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Formal Total Synthesis of RK-397 via an Asymmetric Hydration and Iterative Allylation Strategy

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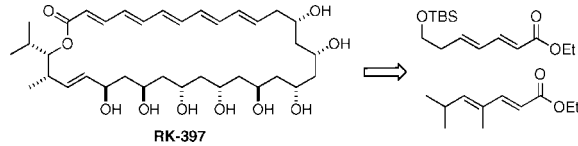
ABSTRACT



A formal total synthesis of the oxopentaene macrolide antibiotic RK-397 has been achieved. Nine stereocenters were established by a combination of allylation and our asymmetric hydration reactions and a 1,5-*anti*-selective aldol reaction. The synthesis proceeded in 19 steps from simple achiral conjugated dienoates.

RK-397 (**1**) is a 32-membered oxopentaene macrolide antibiotic which was first isolated from a Japanese soil bacterium and characterized in 1993 by Osada and co-workers.[1] Like all members of this class of compounds, RK-397 possesses antifungal properties; however, unlike the other oxopolyene macrolides, RK-397 exhibits potent oncotoxicity (GI_{50} of 50 μg/mL and 50 μg/mL against HL-60 and K-562, respectively). Due to this unique activity and challenging architecture, RK-397 has garnered much interest from the synthetic community. The first total synthesis of RK-397 (**1**, Figure 1) was reported by McDonald in 2003,[2] which was subsequently followed by two more total syntheses in 2005[3] and 2007.[4] In addition, several approaches to polyol portion also have been reported.[5]

We have been interested in developing new methods for the synthesis of 1,3-*syn*-polyols[6] and applying these methods

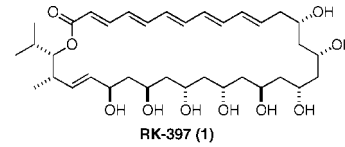


Figure 1. RK-397, a 32-membered oxopentaene antibiotic.

for the synthesis of 1,3-*syn*-polyol-containing natural products.[7] As an outgrowth from these efforts, we became interested in the application of these approaches for the synthesis of the polyene macrolide antibiotic.[8] Herein, we describe our successful efforts to implement these methods for the formal total synthesis of RK-397, which contains a cautionary tale regarding the intricacies of the boron aldol reaction for 1,5-*anti*-control of stereochemistry.[9]

(1) (a) Kobinata, K.; Koshino, H.; Kudo, T.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1616–1618. (b) Koshino, H.; Kobinata, K.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1619–1621.

(2) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495–2500.

(3) Denmark, S. E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127*, 8971–8973.

(4) Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1066–1070.

(5) (a) Schneider, C.; Tolksdorf, F.; Rehfeuter, M. *Synlett* **2002**, 2098–2100. (b) Vogel, P.; Gerber-Lemaire, S.; Carmona, A. T.; Meilert, K. T.; Schwenter, M. E. *Pure Appl. Chem.* **2005**, *77*, 131–137. (c) Gerber-Lemaire, S.; Carmona Asenjo, A. T.; Meilert, K.; Vogel, P. *Eur. J. Org. Chem.* **2006**, *89*, 1–900.

(6) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049–1052.

(7) (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780. (b) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682–2685. (c) Smith, C. M.; O'Doherty, G. A. *Org. Lett.* **2003**, *5*, 1959–1962. (d) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447–4450.

(8) For excellent background on oxopolyene macrolide antibiotics, see: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040. (b) *Macrolide Antibiotics: Chemistry, Biology and Practice*, 2nd ed.; Omura, S., Ed; Academic Press: New York, 2002.

