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Toward the Synthesis of Reidispongiolide A: Stereocontrolled Synthesis of the C_{17}–C_{22} and C_{23}–C_{35} Degradation Fragments

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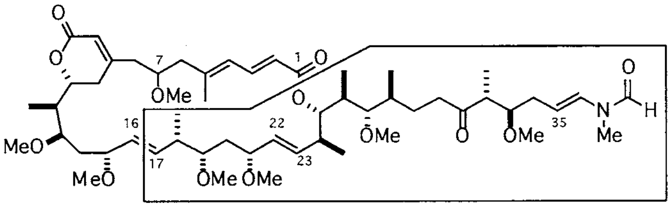
ABSTRACT



Reidispongiolide A

By relying on the asymmetric aldol reactions of chiral ketones, a highly stereocontrolled synthesis of each of the C_{17}–C_{22} and C_{23}–C_{35} degradation fragments of reidispongiolide A has been achieved. This permits a configurational assignment of the complete C_{17}–C_{36} region of this antimitotic macrolide, along with providing advanced intermediates for a projected total synthesis.

The discovery of new cytotoxins that retain activity toward multidrug resistant (MDR) cancer cell lines continues to fuel the burgeoning field of cancer chemotherapy. Recently, a number of actin-binding macrolides of marine origin have attracted attention as novel antimitotic agents that cause rapid loss of microfilaments in cells, without affecting microtubule organization.[1] In particular, the scytophycins,[2] aplyronines,[3] sphinxolides,[4] and reidispongiolides[5] demonstrate pronounced antimicrofilament activity in vitro and potently inhibit the growth of MDR cancer cells. While these preliminary findings highlight their potential, both as candidates for new anticancer drugs and versatile molecular probes of the organization and function of the actin cytoskeleton, the scarcity from the natural sources has generally hampered the biological evaluation and preclinical development of these stereochemically complex macrolides.

The sphinxolide/reidispongolide family of 26-membered macrolactones are prominent members of this emerging class of actin-binding cytotoxic macrolides (Scheme 1). Originally isolated from an unidentified Pacific nudibranch,[5a] these polyketide metabolites have more recently been obtained from the marine sponges *Neosiphonia superstes* and *Reidispongia coerulea*,[5b−d] collected off the coast of New Caledonia. Extensive analysis of sphinxolide A by NMR methods, based largely on the interpretation of proton−carbon $^{2,3}J$ couplings, has recently enabled an assignment of the *relative* configurations in the five isolated stereoclusters, as indicated in the boxed regions of structure **1**.[6] Additionally, controlled ozonolysis of the closely related macrolide reidispongiolide A (having the proposed stereostructure in **2**), followed by

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[1] Reviews: (a) Yeung, K.-S.; Paterson, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4632. (b) Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. *Microsc. Res. Technol.* **1999**, *47*, 18.

[2] Smith, C. D.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Cancer Res*. **1993**, *53*, 1343.

[3] Saito, S.; Watabe, S.; Ozaki, H.; Kigoshi, H.; Yamada, K.; Fusetani, N.; Karaki, H. *J. Biochem*. **1996**, *120*, 552.

[4] Zhang, X.; Minale, L.; Zampella, A.; Smith, C. D. *Cancer Res.* **1997**, *57*, 3751.

[5] (a) Guella, G.; Mancini, I.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1989**, *72*, 237. (b) D'Auria, M. V.; Gomez-Paloma, L.; Minale, L.; Zampella, A.; Verbist, J. F.; Roussakis, C.; Debitus, C. *Tetrahedron* **1993**, *49*, 8657. (c) Carbonelli, S.; Zampella, A.; Randazzo, A.; Debitus, C.; Gomez-Paloma, L. *Tetrahedron* **1999**, *55*, 14665. (d) D'Auria, M. V.; Gomez-Paloma, L.; Minale, L.; Zampella, A.; Verbist, J. F.; Roussakis, C.; Debitus, C.; Patissou, J. *Tetrahedron* **1994**, *50*, 4829.

