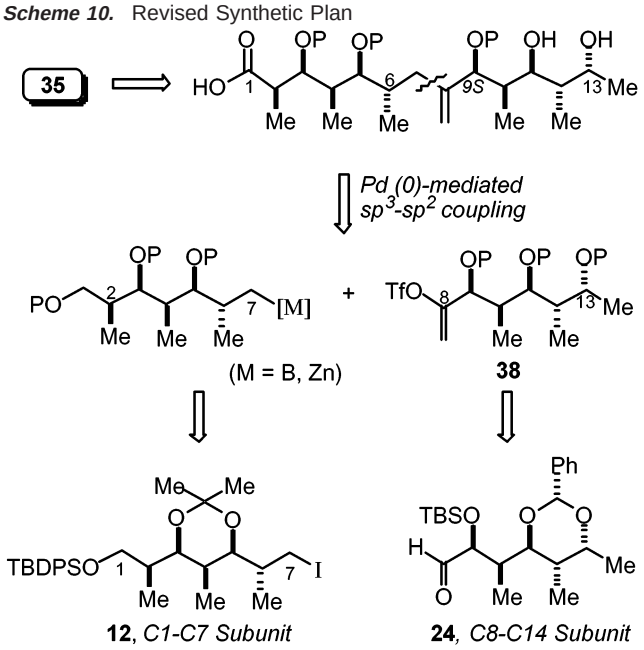
(38) Previous work on the related macrolide antibiotic erythromycin has shown that the stereochemistry at C9 is critical for the efficiency of macrocyclization; see Woodward, R. B., et al. *J. Am. Chem. Soc*. **1981**, *103*, 3213−3215. Also see refs 15 and 16.

(39) A Monte Carlo MM2 energy minimization protocol was used for these calculations.

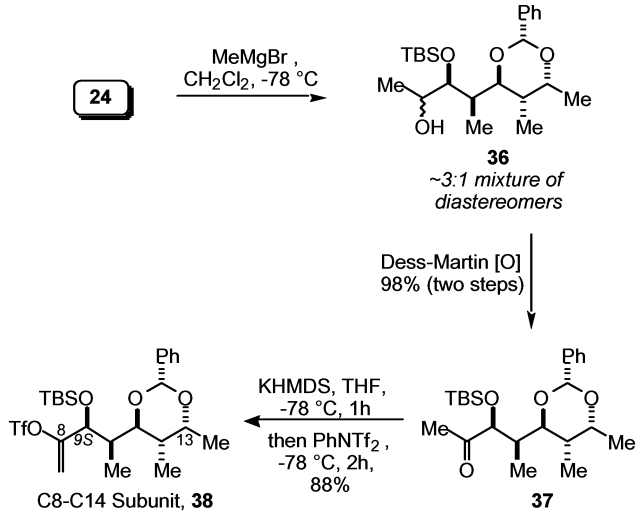
(40) When compound **34** was subjected to standard epoxidation conditions (such as *m*-CPBA or H_2O_2/$KHCO_3$), no epoxidation product was detected and only unchanged starting material was recovered. Also see Table 1.

(41) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem*. **1980**, *45*, 1924−1930.

Scheme 10. Revised Synthetic Plan



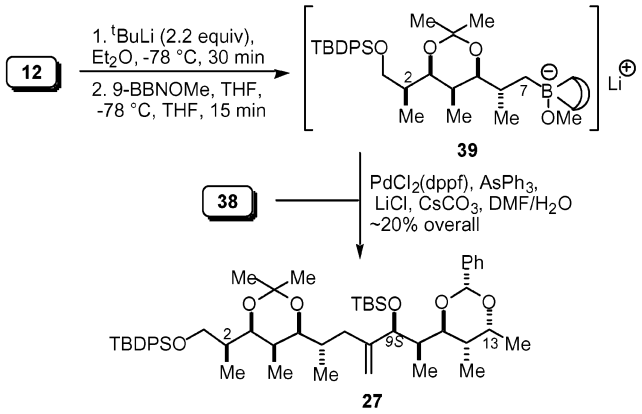
Scheme 11. Revised Synthesis of the C8−C14 Subunit



Particularly compelling were the mild characteristics of the palladium-mediated coupling reaction compatible for highly functionalized cases. Although less structurally complex alkylmetal species are known to undergo cross-coupling reactions with vinyl triflates, the highly functionalized α,β-branched alkylmetal intermediates have received little attention in complex molecule and natural product synthesis.[42] In that context, the use of such a modified Negishi-like coupling would allow for an efficient and highly convergent approach to oleandolide. In addition, the benzylidene functionality between the C9 and C11 hydroxyls would be manipulated prior to macrocyclization.

