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Total Synthesis of the Polyene-Polyol Macrolide RK-397, Featuring Cross-Couplings of Alkynylepoxide Modules

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Abstract: The total synthesis of the natural product RK-397 is based on a new synthetic strategy for assembling polyacetate structures, by efficient cross-coupling of nucleophilic terminal alkyne modules with electrophilic epoxides bearing another alkyne at the opposite terminus. The natural product is constructed from four principal modules: a polyene precursor for carbons 3−9, and three alkyne-terminated modules for carbons 10−16, 17−22, and 23−33. Each module is prepared with control of all stereochemical elements, and the alkynyl alcohols obtained from alkyne−epoxide couplings are converted into 1,3-diols by a sequence of hydroxyl-directed hydrosilylation, C−Si bond oxidation, and stereoselective ketone reduction with induction from the β-hydroxyl group. The highly convergent nature of our synthetic pathway and the flexibility of the modular synthesis strategy for virtually any stereoisomer can provide access to other members of the polyene-polyol macrolides, including stereoisomers of RK-397.

Introduction

Polyacetate structures in the form of 1,3,5-... alternating polyol chains are found in a variety of natural products, such as the polyene macrolides amphotericin B (**1**), nystatin (**2**), mycoticin (**3**), and RK-397 (**4**) (Figure 1), which are well-known for their antifungal activities.[1,2] Relatively minor structural changes can result in significant differences in biological activities. For instance, amphotericin B (**1**) is used for severe systemic and potentially fatal fungal infections but is also relatively toxic, whereas nystatin (**2**) is much milder in activity and has virtually no human toxicity.[3] Mycoticin (**3**) and RK-397 (**4**) both exhibit broad antimicrobial activities against filamentous fungi, yeast, and bacteria at 50−100 μg/mL, yet only RK-397 (**4**) is reported to have in vitro anticancer activity, inhibiting human leukemia cell lines K-562 and HL-60 at 50 and 25 μg/mL, respectively. The anticancer activity for RK-397 (**4**) vs the absence of activity reported for mycoticin (**3**) is rather remarkable when the minor differences in the two compound structures are considered, specifically the additional methyl group at C14 of mycoticin and differing relative stereochemistry of the C19 and C21 alcohols.

Polyacetate compounds are biosynthesized by building up the linear carbon chain two atoms at the time using simple acetate and propionate building blocks.[4] In this regard, the Schreiber chemical synthesis of mycoticin based on iterative aldol equivalent addition to aldehydes might be considered to be an

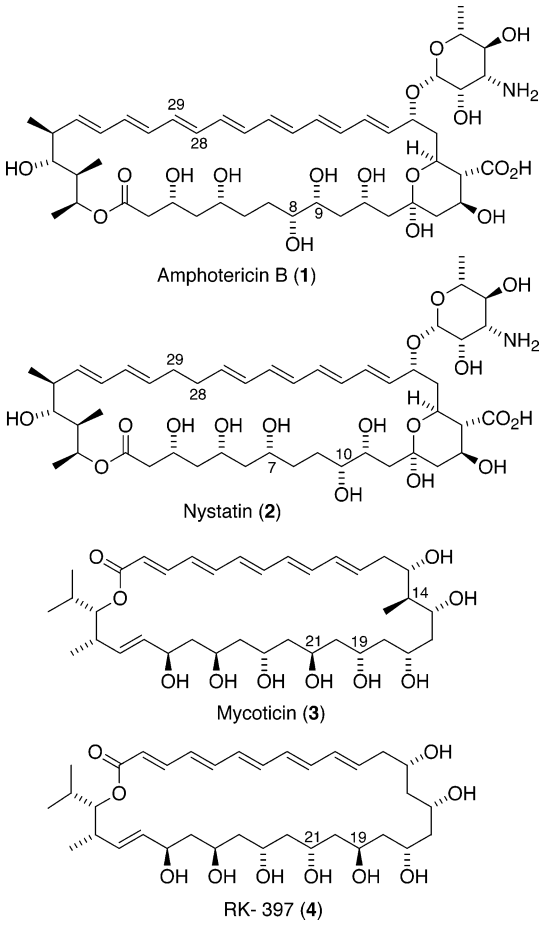

Figure 1. Representative polyene macrolide natural products.