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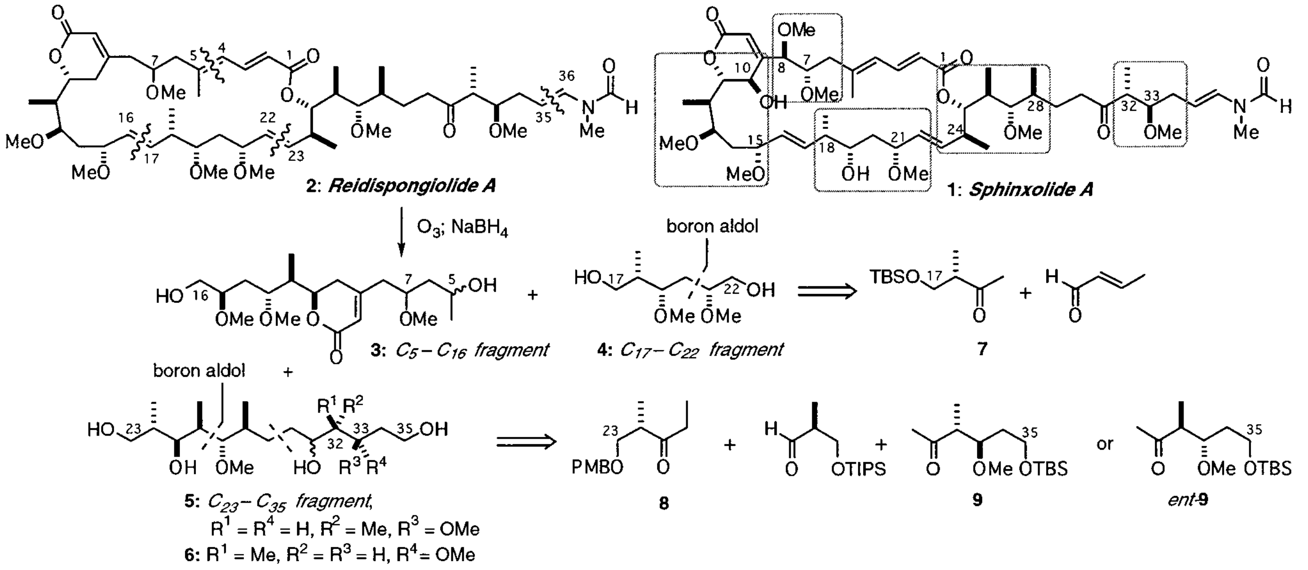
Scheme 1

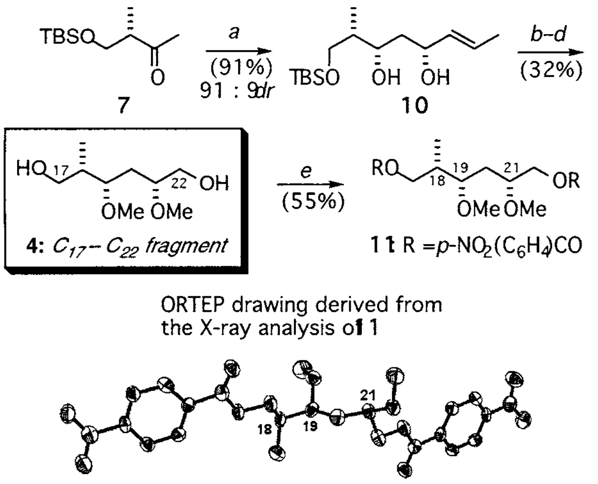


reductive workup with $NaBH_4$, provided three distinct polyol fragments, assigned as structures **3** (mixture of C_5 epimers) and **4** and **5** (mixture of C_{31} epimers), whose spectroscopic data appeared consistent with that of the corresponding segments in **1**.[7] While the full configuration of the sphinxolide/reidispongiolide macrolides could be determined by completing a total synthesis, which remains our ultimate objective, the preparation of these three degradation fragments (or stereoisomers thereof) should simplify the stereochemical quandary and establish the interconnections between the isolated stereoclusters.

We now report an expedient stereocontrolled synthesis of the reidispongiolide fragments **4** and **5**, as well as the diastereomer **6** having the opposite configuration at C_{32} and C_{33}, following the retrosynthetic analysis outlined in Scheme 1. On the basis of our reservations regarding the relationship between the isolated stereoclusters, we designed a flexible and modular synthetic approach using appropriate aldol reactions of the chiral ketones **7**, **8**, **9**, and *ent*-**9**. The present work leads to a configurational assignment for 10 out of the 15 stereocenters in reidispongiolide A, and also sets a solid foundation for ongoing total synthesis efforts.