Revised Synthesis of the C8−C14 Subunit. Synthesis of the C8−C14 vinyl triflate fragment began with aldehyde **24** (Scheme 11). The one-carbon homologation of aldehyde **24** to compound **36** was accomplished by the addition of MeMgBr (3.0 equiv) at low temperature (−78 °C), which produced alcohol **36** as a ∼3:1 mixture of diastereomers. The mixture was oxidized with the Dess−Martin reagent to afford ketone **37** in excellent yield (98% over two steps). The methyl ketone was then converted to vinyl triflate **38** in 88% yield by trapping of the potassium enolate with *N*-phenyltriflimide ($PhNTf_2$, 2.0 equiv), thereby completing the assembly of the C8−C14 subunit.

Scheme 12. Pd(0)-Mediated sp^3-sp^2 Suzuki Coupling



Pd(0)-Mediated Fragment Coupling. With the revised synthesis of the C8−C14 subunit completed, we were in a position to probe the feasibility of a palladium-catalyzed cross-coupling reaction between primary iodide **12** and vinyl triflate **38** to effect C7−C8 bond formation. Recently, Suzuki and coworkers[43] have documented the scope and limitations of the palladium-catalyzed alkyl boronate coupling reactions with triflates and their synthetic applications. We envisioned that a Suzuki coupling sequence may be ideally suited for our fragment coupling, as the required sp^3-hybridized organoboron can be conveniently generated from an alkyllithium (derived from **12**) through Li → B transmetalation.[44,45]

The cross-coupling process was initiated by an iodine → lithium exchange with ^{t}BuLi (2.1 equiv, 30 min) followed by addition of *B*-methoxy-9-BBN to generate the *ate* complex **39**.[45a] Subsequent coupling with vinyl triflate **38** in the presence of the $PdCl_2$(dppf) catalyst and LiCl additive (3.0 equiv) gave the desired coupling product **27** in a disappointing 12% isolated yield, with a large amount of starting vinyl triflate **38** (∼40%) and homocoupling product (25−30%) also isolated (Scheme 12). In efforts to enhance the reaction efficiency, several different combinations of bases, palladium sources, and solvent systems were evaluated; however, only low yields (5−15%) of product could be obtained.[46] The use of higher reaction temperature or longer reaction times did not improve the yield of desired coupling product but produced significant decomposition and increased amount of homocoupling product. Current mechanistic understanding concerning these cross-coupling reactions suggest that the low reaction yields obtained from these

(42) For reviews on vinyl or aryl triflate chemistry, see (a) Ritter, K. *Synthesis* **1993**, 735−762. (b) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47−54.

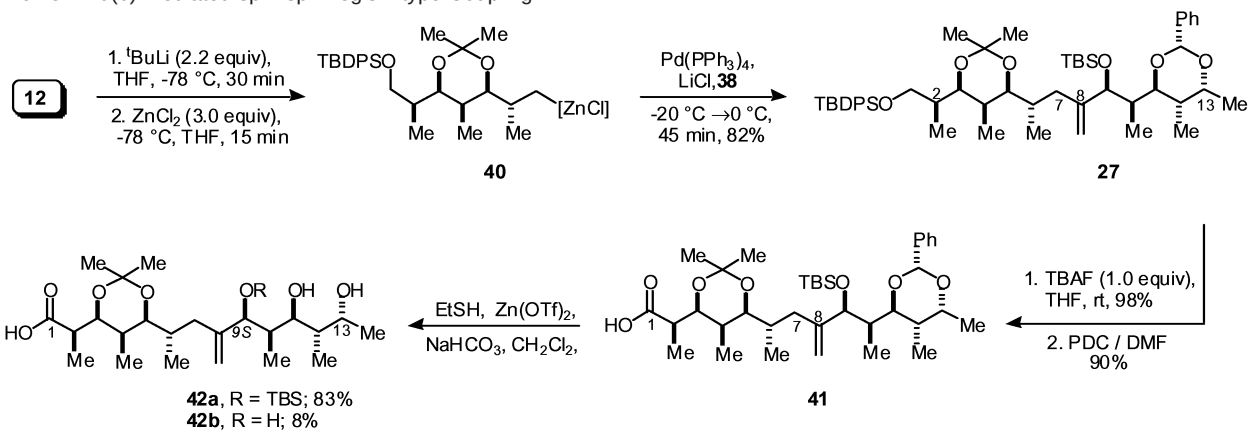
(43) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201−2208.

