Communication

Total Synthesis of RK-397

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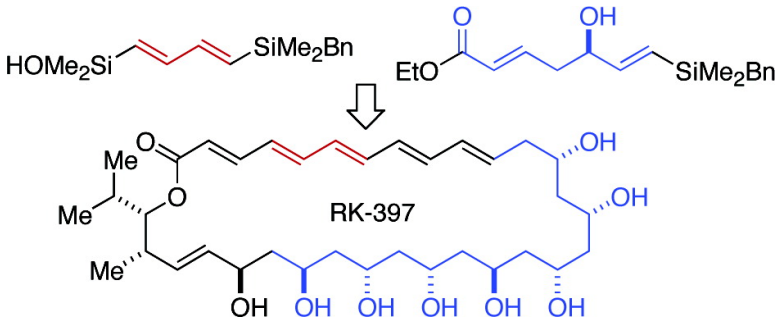

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Total Synthesis of RK-397

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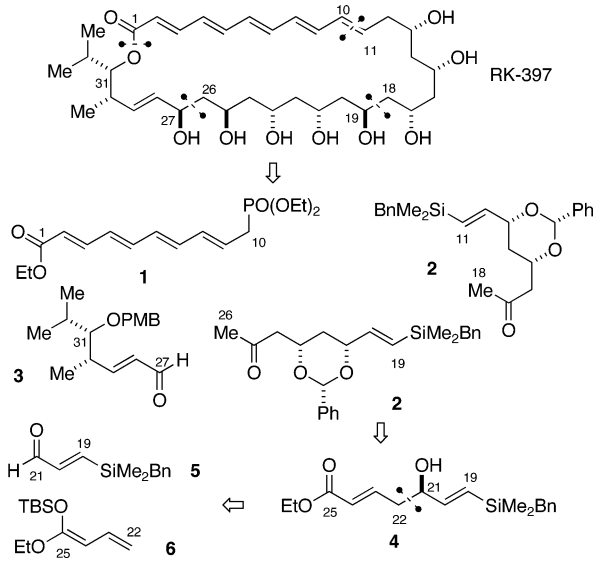
RK-397, a member of a large family of polyene macrolides that includes amphotericins, nystatin, mycoticins, and roxaticins, was isolated and structurally characterized by Osada et al. in 1993.[1] All of these macrolides contain a highly conjugated polyene and a long 1,3-polyol chain. These compounds show variable degrees of antifungal activity; in particular, amphotericin B has been used clinically as one of the most effective antifungal agents.[2] Because of their potent biological activity and structural complexity, these natural products have attracted interest as targets for total synthesis.[3,4] The foremost challenges in the synthesis of RK-397 are the stereocontrolled assembly of the polyol chain and construction of the pentaenoate backbone. We felt that both of these challenges could be efficiently addressed by ongoing methodological programs in our laboratories on the enantioselective, Lewis base-catalyzed aldol addition[5] and silicon-based cross-coupling reactions.[6] Herein, we report an efficient, enantioselective total synthesis of RK-397 utilizing these recently developed methods as key strategic steps.

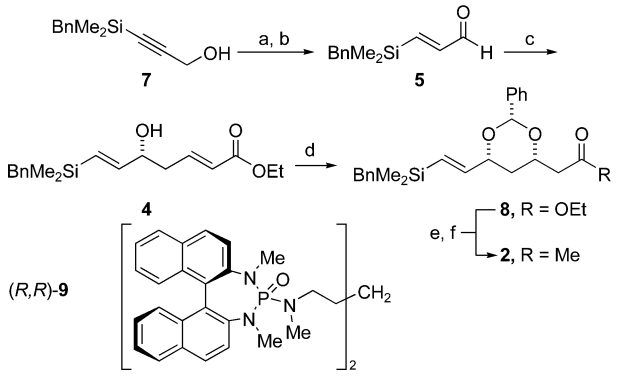
To maximize synthetic convergency, the target was divided into four modules (Scheme 1). The disconnections at the lactone linkage and the C(10)−C(11) bond provide the known polyene phosphonate fragment **1**.[7] Clearly, the polyol fragment lends itself to a myriad of aldol/reduction disconnections.[8] However, by carefully examining the pattern of stereogenic centers on the polyol chain, we concluded that the most efficient synthesis might be achieved by the disconnections at C(18)−C(19) and C(26)−C(27) bonds, which provide C(11)−C(18) and C(19)−C(26) fragments as an identical building block. In forward sense, these disconnections require an aldol addition with 1,5-anti stereoinduction from the methyl ketone **2**. The aldehyde functionality at C(11) and C(19) was masked as a vinylsilane for better functional group compatibility. The key building block **2** was envisioned to arise from vinylogous aldol addition of dienol ether **6**. The remaining C(27)−C(31) fragment would be synthesized by use of Evans' chiral acyl oxazolidinone technology.[9]