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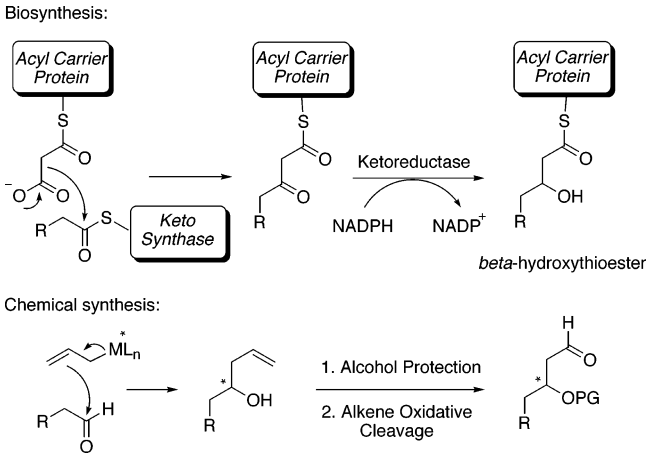

Figure 2. Construction of polyacetates from two-carbon synthons: biosynthesis vs chemical synthesis.

imitation of this biosynthetic pathway (Figure 2).[5] Note that a linear synthesis of a 34-carbon chain from two-carbon synthons requires 16 carbon−carbon bond-forming steps.

Thus, the number of carbon−carbon bond-forming steps can be further reduced by using larger building blocks, such as Carreira's aldehyde condensation approach with four-carbon acetoacetate synthons,[6] or Rychnovsky's sequential cross-couplings of the five-carbon dibromides with 4-cyano-1,3-dioxanes (Figure 3).[7,8]

We anticipated a more efficient modular approach for polyacetate-alternating polyol structures by coupling larger building blocks with six or more carbons in a linear chain,

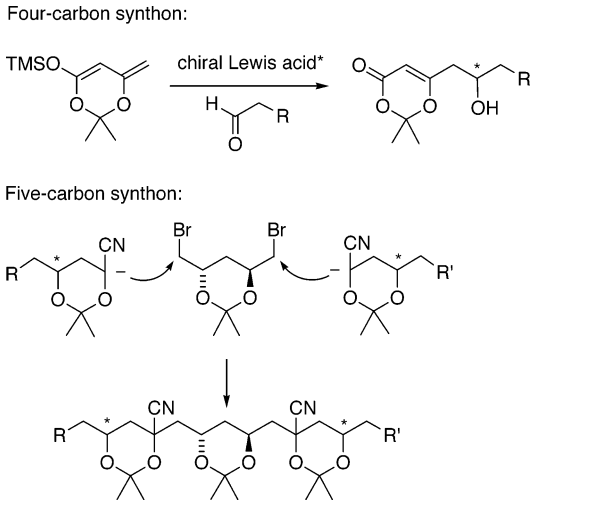

Figure 3. Examples of four- and five-carbon synthons in the synthesis of polyacetates.

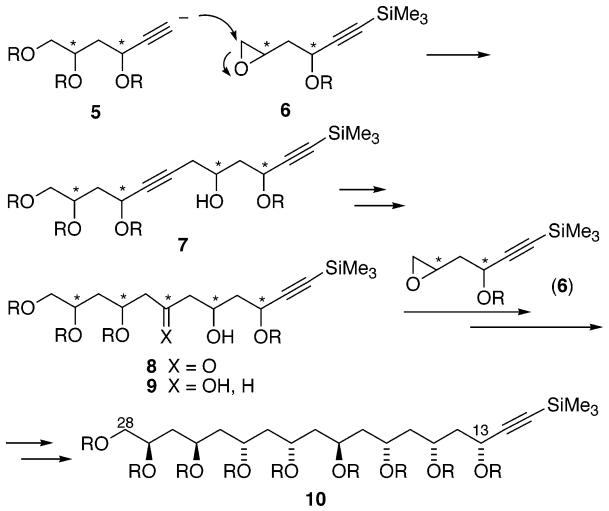

Figure 4. Modular synthesis of polyol segment of RK-397 from six-carbon synthons **5** and **6**.