(44) For recent review on Suzuki coupling, see Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(45) For selected recent synthetic applications of sp^3-sp^2-type Suzuki coupling reactions, see (a) Marshall, J.; Johns, B. *J. Org. Chem.* **1998**, *63*, 7885−7892. (b) Meng, D.; Bertinato, P.; Balog, A.; Su, D.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073−10092. (c) Johnson, C. R.; Braun M. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015.

(46) It is worth pointing out that the presence of a stoichiometric amount of water was necessary for successful cross-coupling reactions. This observation is consistent with studies previously reported by Johnson and Braun; see ref 45c.

Scheme 13. Pd(0)-Mediated sp^3-sp^2 Negishi-type Coupling



experiments may be attributed to the slow rate of transmetalation between the alkyl boronate and the Pd(II) intermediate.[44] The weak σ-donor ligand triphenylarsine ($AsPh_3$) was used to increase the electrophilicity of the Pd(II) intermediate (therefore accelerating the rate-determining transmetalation step); however, only a slight improvement of the yield (~20%) was achieved.[47]

The poor efficiency of the Suzuki coupling reaction in our hands prompted us to turn our efforts toward a Negishi-type coupling, in which an alkylzinc intermediate would be used as the nucleophilic reaction partner in the sp^2-sp^3 cross-coupling reaction.[48] The rationale was that the transmetalation of Zn → Pd would be much faster than the corresponding B → Pd transformation;[49] therefore, higher catalytic turnover and a cleaner reaction might be achieved. Examination of the literature precedents indicated that certain unfunctionalized alkylzinc species can undergo coupling reactions with vinyl triflates;[50] however, the palladium(0)-mediated cross coupling between a functionalized, α,β-branched alkylzinc intermediate and vinyl triflate had not been documented.

As illustrated in Scheme **13**, the alkyllithium reagent derived from **12** (via I → Li exchange) was transmetalated in situ with a solution of anhydrous $ZnCl_2$ (3.0 equiv) in THF at −78 °C for 15 min to afford the sp^3-hybridized alkylzinc species **40**. Since this intermediate was not stable at temperatures above 0 °C, it was crucial to use this material directly in the palladium-catalyzed coupling with vinyl triflate **38** while the reaction temperature was maintained between −20 and 0 °C. In contrast to the Suzuki-like reaction, this one-pot sequence involving an organozinc intermediate sp^3-sp^2 C−C bond formation afforded the C1−C14 carbon backbone **27** in 82% yield.[51] The remarkable efficiency of this cross-coupling reaction appears to be a consequence of the higher reactivity of the alkylzinc species compared to the organoboronate adduct used in the Suzuki reaction.

