

Enantioselective Synthesis of the Macrolide Antibiotic Oleandomycin Aglycon

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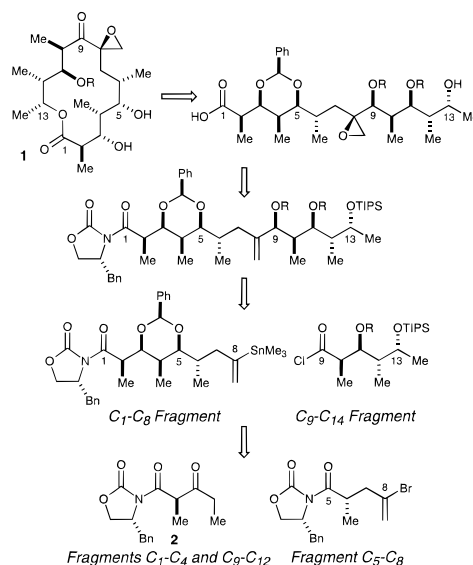
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The stereochemical and heterofunctional complexity of the polypropionate-derived macrolide antibiotics poses a formidable challenge for stereoselective synthesis, and these target structures have provided the stimulus for the development of a host of new enantio- and diastereoselective bond constructions.¹ In this paper we illustrate, in the context of an efficient synthesis of oleandolide aglycon (**1**),² how polypropionate chains may be rapidly assembled using the chiral β -ketoimide building block **2** and its associated aldol reaction methodology recently developed in these laboratories.^{3,4}

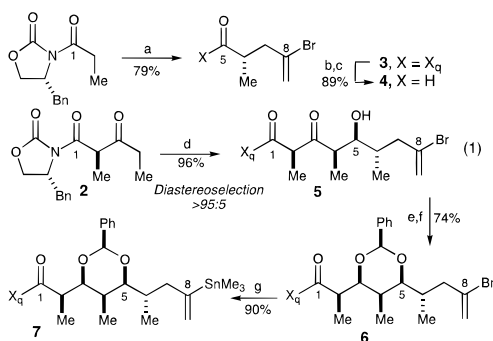
As illustrated in Scheme 1, the synthesis plan relied upon β -ketoimide **2** for the construction of both the C₁–C₈ and C₉–C₁₄ oleandolide fragments. Concurrent application of a sequential aldol reduction strategy to both fragments established 8 of the 10 requisite stereocenters, while an imide enolate alkylation reaction was employed to control the lone C₆ stereocenter in the C₅–C₈ subunit. In the final stereoselective transformation, the introduction of the C₈-epoxide with the desired stereochemistry was effected through the directed VO-(acac)₂/t-BuO₂H epoxidation of the 9-(S)-allylic alcohol prior to macrocyclization.^{5,6} This last step becomes much more challenging to implement when it is postponed until after macrocycle construction as the two previous syntheses of oleandolide have revealed.²

The synthesis of the C₁–C₈ fragment began with the titanium-mediated *syn* aldol reaction between aldehyde **4**⁷ and β -ketoimide **2** (Scheme 2).^{3a,8} This double stereodifferentiating reaction (eq 1) proceeded in excellent yield with high *anti* Felkin diastereoselection. Treatment of aldol adduct **5** with Zn(BH₄)₂ established the C₅-hydroxyl stereocenter *via* a chelate-controlled

Scheme 1

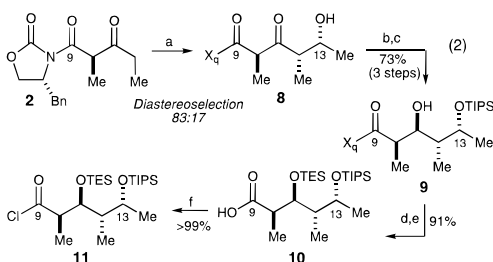


Scheme 2



^a Reagents and conditions: (a) LDA, 2,3-dibromopropene, -78 to -35 °C. (b) LiBH₄, H₂O, 25 °C. (c) (COCl)₂, DMSO, Et₃N, -78 to 0 °C. (d) Ti(O-*i*-Pr)₃, Et₃N, **4**, -78 °C. (e) Zn(BH₄)₂, -78 to -50 °C. (f) (MeO)₂CHPh, CSA, 10 Torr, 25 °C. (g) (Me₃Sn)₂, Pd(PPh₃)₄, *i*-Pr₂NEt, 80 °C.