further reducing the number of carbon−carbon bond-forming steps required for polyacetate synthesis. The optimal modular synthesis would permit maximum variability in product structures with regard to functional groups and stereochemical diversity, which is particularly important for combinatorial and parallel synthetic strategies and methods. To this end we recently reported a new strategy for assembling polyacetate structures based on cross-coupling of six-carbon modules utilizing nucleophilic epoxide opening of electrophilic epoxyalkynol **6** with nucleophilic alkynyltriol **5** (Figure 4). Regioselective water equivalent addition to the internal alkyne of the resulting diyne **7** produced β-hydroxyketone **8**. Depending on the choice of reducing reagent,[9] stereoselective hydroxyl-directed reduction of the β-hydroxyketone functionality in **8** afforded either 1,3-syn or 1,3-anti diol products, therefore permitting rapid preparation of polyacetate structures **9** bearing twelve linear carbons and separate control of all five stereocenters. Additionally, our

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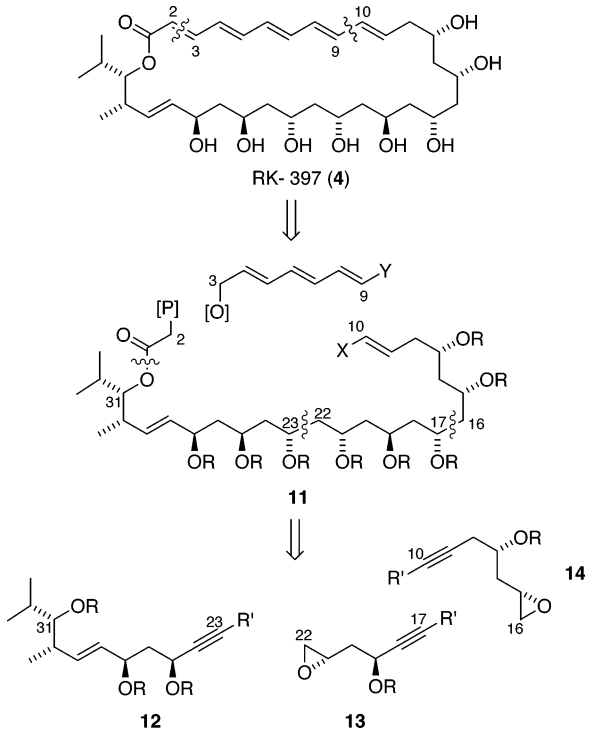


Figure 5. Retrosynthetic analysis of RK-397.

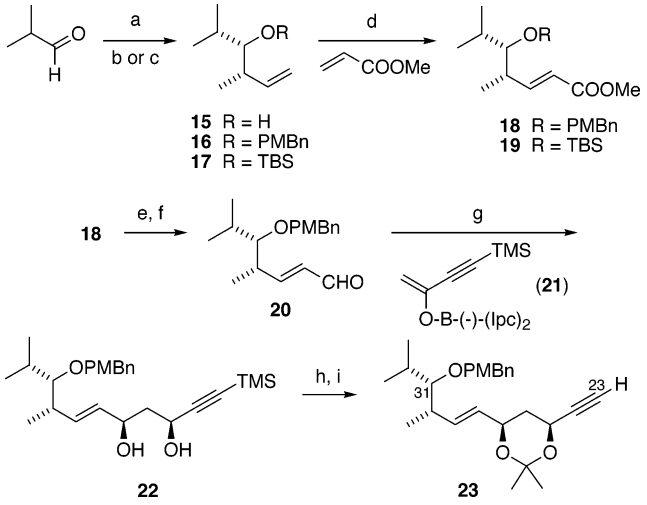
methodology was applied in an iterative mode from **9** and epoxyalkynol **6** to give the C11−C28 substructure of RK-397.[10,11]

We have now completed the total synthesis of RK-397, based on a modification of the modular synthesis approach outlined above using iterative cross-couplings of terminal alkynes with epoxyalkyne modules. In our retrosynthetic analysis, we decided to introduce the light- and air-sensitive polyene at the end of the synthesis *a la* Rychnovsky's method of sequential Stille[8k,l] and macrocyclic Horner−Emmons[12] reaction from **11**, which in turn could be disconnected into the enyne **12**, six-carbon epoxyalkyne **13** (analogous to **6**), and seven-carbon epoxyalkyne **14** (Figure 5).

