Total Synthesis of Oleandolide

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Over the last three decades, the macrolide antibiotics such as oleandomycin and erythromycins have had extensive and effective applications in bacterial chemotherapy. Oleandomycin (**1**) is representative of the 14-membered macrolide antibiotics which is produced by the actinomycete *Streptomyces antibioticus*, originally reported by Sobin et al. in 1955.[1] The complete structure of oleandomycin was established in 1960 by Celmer, Woodward, and co-workers.[2] Its absolute configuration was assigned by NMR techniques in 1965,[3] and later confirmed by X-ray analysis.[4] Oleandomycin inhibits bacterial RNA-dependent protein synthesis by binding to the 50-S ribosomal subunit and blocking either transpeptidation and/or translocation reactions.[5] The stereochemical complexity and extensive functionalization of the macrolide backbones render these molecules synthetically challenging targets. Three syntheses of oleandolide have been reported, the later two employed an aldol-based approach to introduce the polypropionate subunits.[6] Herein, we report a highly convergent total synthesis of oleandolide (**2**) based on the use of chiral crotylsilane methodology developed in our laboratories.

Our synthesis plan relied upon the use of a diastereoselective epoxidation of lactone **23** to introduce the C8-epoxide and a Pd-(0)-catalyzed sp^3-sp^2 cross-coupling reaction between the left- and right-hand subunits. These advanced intermediates were thought to be accessible by the use of Lewis acid promoted asymmetric crotylations for the introduction of the stereogenic centers (Figure 1). After conversion of oleandolide into its seco acid **3**, it was further divided into two halves, the left- and right-hand subunits (C1−C7) and (C8−C13) **4** and **5**, respectively. Further analysis of the individual subunits produced silane reagents **6**−**8**[7] of which (*S*)-**7** and (*S*)-**8** were used in two highly selective double stereodifferentiating *anti*-crotylations.[8] This plan allowed for the introduction of the (*9S*)-stereocenter early in the synthesis, which was critical for an efficient macrocyclization and the stereoselective introduction of the C8 epoxide.

The synthesis of the left-hand subunit **4** utilizes two asymmetric crotylations for the introduction of the C3−C4 and C5−C6 stereogenic centers. Its construction began with an asymmetric crotylation between α-methyl aldehyde **9** and silane (*R*)-**6**[7a] generating homoallylic alcohol **10** (Scheme 1). This syn-selective crotylation was thought to proceed through an open transition state where the observed stereochemistry is consistent with an anti-S_E' mode of addition.[8] The homoallylic alcohol **10** was converted to the silyl protected aldehyde **11** with a three-step sequence in 87% overall yield. This material was used in a double

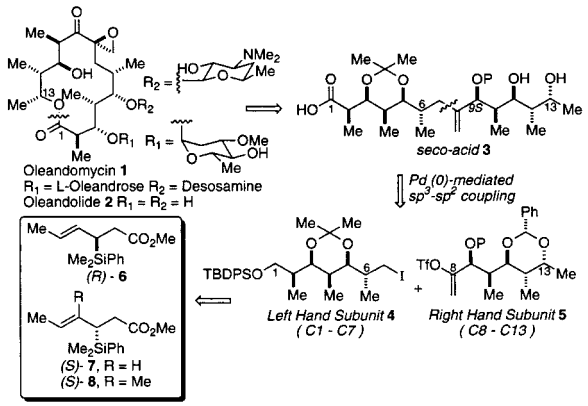
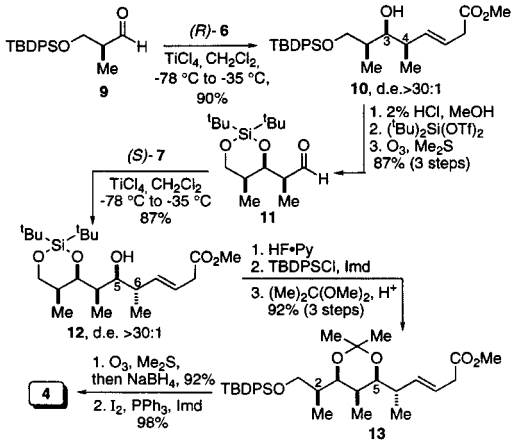


Figure 1.