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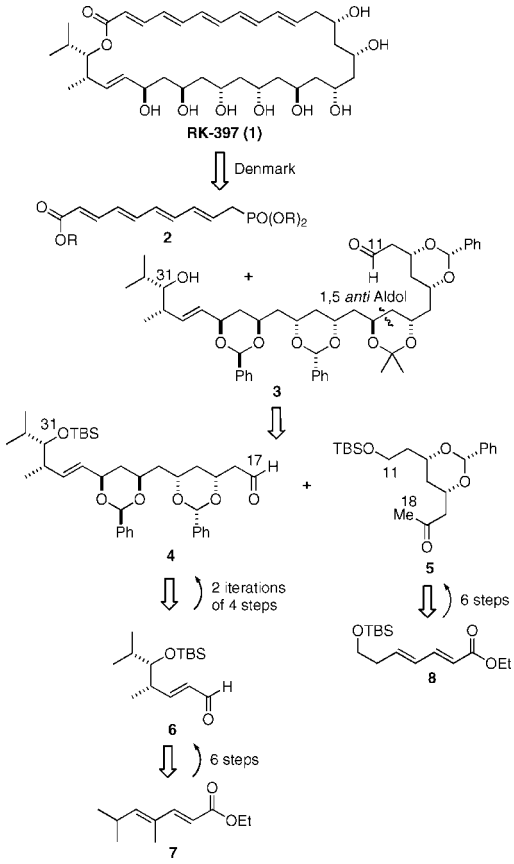
Our retrosynthetic analysis of RK-397 (**1**) is outlined in Scheme 1. We targeted the known polyol fragment **3**, which

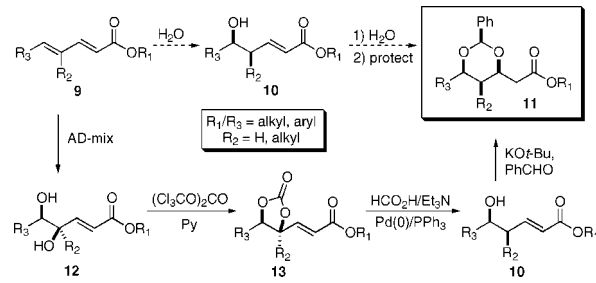
Scheme 1. Retrosynthetic Analysis of RK-397 (**1**)



Denmark has previously synthesized and converted in five steps to RK-397 (**1**) by coupling with polyene **2**.[3] We envisioned **3** could be constructed from aldehyde **4** and ketone **5** via a boron aldol reaction. The aldehyde fragment **4** could be obtained by iterative use of Leighton allylation,[10] Evans' diastereoselective hemiacetal addition, cross-metathesis olefination, and reduction in sequence from aldehyde **6**. Eventually, both aldehyde **6** and ketone **5** could be derived from dienoates **7** and **8** by an asymmetric hydration sequence, respectively.

Recently, we have developed an asymmetric hydration strategy that employs easily produced dienoates as the carbon skeleton for polyketide synthesis (Scheme 2). The transformation relies upon a Sharpless asymmetric dihydroxylation[11] followed by a palladium-catalyzed allylic reduction[6,12] (**13** to **10**) to control both the regio- and enantioselectivity of the

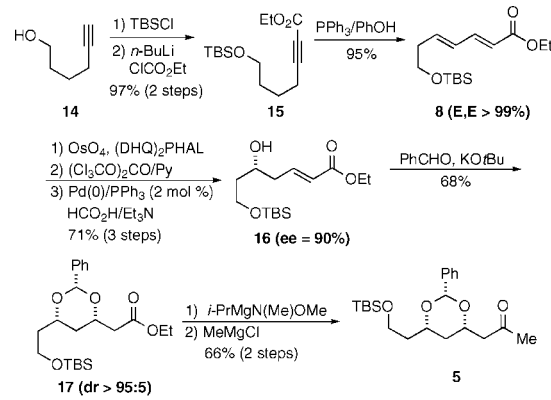
Scheme 2. Asymmetric Hydration of α,β,δ,γ-Unsaturated Dienoates



first hydration and an Evans' hemiacetal addition[13] to achieve diastereoselectivity in the second hydration (**10** to **11**).[14] As part of an effort to test the robustness of this approach, we decided to use it to establish the initial asymmetry of RK-397 (i.e., **7** to **6** and **8** to **5**).

Our synthesis of the ketone subunit **5** commenced with 5-hexyn-1-ol **14** (Scheme 3), which was converted into ynoate

Scheme 3. Asymmetric Hydration in the Synthesis of Ketone **5**



15 via TBS-protection and carboethoxylation in excellent yield (97% for two steps). Exposure of ynoate **15** to the Trost PPh_3/PhOH-promoted isomerization[15] yielded dienoate **8** in 95% yield and 99% *E*,*E*-isomer. Using our standard asymmetric hydration protocol involving Sharpless dihydroxylation (ee 90%), carbonate formation, and palladium-catalyzed reduction, dienoate **8** was regio- and enantioselectively transformed into δ-hydroxy enoate **16** in good overall yield and high enantioselectivity (71%, 3 steps).[16] An Evans' diastereoselective hemiacetal addition reaction installed the *syn*-1,3-diol stereochemistry of benzylidene acetal **17** (68%, dr 95:5). Finally, the desired ketone **5** was readily produced via the Weinreb amide formation and subsequent methyl Grignard addition in good yield (66%, two steps).