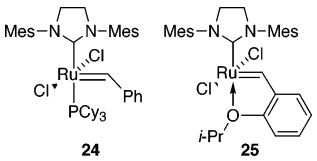
Results and Discussion

I. Synthesis of Modules 12, 13, and 14. The synthesis of the C23−C31 module **12** began with synthesis of homoallylic alcohol **15** from the reaction of isobutyraldehyde with (*Z*)-crotyldiisopinocampheylborane[13] (derived from commercially available (1*S*)-(−)-α-pinene, 89% ee; Scheme 1). In our hands, alcohol **15** was difficult to separate from the isopinocampheol byproduct of auxiliary oxidation, therefore **15** was isolated in 75% purity and was taken to the next step without additional purification. After protection of the free hydroxyl group as a *p*-methoxybenzyl ether and purification, this compound **16** was subjected to ruthenium-catalyzed olefin cross-metathesis with methyl acrylate.[8d,14] This reaction can be catalyzed either with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene Ru(=CHPh)-

Scheme 1. Synthesis of C23−C31 Module[a]



[a] Reagents and conditions: (a) *Z*−crotylborane−(−)-(Ipc)$_2$, then H_2O_2, 3 N NaOH (50% yield, 77% ee); (b) *p*-methoxybenzyltrichloroacetimidate, cat. CSA, CH_2Cl_2 (67% yield); (c) TBSCl, imidazole, DMF (60% yield); (d) methyl acrylate (3 equiv), cat. **24** or **25**, CH_2Cl_2 (see below); (e) DIBAL-H, CH_2Cl_2, −78 °C (91% yield); (f) SO_3−pyr, DMSO, CH_2Cl_2 (89% yield); (g) **21**, Et_2O, −78° to −30 °C, then −78 °C, $NaBH_4$, MeOH, then AcOH quench, then H_2O_2, 3 N NaOH (97% yield, 4:1 dr); (h) K_2CO_3, MeOH. (i) $Me_2C(OMe)_2$, cat. TsOH (75%, two steps).



to **18** R = PMB, 60% (with 2 mol% of **24**), 66% (with 2 mol% of **25**)
to **19** R = TBS, 23% (with 10 mol% of **24**), 74% (with 2 mol% of **25**)

$(PCy_3)Cl_2$ **24**[14] or the corresponding *o*-isopropoxybenzylidene-ruthenium carbene **25**.[15] Catalyst **24** produced the α,β-unsaturated ester **18** in 60% yield after 16 h at ambient temperatures. However, the more reactive phosphine-free Ru catalyst **25** also provided **18** in 66% yield after 5 h at 36 °C. More dramatic results were observed in the reaction of *tert*-butyldimethylsilyl ether **17** with methyl acrylate. Grubbs's second generation metathesis catalyst **24** was a very poor catalyst for this transformation, generating a low yield (23%) of desired α,β-unsaturated ester **19** even with 10 mol % loading of catalyst **24**. In contrast, α,β-unsaturated ester **19** was obtained in good yield (74%) when only 2 mol % of phosphine-free Ru catalyst **25** was applied. In all cases only the *trans*-alkene isomers **18** and **19** were obtained from olefin cross-metathesis. Enantioselective aldol addition of the unsaturated aldehyde **20** with the enolborinate **21** (from 4-(trimethylsilyl)-3-butyn-2-one and (−)-(Ipc)$_2$BOTf/Et_3N[16]) gave the expected β-hydroxyketone in low yield. Recalling that Paterson successfully utilized a one-pot boron aldol addition and stereoselective reduction of the intermediate boron chelate with $NaBH_4$,[17] we applied the same one-pot aldol−reduction procedure from **20** and **21** to provide *syn*-diol **22** as an 4:1 mixture of diastereomers in excellent yield. After basic methanolysis of the alkynylsilane **22** and acetonide