Scheme 3



^a Reagents and conditions: (a) Sn(OTf)₂, Et₃N, acetaldehyde, -78 °C. (b) NaBH(OAc)₃, HOAc, 25 °C. (c) TIPS-OTf, 2,6-lutidine, -5 °C. (d) TES-OTf, 2,6-lutidine, 25 °C. (e) LiOOH, 0 °C. (f) (COCl)₂, DMF, 25 °C.

syn reduction (diastereoselection >95:5)⁹ while subsequent diol protection afforded vinyl bromide **6**. Further elaboration of this intermediate to the 1,1-disubstituted vinylstannane **7** completed the synthesis of the C₁–C₈ oleandolide subunit.

The synthesis of the C₉–C₁₄ subunit was initiated from the same β -ketoimide building block **2** *via* a Sn(II)-mediated aldol reaction with acetaldehyde to afford the complimentary *syn* aldol adduct (Scheme 3, eq 2).^{3a} It is noteworthy that both of the requisite *syn* aldol bond constructions may be accessed from

(1) (a) Mulzer, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1452–1454. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (c) *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukas, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2.

(2) (a) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314. (b) Paterson, I.; Lister, M. A.; Norcross, R. D. *Tetrahedron Lett.* **1992**, *33*, 1767–1770. (c) Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 1311–1314. (d) Tatsuta, K.; Ishiyama, T.; Tajima, S.; Koguchi, Y.; Gunji, H. *Tetrahedron Lett.* **1990**, *31*, 709–712. (e) Tatsuta, K.; Kobayashi, Y.; Gunji, H. *J. Antibiot.* **1988**, *41*, 1520–1523. (f) Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975–3978.

(3) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127–2142.

(4) The sequence of β -ketoimide aldol coupling followed by reduction, thereby establishing four stereocenters in two steps, has been applied to the recent total syntheses of calyculin, rutamycin, and lonomycin: (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446–11459. (c) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448–3467.

(5) (a) The precedent for the stereochemical outcome of this reaction has been established: Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63–73. (b) For a general review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

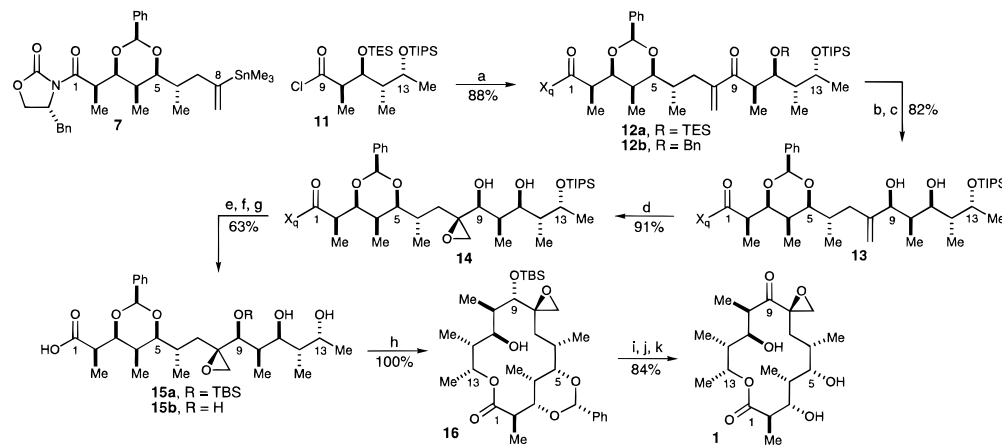
(6) Initial attempts to directly form the C₉ stereocenter from vinyl metal addition to the aldehyde proved either unselective or resulted in decomposition.

(7) The known aldehyde **4** was prepared from *N*-propionyl-4-(*R*)-(phenylmethyl)-oxazolidinone in direct analogy to the reported procedure: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.

(8) Use of Ti(O-*i*-Pr)₃ rather than the standard TiCl₄ was found to maximize conversion in the coupling of β -ketoimide **2** with aldehyde **4**.

(9) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338–344.

Scheme 4

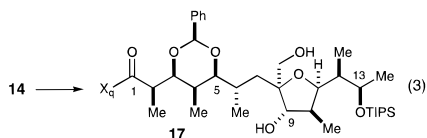


^a Reagents and conditions: (a) Pd₂(dba)₃, *i*-Pr₂NEt, benzene, 25 °C. (b) HF·pyr, 0 °C. (c) Zn(BH₄)₂, -45 °C. (d) VO(acac)₂, *t*-BuOOH, 25 °C. (e) TBS-OTf, 2,6-lutidine, -78 °C. (f) LiOOH, 0 °C. (g) Et₃N·HF, 25 °C. (h) 2,4,6-trichlorobenzoyl chloride, *i*-Pr₂NEt, DMAP, 25 °C. (i) HF·pyr, 25 °C. (j) SO₃·pyr, Et₃N, 25 °C. (k) 20% Pd(OH)₂/C, H₂, dioxane 25 °C.