(9) For the application of the boron aldol reaction for 1,5-*anti*-stereocontrol in the synthesis of oxopolyene macrolide antibiotics, see: Dreher, S. D.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341–342, and refs 3 and 4.

(10) (a) Kubota, K.; Leighton, J. L. *Angew Chem., Int. Ed* **2003**, *42*, 946–948. (b) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375–4377. (c) Zhang, X.; Houk, K. N.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 938–941.

(11) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.

(12) Ahmed, M. M.; Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741–7746.

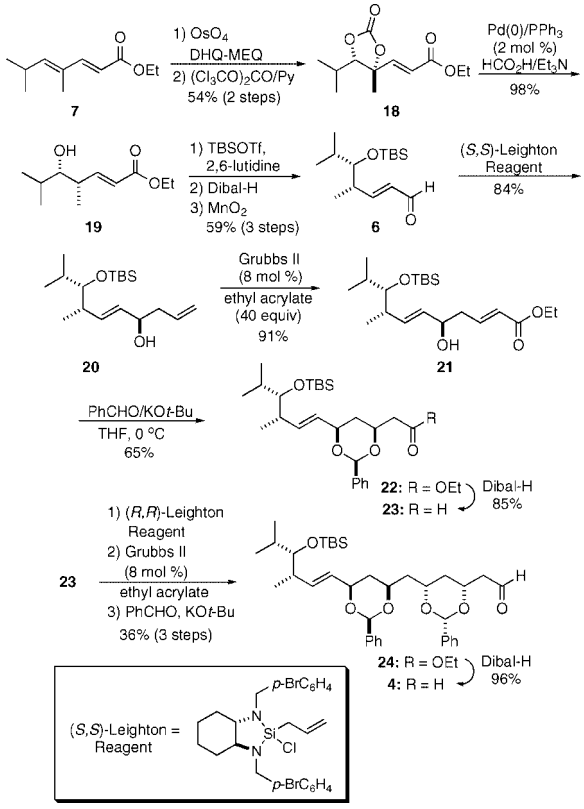
(13) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446–2453.

(14) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401–404.

(15) (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659–2660. (b) Trost, B.; Kazmaier, U *J. Am. Chem. Soc.* **1992**, *114*, 7933–35.

We next turned to the C-17 to C-31 fragment **4** which started with achiral dienoate **7**. The asymmetric hydration of dienoate **7** proceeded uneventfully to yield the desired δ-hydroxy enoate **19**. While any of the Sharpless ligands could be used for this transformation, we found monomeric 4-methyl-2-quinolyl ether linked DHQ ligand provided the best balance in terms of regio- and stereoselectivity. Thus, dihydroxylation (Scheme 4) of the

Scheme 4. First Iteration of Allylation/Metathesis/ Hemiacetal−Addition/Reduction Sequence

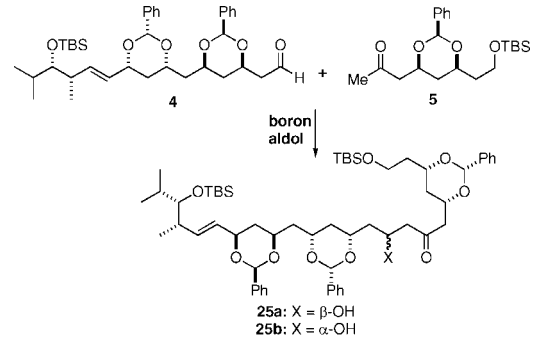


dienoate **7** (OsO_4/DHQ-4-MEQ, 80% ee)[16] followed by carbonate formation resulted in cyclic carbonate **18** in good overall yield (54%, two steps). Exposure of carbonate **18** to the palladium-catalyzed reduction conditions in the presence of triethylammonium formate as hydride source provided δ-hydroxy enoate **19** in excellent yield (98%).