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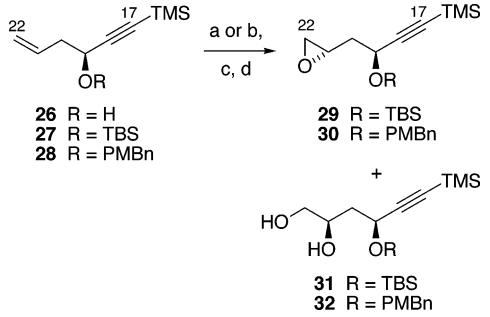
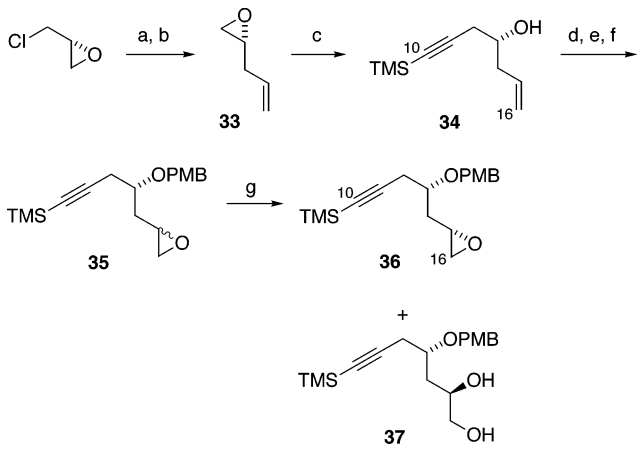
Scheme 2. Synthesis of the C17−C22 Module[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF (85% yield); (b) *p*-methoxybenzyl trichloroacetimidate, cat. CSA, CH_2Cl_2 (74% yield); (c) *m*-CPBA, CH_2Cl_2 (79−83% yield); (d) (*S*,*S*)-salenCo(III)OAc (polymer-supported), H_2O (for R = TBS, 46% yield epoxide (**29**) + 43% yield diol (**31**); for R = PMBn, 42% yield epoxide (**30**) + 54% yield diol (**32**, 4:1 dr)).

Scheme 3. Synthesis of C10−C16 Module[a]



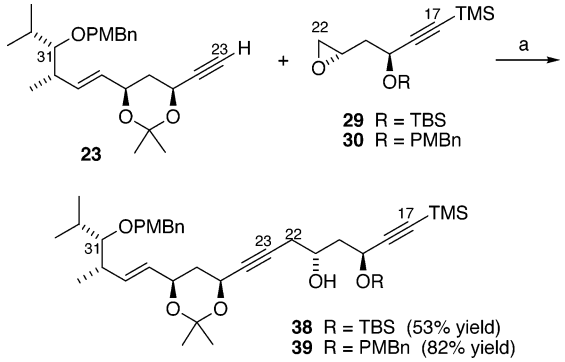
[a] Reagents and conditions: (a) Vinylmagnesium bromide, CuBr, THF, −70° to −40 °C (84% yield); (b) KOH (81% yield); (c) TMS-acetylene/*n*-BuLi/BF_3−OEt_2, THF, −78 °C (75% yield); (d) *m*-CPBA, CH_2Cl_2 (77% yield, 1.2:1 dr); (e) NaH, PMBnCl, Bu_4NI, DMF (73% yield); (f) *n*-BuLi, TMSCl, THF, −55° to −40 °C (55% yield); (g) 10% (*S*,*S*)-salenCo(III)OAc, THF/H_2O (**36**, 32% yield + **37**, 47% yield).

protection of the 1,3-diol, the diastereomeric mixture was purified by silica gel flash chromatography to provide single diastereomer **23** (corresponding to generalized structure **12**).[18,19]

The C17−C22 module was prepared as previously described from the (*S*)-enynol **26**.[10] Epoxidation of either the silyl ether **27** or *p*-methoxybenzyl ether **28** gave a ca. 1:1 mixture of diastereomers, and single diastereomers **29** and **30** could be prepared by Jacobsen's hydrolytic kinetic resolution procedure[20] (Scheme 2).