First, an asymmetric synthesis of the C_{17}—C_{22} fragment **4** of reidispongiolide A using a convenient one-pot aldol/reduction sequence[8] with methyl ketone **7**[9] and crotonaldehyde was developed (Scheme 2). In previous work with such ketones,[8−11] we had shown that high levels of diastereoselectivity can be obtained for 1,4-*syn* adducts by appropriate choice of Ipc ligand chirality in boron aldol reactions. By using our standard conditions with (−)-Ipc_2BCl/Et_3N, the resulting boron aldolate was reduced[8b] in situ with $LiBH_4$ to provide the 1,3-*syn* diol **10** with high diastereoselectivity (91%, 91:9 dr). Conversion into the bis-methyl ether (NaH, MeI) was then followed by ozonolysis and in situ reduction ($NaBH_4$) of the ozonide to give the corresponding alcohol. Finally, TBS ether removal (TBAF) afforded the diol **4**, obtained in four synthetic transformations and 27% yield from **7**.

Scheme 2[a]



[a] Conditions: (a) (−)-Ipc_2BCl, Et_3N, Et_2O, −78 °C; crotonaldehyde; $LiBH_4$; (b) NaH, MeI, THF; (c) O_3, CH_2Cl_2, −78 °C; MeOH, $NaBH_4$, −78 °C; (d) TBAF, THF; (e) *p*-nitrobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2.

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(6) Bassarello, C.; Bifulco, G.; Zampella, A.; D'Auria, M. V.; Riccio, R.; Gomez-Paloma, L. *Eur. J. Org. Chem.* **2001**, 39.

(7) Zampella, A.; Bassarello, C.; Bifulco, G.; Gomez-Paloma, L.; D'Auria, M. V. *Eur. J. Org. Chem.* **2002**, 785.

(8) (a) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801.

(9) Prepared in 3 steps (51%) from methyl (*S*)-2-methyl-3-hydroxypropionate in an analogous manner to the corresponding TIPS ether, see: Paterson, I.; Oballa, R. M. *Tetrahedron Lett.* **1997**, *38*, 8241.

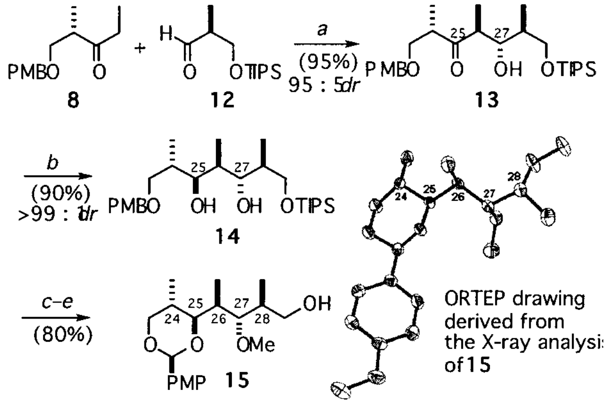
(10) For a review on asymmetric aldol reactions with boron enolates, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

(11) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.

The ^{1}H and ^{13}C NMR data exhibited by this diol **4** were consistent with that reported by D'Auria and co-workers for both the $C_{17}-C_{22}$ fragment obtained from the chemical degradation of natural reidispongiolide A and that of a synthetic sample of *ent*-**4**.[7] The absolute configuration of the degradation fragment was further confirmed as (18*S*,19*S*,21*R*) through comparison of the specific rotation values.[12] Additionally, treatment of the diol **4** with *p*-nitrobenzoyl chloride (Et_3N, DMAP) gave the bis-ester **11**, where single-crystal X-ray analysis confirmed the *all-syn* stereochemistry.