The δ-hydroxy enoate **19** was converted into enal **6** (Scheme 4) via a three-step procedure (TBS-protection, Dibal-H reduction, and MnO_2 oxidation) in good overall yield (59%). The enal **6** was subjected to Leighton allylation ((*S*,*S*)-Leighton reagent) to generate homoallylic alcohol **20** in good yield and selectivity (84%, de >94%).[16] Exposing alcohol **20** to cross-metathesis conditions provided enoate **21** as only the *E* isomer in excellent yield (91%).[17] To prevent the reaction at the internal olefin of alkene **20**, 40 equiv of ethyl acrylate and 8% Grubbs II catalyst were found to be optimum conditions. Next, diastereoselective Evans hemiacetal addition (PhCHO/KO-*t*-Bu) of hydroxy enoate **21** afforded *syn*-1,3-diol **22** in excellent selectivity (>99%) and good yield (65%). The subsequent reduction with 2 equiv of Dibal-H being added to a dilute solution of **22** allowed for a high yield of the desired aldehyde **23**, which was next subjected to another iteration of the four-step sequence. Diastereoselective Leighton allylation ((*R*,*R*)-Leighton reagent), cross-metathesis coupling (Grubbs II/ethyl acrylate), and Evans' hemiacetal addition (PhCHO/KO-*t*-Bu) of aldehyde **23** provided benzylidene acetal **24** in good overall yield (36%, three steps). Once again, Dibal-H reduction proved difficult, and the conditions employed in the first iteration (**22**−**23**) were not sufficient for complete reduction to aldehyde. This time, a dilute (0.01 M) solution of ester **24** could be selectively and efficiently reduced to desired aldehyde **4** when treated with 8 equiv of Dibal-H (96%).

With aldehyde **4** in hand, we began to investigate the 1,5-*anti*-selective boron aldol reaction (Scheme 5). The initial

Scheme 5. Investigation of Boron Aldol Coupling



entry[a]	*i*-Pr_2NEt (equiv)	Bu_2BOTf (equiv)	yields (%)	ratio (25a/25b)
1	1.44	1.32	40	1:1
2	2.0	2.0	51	1:1
3	3.0	2.4	41	1:1
4[b]	3.0 Et_3N	2.4 Cy_2BCl	81	10:1

a) all reactions run with 1.2 equiv ketone
b) reaction run at -78 °C then overnight at -10 °C

conditions attempted were chosen to match those successfully used by Denmark.[3] Our coupling partners differed only at locations remote from the reacting centers, so the reaction was anticipated to proceed according to precedent. When 1.44 equiv of *i*-Pr_2NEt, 1.32 equiv of Bu_2BOTf, and 1.2 equiv of ketone **5** were used, much to our dismay, a 1:1 mixture of products **25a** and **25b** was formed (40%). A rationale for this lack of selectivity and discrepancy with the previous result was not readily apparent; however, further repetitions of the reaction confirmed the selectivity. Several additional reactions were run which varied the absolute and relative amounts of triethylamine and dibutylboron triflate but failed

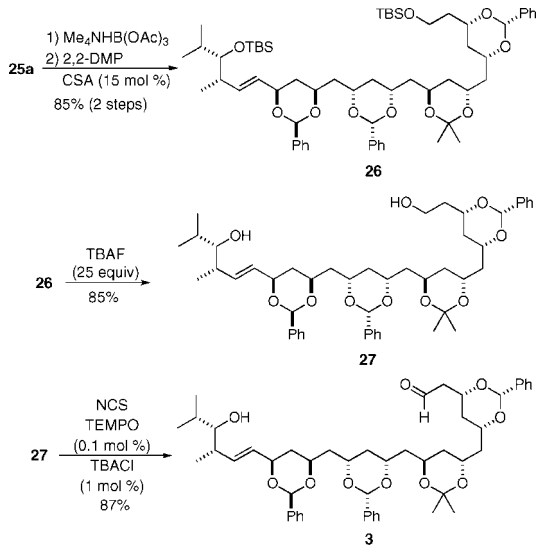
(16) The absolute stereochemistry and the level of enantioexcess for **16** and **20** were determined by chiral HPLC and Mosher ester analysis: (a) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143–2147. (b) Yamaguchi, S.; Yasuhara, F.; Kabuto, K. T. *Tetrahedron* **1976**, *32*, 1363–1367.