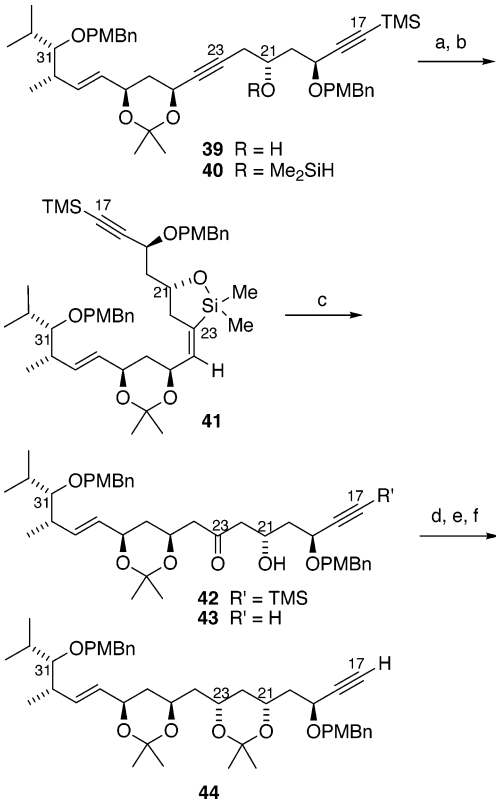
The seven-carbon C10−C16 module was constructed from (*R*)-epichlorohydrin and copper bromide-promoted addition of vinylmagnesium bromide followed by subsequent distillation from KOH to give **33**,[21] which was converted into the enynol **34** (Scheme 3). We originally first protected the hydroxyl as a *p*-methoxybenzyl ether, followed by epoxidation, but the mixture of epoxides was determined to contain the desired diastereomer **36** as the minor component of a 1.7:1 mixture of diastereomers. However, when epoxidation was conducted on the alcohol **34** followed by PMBn ether formation (desilylation also occurred under the basic conditions, which required resilylation of the epoxyalkyne) the mixture of epoxides favored **36** in a 1.2:1 diastereomeric ratio. Hydrolytic kinetic resolution provided **36** as a single stereoisomer which was easily separated from the more polar diol **37**.

Scheme 4. Coupling of C17−C22 and C23−C31 Modules[a]



[a] Reagents and conditions: (a) **23**, *n*-BuLi, THF, −50 °C, then BF_3−OEt_2, −78 °C, then **29** or **30**.

Scheme 5. Hydroxyl-Directed Hydrosilylation−Oxidation[a]



[a] Reagents and conditions: (a) $(Me_2SiH)_2NH$, 100 °C; (b) cat. Pt(DVDS), THF; (c) 30% aq. H_2O_2, $KHCO_3$, KF, MeOH/THF (**42**, 43% yield + **43**, 13% yield); (d) Et_2BOMe, THF/MeOH, $NaBH_4$, −78 °C; (e) K_2CO_3, MeOH; (f) $Me_2C(OMe)_2$, cat. TsOH, 3Å MS (67% yield, three steps).

(18) Although a similar reaction sequence could be accomplished from **19** to give the silyl ether analogue of **23**, the mixture of diastereomers could not be efficiently separated.

(19) Relative and absolute configuration of **23** was confirmed by X-ray diffraction analysis of the secondary alcohol resulting from DDQ oxidative removal of the *p*-methoxybenzyl ether protective group. Please see Supporting Information for details.

