Tetrahedron Letters, Vol.31, No.23, pp 3275-3278, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A STEREOSELECTIVE OSMYLATION APPROACH TO POLYOXYGENATED NATURAL PRODUCTS. SYNTHESIS OF C(1)-C(7) AND C(7)-C(13) SUBUNITS OF ERYTHRONOLIDE A

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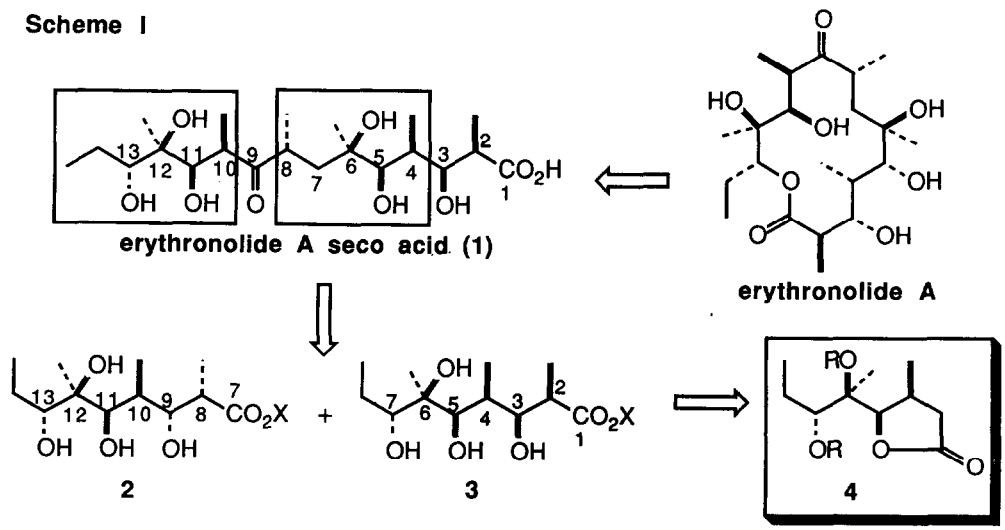
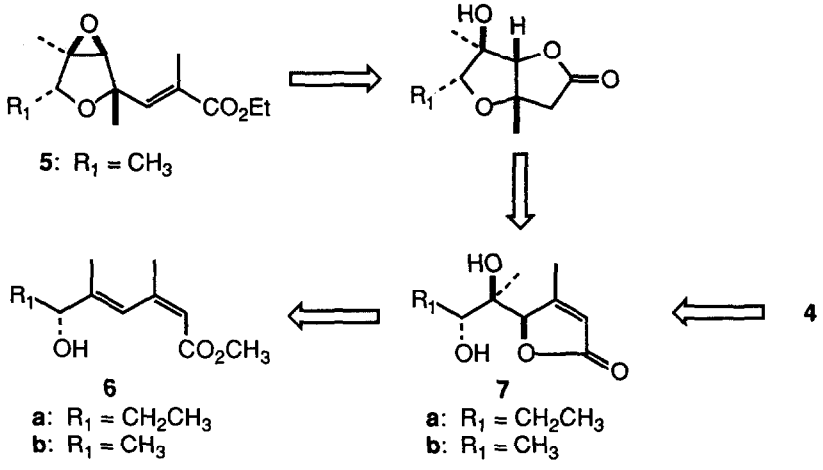
Abstract: The key synthons **2** and **3** [with suitable protecting groups] of the erythronolide A seco acid (**1**) have been prepared in an enantiomerically pure form, utilizing a stereoselective osmylation of chiral hydroxy (*Z,E*)-diene ester **6a** and subsequent hydrogenation.

Recent interest in macrolide and ionophore antibiotics has stimulated the development of efficient methods for the stereocontrolled synthesis of densely functionalized acyclic or tetrahydrofuran or -pyran molecules [*e.g.*, erythronolide A seco acid (**1**)].[1-3] As a part of our research objectives directed at the total synthesis of these polyoxygenated natural products (Scheme I), we previously reported an efficient, enantio- and stereoselective preparation of a highly substituted tetrahydrofuran **5** through the use of a "butenolide" template.[4] As outlined in Scheme II, the pivotal step involves a highly regio- and stereoselective osmylation of a chiral diene ester **6**.[5] It appeared to us that this butenolide protocol would also be very useful for the preparation of other polyoxygenated acyclic compounds. For example, the stereoselective hydrogenation of **7** might be accomplished by taking advantage of the bulky side chain, and would thus provide an efficient assembly of four contiguous stereocenters with the appendage suitable for further elaboration. Herein we describe successful realization of this osmylation-based strategy in an expeditious synthesis of two key fragments **2** and **3** (*i.e.*, C1-C7 and C7-C13 with their protecting groups) of the erythronolide A seco acid *via* the common synthon **4**.[2,3]