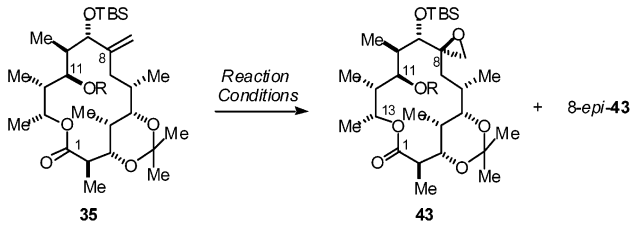
With an efficient approach to the advanced intermediate **27** being established, the final stages of the synthesis could now be addressed. The primary C1-TBDPS protecting group of **27** was selectively removed, and the resulting primary alcohol was oxidized to the corresponding carboxylic acid by use of PDC (10 equiv, DMF, room temperature),[52] affording **41** in 90% yield (Scheme 13). Selective removal of the benzylidene acetal from the C11 and C13 oxygens proved to be quite challenging. Conditions for deprotection (BCl_3, $FeCl_3{\cdot}SiO_2$, $FeCl_3{\cdot}6H_2O$, I_2/MeOH) were unselective as competing deprotection of the C9-OTBS and/or C3−C5 acetonide were observed. Furthermore, reduction by use of dissolving metal (Na/NH_3, $Li/EtNH_2/EtOH$) gave complicated reaction mixtures, and catalytic phase-transfer hydrogenolysis, with 20% $Pd(OH)_2$ on carbon and cyclohexene as the hydrogen donor at reflux, did provide the desired product in a modest 41% yield.[53] Under the best conditions identified thus far, the desired seco acid **42a** could be obtained in 83% yield by use of $EtSH/Zn(OTf)_2$ in CH_2Cl_2 buffered with $NaHCO_3$ powder.[54] During the course of this reaction, approximately 8% triol acid **42b** was also isolated as a side product.

Macrocyclization and Epoxidation of C8 Exocyclic Olefin. The seco acid **42a**, bearing the C11−C13 diol, was cyclized under modified Yamaguchi conditions[40] to afford the 14-membered macrolide **35** in excellent yield. No trace of the undesired 12-membered lactone was detectable by ^1H NMR spectroscopy (Scheme 14).[55] It was postulated that the strong conformational preference of the seco acid containing a large substituent at 9*S* predisposes the dihydroxy acid to cyclize efficiently. In this case, the 9*S*-OTBS group eventually achieved a thermodynamically favored pseudoequatorial position.

The elaboration of macrocycle **35** to oleandolide required the stereoselective introduction of an epoxide at C8. In this regard, molecular modeling[39] studies suggested that good levels of *si* (β) face selectivity could be expected in electrophilic additions to the C8 alkene of the macrolide, as the bulky allylic TBS ether blocks the *re* (α) face of the alkene. Indeed, the crucial epoxidation with *m*-CPBA (CH_2Cl_2, room temperature, 4 h) turned out to be remarkably selective, affording the β-epoxide

(47) The benefits of $AsPh_3$ in the Stille reaction have been well documented; see Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585−9595.
(48) Negishi, E. *Acc. Chem. Res*. **1982**, *15*, 340−348.
(49) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N.; *J. Am. Chem. Soc*. **1987**, *109*, 2393−2401.
(50) For reviews on organozinc reagents in organic synthesis, see (a) Knochel, P.; Singer, R. D. *Chem. Rev*. **1993**, *93*, 2117−2188. (b) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648.
(51) Although this cross-coupling reaction proceeded well with THF as solvent, the same reaction in diethyl ether or THF/Et_2O was much more sluggish.
(52) Corey, E. J.; Schmidt, G.; *Tetrahedron Lett.* **1978**, *5*, 399−402.
(53) Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396−397.
(54) Nicolaou, K. C.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl*. **1990**, *30*, 300−303.
(55) Although triol acid **42** was isolated as a side product during the deprotection of the benzylidene, the amount obtained was sufficient to attempt macrocyclization. When this material was subjected to the identical macrocyclization conditions used before, a complicated mixture of monolides and diolides was obtained.

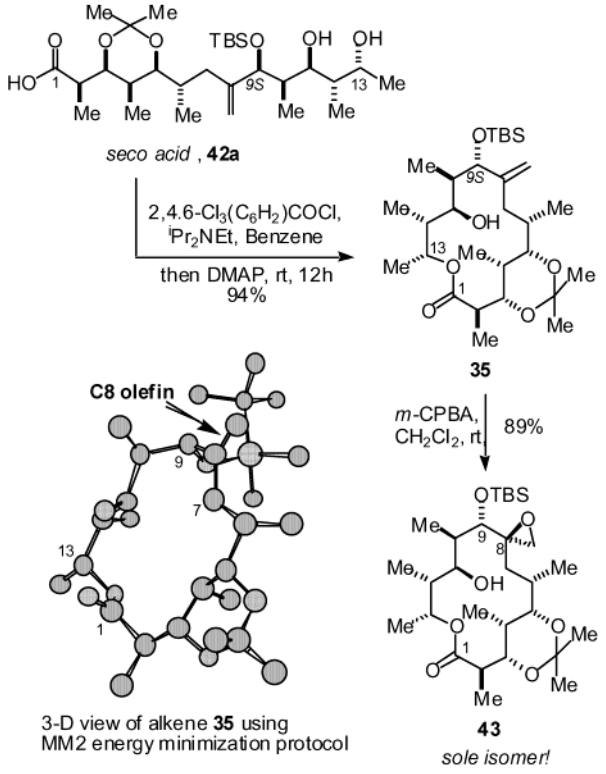
Table 1. Substrate-Controlled Epoxidation of the C8 Exocyclic Olefin