Scheme 1



stereodifferentiating *anti*-crotylation reaction with silane (*S*)-**7**.[7a] The $TiCl_4$ promoted reaction produced the anti homoallylic alcohol **12** (dr >30:1 5,6-anti/5,6-syn) with Felkin induction. The silicon protecting group on the aldehyde prevents chelation with the bidentate Lewis acid while reinforcing Felkin induction, while the stereochemistry of the emerging methyl group at C6 is controlled by the absolute chirality of the silane reagent. This intermediate was converted to acetonide **13** in a three-step sequence: [i] deprotection of the 1,3-diol (HF•Py), [ii] selective protection of the primary hydroxyl as its silyl ether, and [iii] protection of the C3−C4 diol as its acetonide. The left-hand subunit was completed by ozonolysis (O_3/DMS) of the (*E*)-double bond followed by reduction of the crude aldehyde ($NaBH_4$) to give a primary hydroxyl that was converted directly to the iodide **4** in 91% overall yield.[9]

The synthesis of the right-hand subunit **5** began with the syn-selective crotylation of aldehyde **14** with silane (*R*)-**6**. This BF_3•OEt_2 promoted reaction gave diol **15** with high selectivity and installed the C9 stereocenter (Scheme 2).[10] This diol was converted to the α-methyl aldehyde by protection as its bis-TBS-ether and oxidative cleavage of the double bond (O_3/Me_2S) to afford **16**. This aldehyde was used in the second double stereodifferentiating crotylation reaction with chiral *β*-methylsilane (*S*)-**8**[7b] in CH_2Cl_2 at −50 °C. The $TiCl_4$-promoted reaction produced anti homoallylic alcohol **17** (88% yield; dr >30:1, anti/syn) with Felkin induction.[8] This intermediate was converted to the *anti*-1,3-diol **18** by oxidation of the trisubstituted double bond

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(10) Although the C9-stereocenter would be eventually lost through oxidation to the ketone, the (*9S*)-isomer has been shown to be crucial in the success of the macrocyclization reaction, see ref 6b for further discussion.

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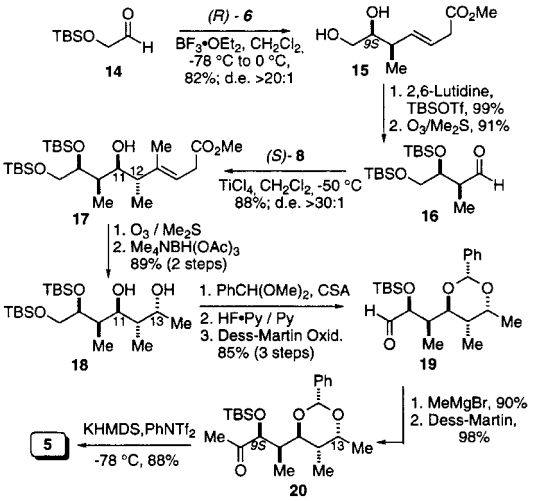
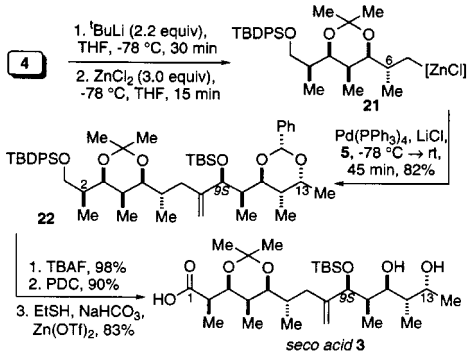
Scheme 2