This synthesis plan was reduced to practice with the preparation of key building block **2** (Scheme 2). Stereoselective Red-Al reduction of 3-benzyldimethylsilyl propargyl alcohol **7**[10] provided the *E*-allyl alcohol,[11] which was oxidized to 3-benzyldimethylsilyl-2-propenal (**5**) in good yield (61%, two steps). The vinylogous aldol reaction of ketene acetal **6** using chiral bisphosphoramide (*R,R*)-**9** smoothly provided **4** in good yield with excellent γ-selectivity and enantioselectivity (75%, er 98/2).[12] The protected syn-diol function was installed using the tandem alkoxide addition/conjugate addition sequence developed by Evans.[13] Finally, the synthesis of building block **2** was completed by conversion of the ester group into a methyl ketone in excellent yield (58%, three steps) via the Weinreb amide.[14] The C(27)−C(31) fragment was prepared from the known aldehyde **10**[15] by a Wittig olefination/reduction/oxidation sequence in good yield (61%, three steps, Scheme 3). On the basis of previous studies,[16] we initially chose to test the aldol addition of the trichlorosilyl enolate derived from **2** (Scheme 4). TMS enol ether **11** (prepared from methyl ketone **2** with TMSOTf,[17] 94%) was transformed to the corresponding trichlorosilyl enolate using Hg(II)-catalyzed transsilylation.[18] By the use of (*R,R*)-**13** as the catalyst, aldol product **12** was obtained in good yield (81%); however, the diastereoselectivity was only 2/1 favoring the desired diastereomer (27*R*)-**12**. Interestingly, by use of the enantiomeric catalyst (*S,S*)-**13**, diastereomer (27*S*)-**12** was obtained in good yield (72%) with a 4/1 diastereomeric ratio. These results indicate that (27*S*)-**12** arises from the matched case resulting from 1,5-syn stereoinduction in the aldol addition.[19] Deeper analysis of this triple diastereoselective process is difficult without exploring all pairwise combinations of components. Better 1,5-anti stereoinduction could be achieved by substrate-controlled aldol addition using the dibutylboron enolate derived from **2** (Scheme 5).[20,21] The boron aldol addition of **2** to **3** afforded **12** with excellent diastereoselectivity (85%, dr >19/1).

Scheme 1



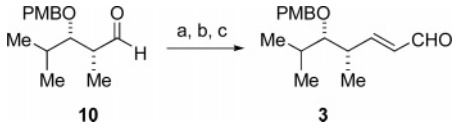
Scheme 2 [a]



[a] Conditions: (a) Red-Al (74%); (b) DMSO, $(COCl)_2$, Et_3N (83%); (c) (*R,R*)-**8**, **6**, $SiCl_4$ (75%, er 98/2); (d) PhCHO, KHMDS (74%, dr >19/1); (e) HN(OMe)Me−HCl, *i*-PrMgCl (87%); (f) MeMgBr (90%).

10.1021/ja052226d CCC: $30.25

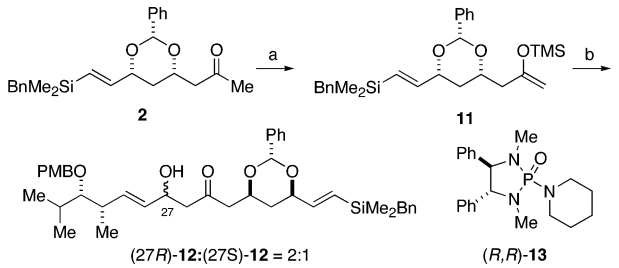
Scheme 3 [a]



10 3

[a] Conditions: (a) Ph_3PCHCO_2Et (90%); (b) DIBAL-H (97%); (c) MnO_2 (70%).