the (*Z*)-enolate of **2** by judicious choice of metal center (eq 1 vs eq 2).^{3a} Subsequent *anti* reduction of **8** with NaBH(OAc)₃¹⁰ and regioselective protection of the C₁₃-alcohol yielded triisopropylsilyl (TIPS) ether **9** in good overall yield and selectivity. At this stage, the C₁₁-hydroxyl moiety was protected as its derived triethylsilyl (TES) ether with the anticipation that it might be selectively revealed after fragment coupling in the presence of the C₁₃-OTIPS protecting group (*vide infra*). Imide hydrolysis followed by treatment with oxalyl chloride provided the C₉-C₁₄ acid chloride **11** suitably activated for fragment coupling.

The palladium-catalyzed acylation¹¹ of vinylstannane **7** (C₁-C₈) with acid chloride **11** (C₉-C₁₄) proved to be an excellent fragment coupling process (Pd₂(dba)₃, *i*-Pr₂NEt, benzene, 25 °C, 88% yield) (Scheme 4). The use of the trimethylstannyl derivative was found to be essential for a high-yielding transformation, in accord with literature precedent indicating reaction sensitivity to steric effects at the stannyl moiety.¹¹ Treatment of enone **12a** with HF·pyridine effected selective deprotection of the C₁₁-OTES moiety in the presence of the C₁₃-OTIPS ether, and the subsequent Zn(BH₄)₂ reduction, directed by the newly revealed C₁₁-OH, afforded allylic alcohol **13** with the desired (*S*)-stereochemistry at C₉ as a single isomer. It is noteworthy that the analogous reduction of benzyl ether **12b**, contrary to expectation, produced the undesired 9-(*R*)-alcohol diastereomer as the major product, despite ample precedent for the operation of chelate control on similar substrates.¹² With the 9-(*S*)-hydroxyl configuration established as a controller for directed epoxidation, treatment of **13** with VO(acac)₂/*tert*-butylperoxide afforded the desired epoxy alcohol **14** as a single diastereomer,⁵ thereby establishing the 10 requisite oleandolide stereocenters in 11 linear steps.

Unfortunately, attempts to move forward with the C₉,C₁₁-diol **14** met with failure, since the diol epoxide moieties proved too labile to survive subsequent steps. Although some of the carboxylic acid triol **15b** was obtained, all macrocyclization attempts led only to substrate decomposition. Even under buffered conditions, this series of epoxide-containing intermediates readily rearranged to the corresponding tetrahydrofurans, as shown for the conversion of **14** to **17** (eq 3).



In an attempt to inhibit this rearrangement, diol **14** was treated with *tert*-butyldimethylsilyl triflate (TBS-OTf). It is of note

that only the C₉-position was silylated; all attempts to modify the C₁₁-alcohol failed. Nonetheless, this added protecting group did attenuate the reactivity of the epoxide, possibly through enforcing a conformation less prone to rearrangement by an alteration of the hydrogen bonding network. Following imide hydrolysis, the C₁₃-OTIPS ether was selectively removed in the presence of the C₉-OTBS moiety through the use of triethylammonium fluoride to afford **15a**.¹³ Gratifyingly, the macrocyclization of this substrate proceeded in quantitative yield with 2,4,6-trichlorobenzoyl chloride.¹⁴ Silyl deprotection, oxidation, and acetal hydrogenolysis then afforded oleandolide (**1**) in 84% overall yield. The spectral and chromatographic characteristics of **1** proved identical to the published data.^{2a} As further proof of structure, the triacetate derivative of **1** was also prepared, and its properties proved to be identical to published data as well.^{2a}

Synthesis of oleandolide was completed in 18 linear steps with a 15% overall yield. Utilizing auxiliary-controlled aldol reactions, directed reductions, and a directed epoxidation, the 10 stereocenters of oleandolide were established on the acyclic carbon framework from the chiral β -ketoimide building block **2**.

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Supporting Information Available: Spectral data for all compounds are provided (7 pages). See any current masthead page for ordering and Internet access instructions.

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(11) (a) Labadie, J. L.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129-6137 and references cited therein. (b) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040.

(12) Rietz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462-468 and references cited therein.

(13) Et₃N·HF was prepared from the HF·pyridine complex and Et₃N. The excess base was removed *in vacuo*, and the resultant white crystalline solid was stored under argon.

(14) (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367-6370. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7-9. (c) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.