R	reagent	solvent	**43**:8-epi-**43**[a]	yield[b] (%)
H	*m*-CPBA	CH_2Cl_2	100:0	89
	m-CPBA	Et_2O	100:0	58
	$CF_3CO_3H/NaHCO_3$	benzene	100:0	82
Me	*m*-CPBA	CH_2Cl_2	100:0	28
	$CF_3CO_3H/NaHCO_3$	benzene	96:4	31
Bn	*m*-CPBA	CH_2Cl_2		0
	$CF_3CO_3H/NaHCO_3$	benzene		0

[a] Ratio determined by ^{1}H NMR analysis of crude sample. [b] Isolated yield after SiO_2 column chromatography.

Scheme 14. Stereoselective Epoxidation

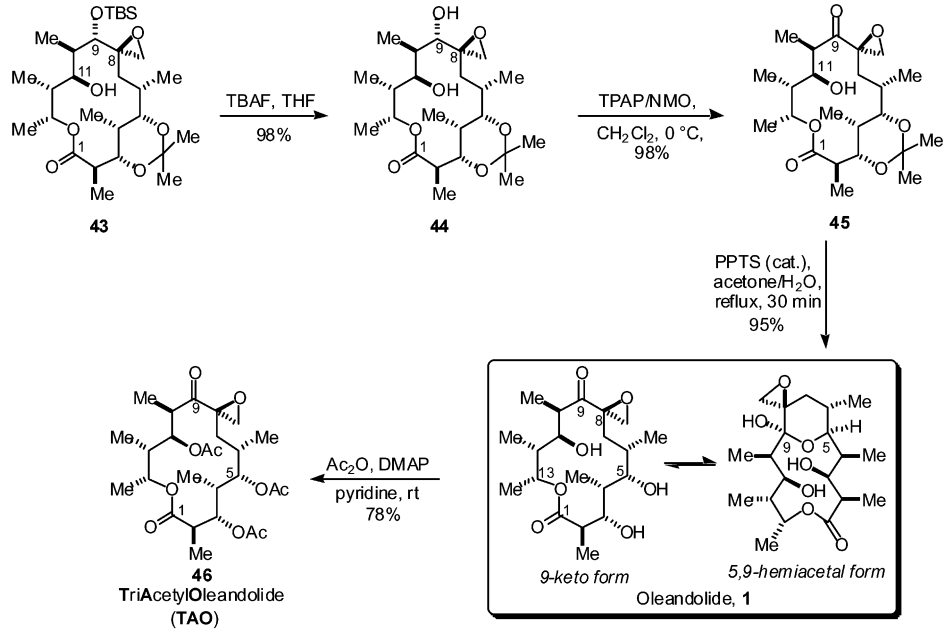


43 as a single diastereomer in excellent yield (Table 1).[56] This reaction is perhaps a nice illustration of the Henbest principle as it translates to a 14-membered macrolide in a transannular epoxidation reaction.[57] Interestingly, in the absence of the directing influence of the hydroxy group, the epoxidation of the methyl ether version of **35** proceeded at a much slower rate (room temperature, 24 h) and only ~30% yield could be achieved. As suggested by a reviewer, the reduced reaction rate and efficiency observed in the epoxidation of the methyl ether version may simply reflect the branched nature of the methyl ether relative to a hydroxyl group. This notion is supported by the early work of Chan and Rickborn[58] concerning their results on methoxy-directed cyclopropanations of allylic and homoallylic cyclohexenols. Finally, our attempts to introduce the C8-epoxide on the C11-benzyl ether of **35** (Scheme 9, substrate **34**) were unsuccessful, as no trace of epoxide was detected under several different epoxidation conditions. These experimental results are consistent with a steric control approach and underscore the important role of the remote C11-hydroxy (methyl ether) as a heteroatom directing group in substrate-controlled epoxidation.[59]