Scheme 3

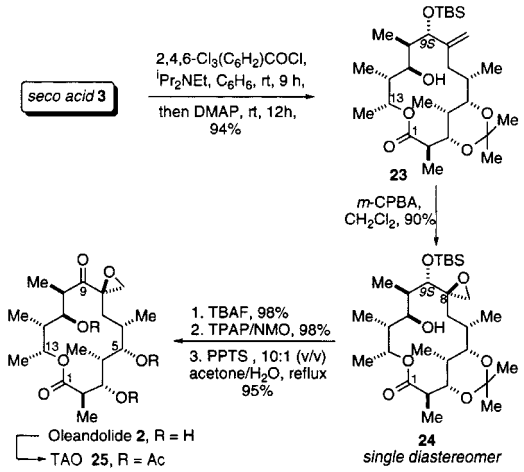


(O_3/Me_2S) to afford the methyl ketone followed by a substrate-directed hydride reduction of the derived β-hydroxy ketone using $Me_4NBH(OAc)_3$.[11] The two-step sequence afforded the *anti*-1,3-diol in 89% yield as a single diastereomer. To complete the preparation of the right-hand fragment, the 1,3-diol was protected as the benzylidine acetal and selectively deprotected at the C8 primary hydroxyl group. The primary alcohol was converted to aldehyde **19** by Dess−Martin oxidation.[12] This material was homologated to methyl ketone **20** using a two-step procedure [i] nucleophilic addition using MeMgBr (3 equiv, CH_2Cl_2, 90%) and Dess−Martin oxidation. Methyl ketone **20** was then converted to vinyl triflate **5** in 88% yield by trapping the potassium enolate with $PhNTf_2$ (2.0 equiv) completing the assembly of subunit **5**.

With the synthesis of the left- and right-hand subunits completed, the Pd(0)-catalyzed cross coupling between primary iodide **4** and vinyl triflate **5** was investigated (Scheme 3). The cross-coupling process was initiated with a I → Li exchange using ^{t}BuLi (2.1 equiv) followed by in situ transmetalation with anhydrous $ZnCl_2$ (3.0 equiv, −78 °C, 15 min) to afford the sp^3-hybridized alkyl zinc intermediate **21**, which was used directly in the Pd(0)-catalyzed coupling with vinyl triflate **5**.[13] This one-pot sequence involving a rare sp^3-sp^2 C−C bond formation gave the fully protected seco acid precursor **22** in 82% yield, completing assembly of the carbon framework of oleandolide.[14]

With the cross-coupling chemistry establishing an efficient approach to the advanced intermediate **22**, the final stages of the

Scheme 4



synthesis began with the selective deprotection of **22** and conversion of the derived primary alcohol to the carboxylic acid using PDC (10 equiv, DMF, 92% yield).[15] Removal of the C11−C13 benzylidine acetal [EtSH, $NaHCO_3$, $Zn(OTf)_2$][16] afforded the seco acid **3**. This substance bearing the C11−C13 diol was cyclized under modified Yamaguchi conditions to give the macrocycle **23** bearing a C8 exocyclic olefin in 94% yield.[17] The epoxidation reaction using an excess of *m*-CPBA turned out to be remarkably efficient (90% yield) and selective, affording epoxide **24** as a single diastereomer. The stereochemical outcome of this reaction is consistent with a steric controlled reaction and underscores the usefulness of conformationally biased systems as a stereocontrol element in electrophilic additions.[18] The synthesis of oleandolide was completed by the deprotection of the C9 silyl ether and selective oxidation of the C9 hydroxyl with TPAP/NMO (CH_2Cl_2, 0 °C, 30 min) to afford the corresponding epoxy ketone in 97% yield over two steps.[19] Final deprotection of the C3−C5 acetonide using PPTS in acetone/water at reflux gave oleandolide (95% yield) as a 1:3 mixture of lactone **2** and its 5,9-hemiacetal tautomer. The spectral data and physical properties [^{1}H and ^{13}C NMR, IR, $[\alpha]_D$, R_f, and HRMS] were identical with the published data.[6b,6c] Further confirmation was obtained by conversion of oleandolide to its triacetate **25** whose spectral data proved to be identical with published data as well.[6b,c]

A convergent enantioselective total synthesis of oleandolide has been completed utilizing an under-developed subunit coupling reaction between a functionalized alkyl zinc species and vinyl triflate intermediate. The approach represents an application of chiral crotylsilane based methodology in the assembly of polypropionate-like subunits, while offering a complementary solution to the aldol-based approach to these natural products.

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Supporting Information Available: Experimental procedures, spectral data and ^{1}H and ^{13}C NMR spectra for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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(18) Attempts to introduce the C8-epoxide on the C11 benzyl ether of **23** were unsuccessful, as no trace of epoxide was detected using *m*-CPBA.

(19) (a) The selectivity of this TPAP oxidation is believed to originate from the positioning of the C11 equatorial proton 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 (cf.: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666). (b) For the selective chromic acid oxidation see: Corey, E. J.; Melvin, L. S. *Tetrahedron Lett.* **1975**, 929−932.