The convergent assembly of the $C_{23}-C_{35}$ fragments commenced with a substrate-controlled, boron-mediated aldol reaction (*c*-Hex_2BCl, Et_3N)[8a,10] between the ethyl ketone **8**[13] and aldehyde **12** (Scheme 3). Upon standard oxidative workup, the expected *anti*−*anti* adduct **13**, resulting from the high level of π-face discrimination exercised by the intermediate (*E*)-enolate,[8] was obtained in 95% yield (95:5 dr). This adduct provided a suitable substrate for hydroxyl-directed reduction to set up the $C_{23}-C_{29}$ stereopentad. By employing $Me_4NBH(OAc)_3$,[14] the desired 1,3-*anti* diol **14** was obtained cleanly (90%, >99:1 dr). With the five contiguous stereocenters now secured in a concise manner, the differentiation of the two hydroxyl groups was required. Treatment of the diol **14** under DDQ-mediated oxidative cyclization conditions[15] resulted in the exclusive formation of the corresponding six-membered PMP acetal, as a single diastereomer. Finally, methylation of the free hydroxyl (NaH, MeI) and removal of the TIPS ether (TBAF) afforded the crystalline alcohol **15** in 80% overall yield from **14**. At this point, the relative stereochemistry of this $C_{23}-C_{29}$ subunit was confirmed by X-ray crystallographic analysis of **15**.

Scheme 3[a]



[a] Conditions: (a) *c*-Hex_2BCl, Et_3N, Et_2O, −78 °C; (b) $Me_4NBH(OAc)_3$, MeCN/AcOH; (c) DDQ, 4 Å MS, CH_2Cl_2; (d) NaH, MeI, THF; (e) TBAF, THF.

With the required stereopentad **15** in hand, we turned to preparing the methyl ketones **9** and *ent*-**9** to access both possible *anti*-relationships at C_{32} and C_{33} in the extended $C_{23}-C_{35}$ fragment (Scheme 4). By using Brown's methodology,[16] the aldehyde **16** was treated with the (*E*)-crotylborane reagent derived from *trans*-butene and (−)-Ipc_2BOMe to afford the *anti*-adduct **17** in 81% yield (95:5 dr, 95% ee).[17] Following methyl ether formation (NaH, MeI), the terminal alkene was oxidized to give **9** (71%)[18] under modified[19] Wacker conditions. By using (+)-Ipc_2BOMe, the enantiomeric methyl ketone *ent*-**9** was prepared from **16** in an analogous manner.

We next examined the coupling of the ketone **9** and the aldehyde **18**, obtained by Dess−Martin oxidation of **15** (99%). This pivotal aldol coupling step was best achieved by generation of the lithium enolate of **9** (LDA, THF, −78 °C) and addition of a solution of **18** (0.5 equiv, 30 min) to give the β-hydroxy ketone **19** in 85% yield, as an inconsequential 4:1 mixture of diastereomers. Subsequent elimination, through formation of the corresponding mesylate (MsCl, Et_3N) and in situ treatment with DBU, provided (*E*)-enone **20** (65%). Subjection of **20** to standard hydrogenation conditions (H_2, Pd/C) then effected both clean hydrogenolysis of the PMP acetal and reduction of the alkene. Finally, ketone reduction ($NaBH_4$) and TBS ether removal (TBAF) provided the alcohols **5**, obtained as a 4:1 mixture of epimers at C_{31}, which were separated by flash chromatography.

Notably, the ^{1}H NMR data (500 MHz, CD_3OD) of the alcohols **5** were in close agreement[20] to that reported by D'Auria and co-workers for the $C_{23}-C_{35}$ fragment obtained in their degradation work,[7] thus supporting this relationship between the two remote stereoclusters at $C_{24}-C_{28}$ and $C_{31}-C_{33}$ in reidispongiolide A. At the time, inconsistencies between our ^{13}C NMR data and that reported by the Naples group led us to prepare **6** having the other *anti* stereorelationship at $C_{31}-C_{32}$. This involved the analogous aldol coupling between **18** and *ent*-**9** to give **21** followed by elaboration into **6**, obtained as a 4:1 mixture of epimers at C_{31}. Spectroscopic analysis[20] of the separated alcohols **6** revealed that these were clearly diastereomers of the $C_{23}-C_{35}$ fragment obtained by ozonolysis of reidispongiolide A. Subsequently, comparison of the ^{13}C NMR data for synthetic fragments **5** and **6** with the revised data provided[21] for material obtained by chemical degradation allowed the confident assignment of the *relative* stereochemistry for the $C_{23}-C_{35}$ sequence of reidispongiolide A.

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[12] The low value of $[\alpha]^{20}_{D}$ recorded for synthetic **4** (+4.1, MeOH) was in accord with that reported (ref 7) for the corresponding degradation fragment. The bis-(*S*)-MTPA ester was also prepared for spectroscopic comparison.