(17) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H *Tetrahedron Lett.* **1999**, *40*, 2247–2250.

to improve the stereocontrol.[18] To our surprise, switching the alkyl groups on boron from butyl to cyclohexyl, the conditions preferred by Paterson, solved this problem. Thus, when the reaction was performed using Paterson's conditions[19] (Cy_2BCl/Et_3N), the aldol reaction occurred to give the desired aldol adduct **25a** with good 1,5-*anti*-selectivity (10:1) and improved yield (81%).

The aldol adduct **25a** was selectively reduced to the *anti*-1,3-diol using $Me_4NHB(OAc)_3$/AcOH (Scheme 6). Acetonide

Scheme 6. Completion of Formal Synthesis via Selective Oxidation

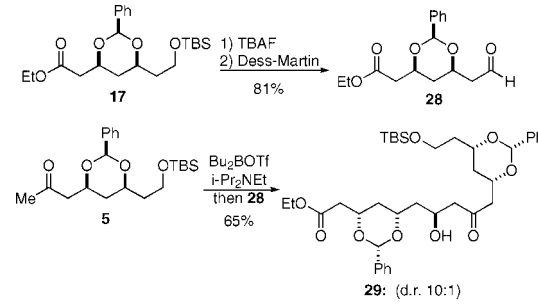


protection proceeded uneventfully using CSA/2,2-DMP/acetone to give bis-TBS ether **26** in excellent yield. The bis-TBS ether **26** was then subjected to 25 equiv of tetrabutylammonium fluoride in THF. After 1 h, a new product was formed, which was tentatively assigned as the free primary alcohol. This alcohol was allowed to react further (3 d) until a new more polar product was formed in good yield, diol **27** (85%).

To complete the formal synthesis, the primary alcohol in **27** was selectively oxidized with TEMPO using the Einhorn conditions[20] (NCS/TEMPO/TBACl). This selective oxidation occurred in good yield (87%) with no trace of overoxidation. The physical and spectral data for our synthetic hydroxy aldehyde **3** was identical to the data reported by Denmark (^{1}H NMR, ^{13}C NMR, optical rotation, and melting point).[3]

To verify that the poor selectivity in the 1,5-*anti*-selective boron aldol reaction was not due to the quality of our Bu_2BOTf reagent, we investigated its use in a dibutylboron aldol reaction with a related aldehyde, **28**. Aldehyde **28** could readily be prepared from **17** via a TBS deprotection (TBAF, 93%) and Dess−Martin oxidation (87%). In contrast to aldehyde **4**, when aldehyde **28** was coupled with the dibutylboron enolate generated from **5** ($Bu_2BOTf/i\text{-}Pr_2NEt$), the aldol reaction occurred to give the desired aldol adduct **29** with good 1,5-*anti*-selectivity (10:1) and yield (65%). Like the unselective dibutylboron aldol between **4** and **5**, the aldol between **28** and **5** occurred reproducibly with different batches of Bu_2BOTf.

Scheme 7. Reinvestigation of the Boron Triflate Aldol Coupling



In summary, a formal total synthesis of oxopentaene macrolide antibiotic RK-397 has been developed with the synthesis of **3** in 19 steps from achiral $\alpha,\beta,\gamma,\delta$-unsaturated dienoate **7**. This highly stereocontrolled route further demonstrates the synthetic utility of our asymmetric hydration strategy for the asymmetric synthesis of complex 1,3-polyol natural products. Interestingly, the anticipated aldol coupling proceeded without stereocontrol when $Bu_2BOTf/i\text{-}Pr_2NEt$ was used; this is surprising in light of the similarities with reaction to the one reported by Denmark. However, when the Paterson variant (Cy_2BCl/Et_3N) was used instead, the reaction occurred with the expected high selectivity. Further investigations into the application of this methodology for the synthesis of other oxopolyene macrolides are ongoing.

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

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(18) To confirm that the poor stereocontrol came from the aldol reaction and not from racemic material, a 1:1 mixture of **25a** and **25b** was dehydrated via the mesylate. The ^{13}C NMR of this material displayed only the signals corresponding to one isomer and thereby corroborated the hypothesis of an unselective aldol reaction.

(19) (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585–8588. (b) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187–1191.

(20) (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452–7454. (b) Sinz, C. J.; Rychnovsky, S. D *Angew. Chem., Int. Ed.* **2001**, *40*, 3224–3227.