At this juncture, the completion of the oleandolide synthesis required two deprotection steps and the oxidation of the C9-hydroxyl to the corresponding ketone. The C9 silyl ether of **43** was cleanly removed by use of TBAF (1.5 equiv, THF, room temperature, 30 min), affording diol **44** in 98% yield. Taking advantage of the steric nature of tetrapropylammonium perruthenate (TPAP),[60] the selective oxidation of diol **44** at the C9 hydroxy was accomplished with TPAP/NMO in CH_2Cl_2 at 0 °C, giving the epoxy ketone **45** in 98% yield (Scheme 15). The selectivity of this TPAP oxidation is believed to originate from the positioning of the C11 pseudoequatorial hydrogen into the center of the macrocycle making it inaccessible in the oxidative addition step involving the α-C−H bond to the oxo metal bond.[61,62] Finally, deprotection of the C3−C5 acetonide by use of PPTS in acetone/water (10:1 v/v) under reflux for 30 min cleanly produced oleandolide **1** in 95% yield,[63] which was obtained as an expected 1:3 mixture of 9-keto and 5,9-hemiacetal tautomers (Scheme 15). The spectral data and physical properties [^{1}H and ^{13}C NMR, IR, $[\alpha]_D$, R_f , and high-resolution mass spectrometry (HRMS)] were identical with the published data.[15,16] As further confirmation of structure, the triacetate derivative **46** was prepared and its properties proved to be identical to the published analytical data as well.[15,16]

(56) The stereochemical assignment of epoxide **43** was made by measurement and analysis of ^{1}H NMR three-bond coupling constants and analysis and nuclear Overhauser effect (NOE) experiments.
(57) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959**, 1968−1965.
(58) (a) Chan, J. H.-H.;.; Rickborn, B.. *J. Am. Chem. Soc.* **1968**, *90*, 6406−6411. (b) Staroscik, J. A.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 738−740.
(59) For a review on heteroatom substrate-directed reactions, see Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.
(60) For a review on TPAP/NMO oxidation protocol, see Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.
(61) For a mechanistic discussion of the TPAP-catalyzed oxidation, see Lee, D. G.; Congson, L. N. *Can. J. Chem.* **1990**, *68*, 1774−1779.
(62) For the first selective oxidation with chromic acid on a related erythrolide B analogue, see Corey, E. J.; Melvin, L. S. *Tetrahedron Lett.* **1975**, 929−932.
(63) Other reaction conditions (5% Rh on carbon/H_2/EtOH; $FeCl_3 \cdot 6H_2O$) proved unsuccessful as the C8 epoxide opening and/or decomposed products were obtained.

Scheme 15. Completion of the Total Synthesis of Oleandolide



Conclusion

A convergent enantioselective synthesis of oleandolide has been achieved in 32 steps (20 steps longest linear sequence) and 16.3% overall yield. Since the two sugar units have been previously introduced onto oleandolide by Tatsuta's group,[14] this work also constitutes a formal total synthesis of oleandomycin.

Key features of the synthesis include high levels of selectivity in the crotylation reactions used to establish seven out of 10 stereogenic centers. An apparent transannular heteroatom-directed epoxidation reaction of the C8 olefin, assisted by the C11-β-OH, was used for the introduction of the 8*R* epoxide. Also of note is the use of a underdeveloped Negishi-type sp^3-sp^2 fragment coupling reaction between a functionalized alkylzinc intermediate **40** and vinyl triflate **38** for the construction of the carbon backbone of oleandolide. On balance, the asymmetric crotylation methodology offers a promising and mechanistic complementary alternative to aldol- and aldol surrogate-based approaches to these natural products.

Acknowledgment. We are grateful to Professor David A. Evans and Dr. Annette S. Kim (Harvard University) and to Dr. Nareshkumar F. Jain (R. W. Johnson PRI) for helpful discussions. Financial support was obtained from NIH (GM55740).

Supporting Information Available: Complete experimental procedures and spectral characterization of all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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