[13] (a) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

[14] Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**.

[15] Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

[16] Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570.

[17] The $[\alpha]^{20}_{D}$ value recorded for **17** (−8.4, $CHCl_3$) was in accord with that previously reported. McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196.

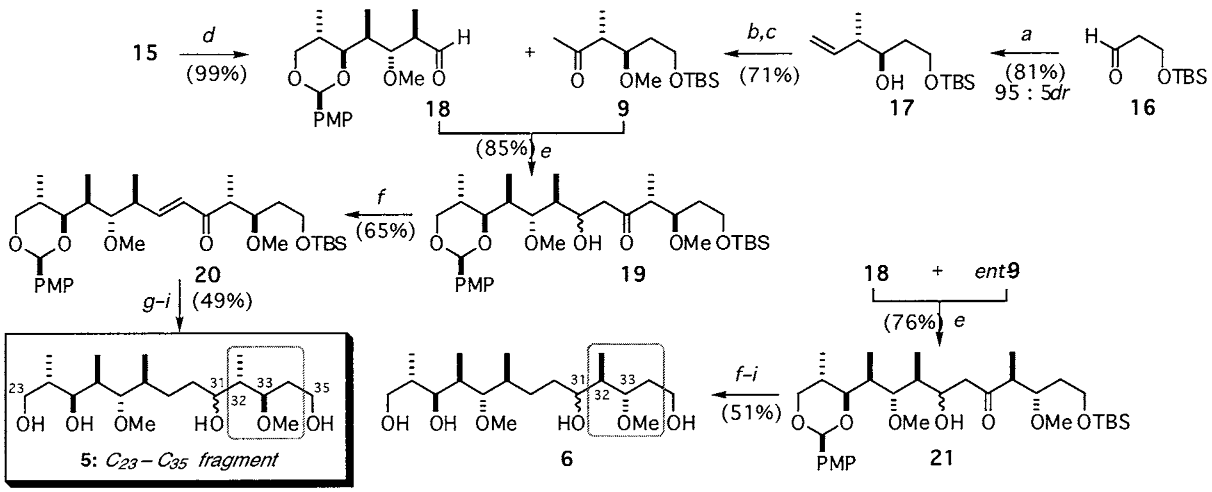
[18] Accompanied by small amounts of the corresponding aldehyde (8%).

[19] Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765.

[20] For tables of spectroscopic data (^{1}H and ^{13}C NMR) for **5** and **6**, see Supporting Information.

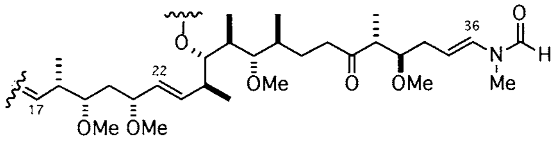
[21] Professor D'Auria has since provided us with revised ^{13}C NMR data for their $C_{23}-C_{35}$ degradation fragment which are in complete agreement with the data we have acquired for the alcohols **5**.

Scheme 4[a]



[a] Conditions: (a) *trans*-butene, *t*-BuOK, THF, *n*-BuLi; (−)-Ipc_2BOMe; $BF_3\cdot OEt_2$; **16**, −78 °C; (b) NaH, MeI, THF; (c) O_2, $Cu(OAc)_2$ (20 mol %), $PdCl_2$ (10 mol %), $AcNMe_2/H_2O$ (4:1); (d) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2; (e) LDA, THF, −78 °C; (f) MsCl, NEt_3, CH_2Cl_2; DBU; (g) H_2, cat. Pd/C, EtOH; (h) $NaBH_4$, MeOH; (i) TBAF, THF.

In conclusion, on the basis of the established absolute configuration in the C_{17}−C_{22} sequence and the relative configuration at C_{23}−C_{35}, and relying on a common biogenesis for the sphinxolide/reidispongioloide family and the structurally related scytophycin and aplyronine macrolides,[1a] a full assignment of the complete C_{17}−C_{36} region of reidispongiolide A, as indicated in **22**, is strongly suggested. Confirmation of this proposal will rely on completing the total synthesis of reidispongiolide A, work that is ongoing in our laboratory.



22: *C_{17}– C_{36} sequence of reidispongiolides*

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Supporting Information Available: Physical and spectroscopic data for new compounds and CIF files for **11** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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