Scheme 4 [a]

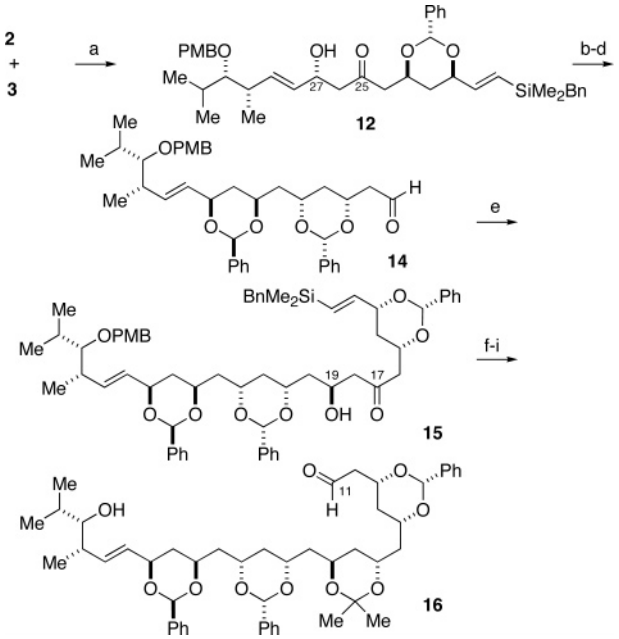


[a] Conditions: (a) TMSOTf, DIPEA (94%); (b) i. $SiCl_4$, $Hg(OAc)_2$; ii. **3**, (*R*,*R*)-**13** (81%, dr 2/1).

The configuration at C(27) was confirmed to be *R* by Mosher ester analysis of the aldol product.[22] The C(25) carbonyl group in **12** was reduced in the presence of diethylmethoxyborane and sodium borohydride, and the resulting syn-diol was protected as a benzylidene acetal (86%, two steps).[23]

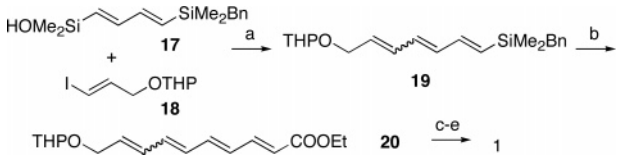
With the coupling of two modules successfully completed, we turned our attention to the next key aldol reaction. Oxidative unmasking of the vinyl silane revealed the aldehyde function at C(19) (73%).[24] With anticipation of 1,5-anti stereoinduction to establish the C(19) stereogenic center, we carried out the second iteration of boron aldol addition using **2**. Aldol product **15** was obtained in high yield and excellent selectivity (88%, dr >19/1) for 1,5-anti stereoinduction. The *S* configuration at C(19) was again confirmed by Mosher ester analysis.[22] The carbonyl group at C(17) was reduced using tetramethylammonium triacetoxyborohydride, and

Scheme 5 [a]



[a] Conditions: (a) Bu_2BOTf, DIPEA (85%, dr >19/1); (b) $NaBH_4$, Et_2BOMe; (c) $PhCH(OMe)_2$, CSA (86%, dr >19/1); (d) TBAF, H_2O_2, $KHCO_3$ (73%); (e) **2**, Bu_2BOTf, DIPEA (88%, dr >19/1); (f) $Me_4NHB(OAc)_3$; (g) $Me_2C(OMe)_2$, CSA (87%, dr >19/1); (h) TBAF, H_2O_2, $KHCO_3$ (86%); (i) DDQ (90%).