Scheme I



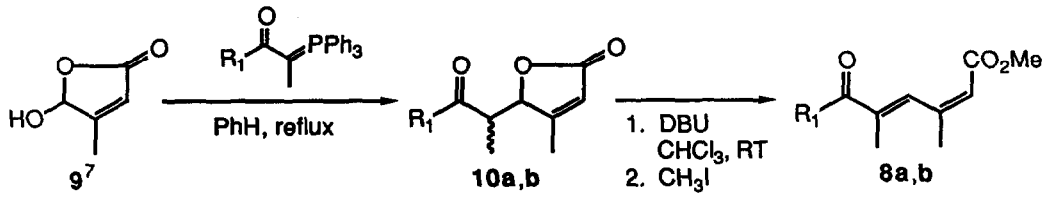
Scheme II[4]



Also included in Scheme I is the correlation of the seco acid of 9(*S*)-9-dihydro-erythronolide A *via* these two key subunits with lactone **4**, containing the four contiguous stereocenters in their correct absolute configurations. We envisaged a one-carbon oxidative degradation of the lactone moiety in the latter compound, followed by a well-established asymmetric aldol methodology.[6]

We felt that our starting (*Z,E*)-diene ester **6a** would be readily prepared by asymmetric reduction of the prochiral ketone **8a**, which in turn might be readily available in one pot by a Wittig olefination. Consequently, the readily available γ-hydroxybutenolide **9**[7] was condensed with 2-triphenyphosphoranylidene-3-pentanone[8] in refluxing benzene to afford adduct **10a** as a diastereomeric mixture (Scheme III).[9] Subsequent elimination (DBU, $CHCl_3$), followed by *in situ* methylation (CH_3I) gave the required (*Z,E*)-diene keto ester **8a** exclusively in ~50% overall yield.[10] With an efficient, stereoselective preparation of (*Z,E*)-diene **8a** in hand, the application of the Itsuno procedure [2 equiv BH_3, (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol, THF, -23°C, 3 hr][11] afforded the desired alcohol **6a**, $[\alpha]_D^{24}$ = -49° (c 1.05, $CHCl_3$), in 88% yield and ≥ 95% enantiomeric excess.[12] The OsO_4-catalyzed hydroxylation (0.02 equiv. OsO_4, 1.2 equiv. NMO,[13] 2:1 THF-H_2O, RT) of **6a** then provided a single butenolide **7a**, mp 93~95° C, $[\alpha]_D^{25}$ = +58° (c 1.01, $CHCl_3$) [IR ($CHCl_3$) 3416, 1726, 1637 cm^{-1}] in 53% yield. None of the other possible regio- and stereoisomers was found. The stereochemical assignment of the osmylation product was initially made in analogy to that of homolog **7b**, $[\alpha]_D^{25}$ = -15.0° (c 0.8, $CHCl_3$).[4]

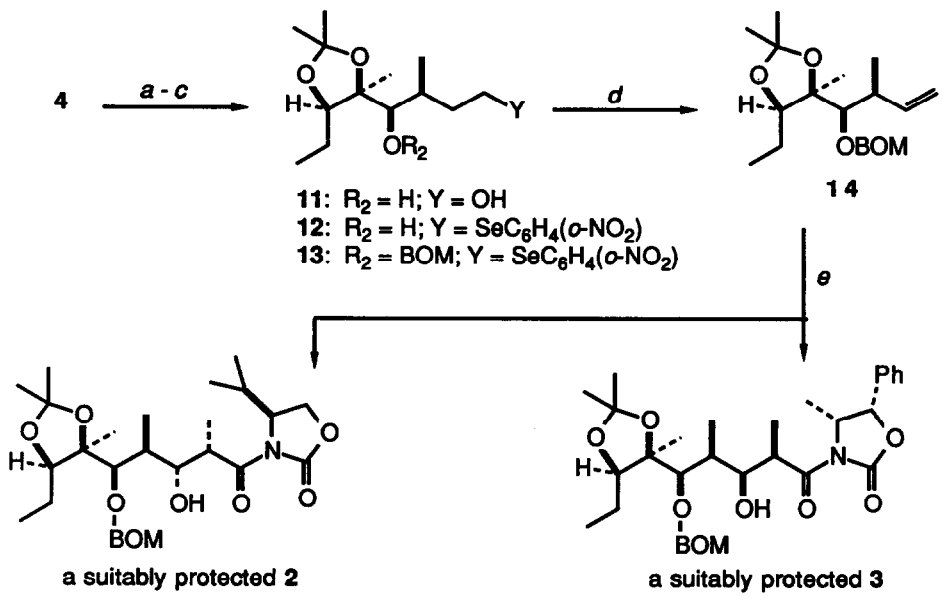
Scheme III



Not surprisingly, subsequent hydrogenation (1 atm H_2, 10% Pd/C) suffered from a poor stereoselectivity. However, removal of the polar hydroxy group by initial acetonide formation (2,2-dimethoxypropane, p-TsOH, 94%) and subsequent hydrogenation (5% Rh/Al_2O_3) afforded a major product **4** [R = $C(CH_3)_2$] [mp 94 ~ 96° C, $[\alpha]_D^{24}$ = -21° (c 1.01, $CHCl_3$)] with an excellent (≥15:1) diastereoselectivity. Because of the expected *syn* addition from the less hindered side and also in accord with similar literature precedents,[14] the stereochemistry of lactone **4** was tentatively assigned and subsequently secured by X-ray crystallography.[15]

With **4** available in multi-gram quantities, the one-carbon oxidative degradation was then accomplished by $LiAlH_4$ reduction, subsequent application of the Sharpless - Grieco protocol,[16] and protection with the BOM (benzyloxymethyl) group to afford olefin **14**, $[\alpha]_D^{24}$ = +48° (c 0.83, $CHCl_3$) in 61% overall yield from lactone **4** (Scheme IV). Finally, ozonolysis of **14**, followed by the asymmetric aldol reaction of Evans[6] afforded a suitably protected left-hand subunit **2** of erythronolide A seco acid in 46% yield. The other fragment **3** was also prepared readily (in 53% yield) by utilizing a different oxazolidinone-derived chiral auxiliary.

Scheme IV



a. $LiAlH_4$, THF, -5°C; *b*. nBu_3P, $(o\text{-}NO_2)C_6H_4SeCN$, THF, -23°C;
c. $ClCH_2OCH_2Ph$, iPr_2NEt, CH_3CN, reflux; *d*. 30% H_2O_2, THF, RT;
e. O_3, CH_2Cl_2, -78°C followed by Ph_3P and ref. 6.

In summary, we have developed an expeditious route to the two key synthons of the carbocyclic backbone of erythronolide A, utilizing a stereoselective osmylation-based "butenolide" formation and subsequent hydrogenation, starting from the readily available homochiral hydroxy (*Z*,*E*)-diene ester **6a**. The final coupling of these two subunits to erythronolide A seco acid is currently in progress. Further synthetic applications of the strategy delineated above to other polyoxygenated natural products will be reported in due course.[17]

References and Footnotes

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4. (a) Cha, J. K.; Cooke, R. J. *Tetrahedron Lett.* **1987**, *28*, 5473. (b) Following the synthetic protocol delineated in this Letter, the homochiral **5** has now been prepared in the correct absolute configuration.

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12. The absolute configuration of alcohol **6a** is based on similar literature examples[11], and also correlates very well with the analogous reduction of **8b** to **6b**. The antipode of the latter was previously prepared in an enantiomerically pure form starting from (*S*)-ethyl lactate.[4]

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14. See *inter alia*: (a) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 499. (b) Schlessinger, R. H.; Damon, R. E. *Tetrahedron Lett.* **1975**, 4551. (c) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170. (d) ref. 2(d).

15. The single-crystal analysis (-120°C) of **4** was carried out by Molecular Structure Corporation, The Woodlands, TX; details will be published in a full paper.

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17. Financial support from the National Institutes of Health (GM 35956) is gratefully acknowledged. We also thank the NIH (BRSG RR07201-10) for partial support toward the purchase of a polarimeter.

(Received in USA 27 February 1990; accepted 18 April 1990)