Scheme 6 [a]

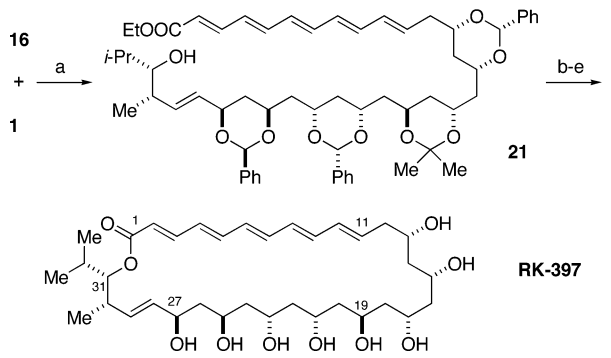


[a] Conditions: (a) NaH; $Pd_2(dba)_3$−$CHCl_3$ (77%, dr 3/1); (b) TBAF; ethyl (*E*)-3-iodopropenoate, $Pd(dba)_2$ (79%, dr 5/1); (c) *p*-TsOH; I_2 (88%); (d) PBr_3, pyridine; (e) $P(OEt)_3$ (93%).

the resulting anti-diol was protected as an acetonide (87%, two steps).[25]

The stage was now set to introduce the polyene fragment which required unveiling the vinylsilane to reveal the aldehyde at C(11) as described previously. Before the installation of polyene fragment, the PMB group was removed using DDQ to afford hydroxy aldehyde **16** (77%, two steps).[26] Although several routes are available to prepare polyene phosphonate **1**,[7,20a] we elected to employ our sequential palladium-catalyzed, cross-coupling of a 1,4-bissilyl-1,3-butadiene **17** for the construction of the tetraene moiety of **1** (Scheme 6**)**.[27] In the first cross-coupling, silanol **17** was activated with NaH, and the resulting silanolate reacted smoothly (77%) with the THP ether of 3-iodo-2-propenol **18**[28] in the presence of $Pd_2(dba)_3$−$CHCl_3$.[29] In the second coupling, benzylsilane **19** reacted with ethyl (*E*)-3-iodopropenoate[30] in the presence of TBAF and $Pd(dba)_2$ to afford tetraenoate **20** in good yield (79%). The THP protecting group was removed under acidic conditions to give the hydroxy ester, and then treatment of this mixture of olefin isomers with a small amount of iodine during workup gave the all *E*-tetraenoate in good yield (88%).[7c] The hydroxy enoate was converted to phosphonate **1** as described in the literature.[7c] The final fragment coupling brought together the phosphonate and the polyol chain using the standard Horner−Wadsworth−Emmons olefination protocol (Scheme 7). From this stage to the final product, all reactions and purifications were performed with careful exclusion of light due to the extreme photosensitivity of the polyene. The olefination proceeded smoothly with the aid of LiHMDS to afford pentaenoate **21** in good yield (77%). The macrolactonization of the seco hydroxy acid (prepared from **21** by saponification with LiOH) was efficiently effected via the mixed anhydride from 2,4,6-trichlorobenzoyl chloride.[31] Closure of the mixed anhydride in the presence of DMAP in high dilution successfully afforded a good yield of fully protected RK-397 with a minimum of larger oligomers (71% over three steps). Although the acetonide was easily hydrolyzed under mildly acidic conditions, removal of the more stable benzylidene acetals was problematic. Surprisingly, the use of concentrated HCl in MeOH was found to be the most effective method for the global deprotection (93%). It was crucial to remove the acid at the end of the reaction with polymer-bound piperidine to avoid decomposition of the final product during purification. The product was stable under silica gel chromatography; however, to obtain the natural product in a state of high purity for thorough and unambiguous structural verification, further purification was carried out using preparative reverse-phase HPLC. Synthetic RK-397 exhibited spectroscopic and physical properties identical to those reported for the natural material (HNMR, CNMR, ORD, HRMS).[1] In conclusion, RK-397 was synthesized by employing a convergent synthetic strategy that features the use of an 8-carbon building block for 16 carbons in the polyol chain. The synthesis highlights the enantioselective vinylogous aldol addition using chiral phosphoramide **9** for the construction of the key intermediate **2**. The stereogenic center created by this reaction established 8 of the 10 stereogenic centers in RK-397 by substrate control. This

Scheme 7 [a]



[a] Conditions: (a) LiHMDS (77%); (b) LiOH; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N; (d) DMAP (71%, three steps); (e) concentrated HCl, MeOH (93%).

synthesis also illustrated the sequential cross-coupling of bissilyl diene **17** to construct the conjugated polyene **1**. The application of Lewis base-catalyzed aldol additions in syntheses of more complex molecules is currently under investigation.

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Supporting Information Available: Full experimental procedures and characterization data for intermediates and synthetic natural product described. This material is available free of charge via the Internet at http://pubs.acs.org.

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