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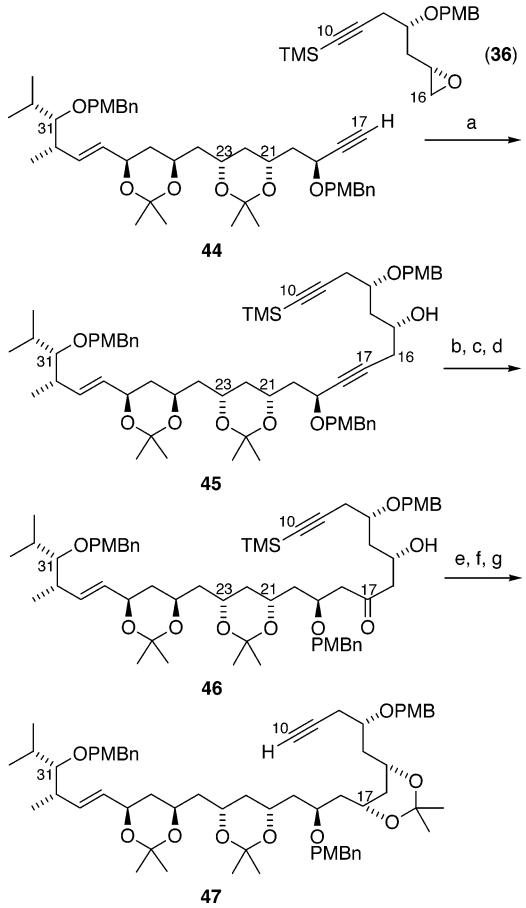
Scheme 6. Coupling to C10−C16 Module and Alkyne Hydration OPMB[a]

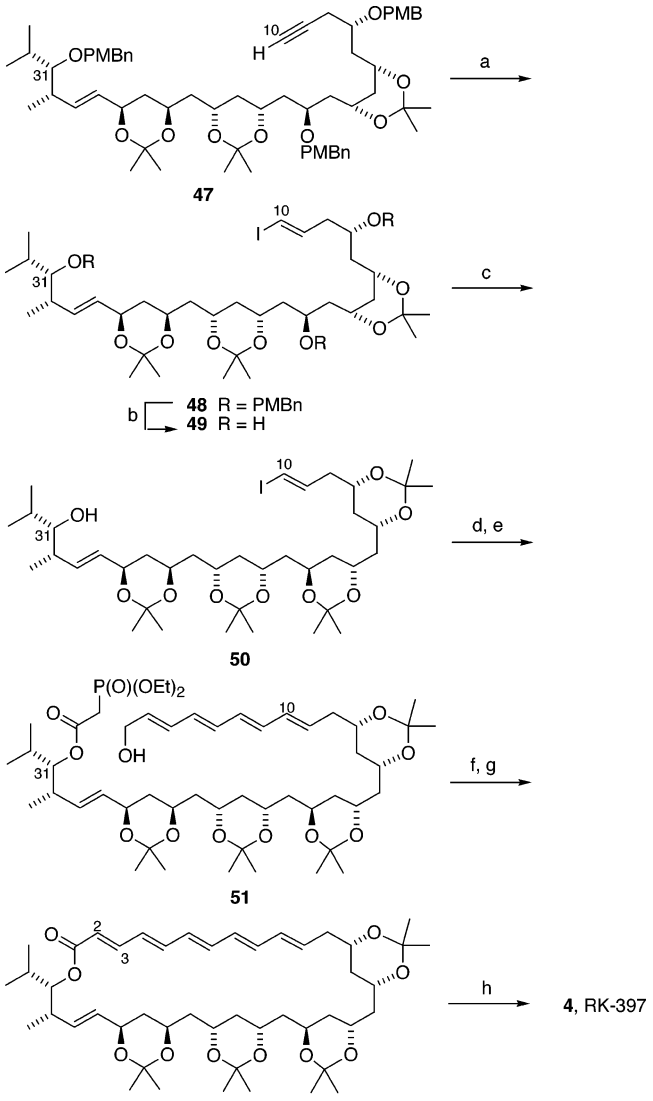


[a] Reagents and conditions: (a) *n*-BuLi, THF, −78°C, then BF_3−OEt_2, −78 °C, then **36** (59% yield); (b) $(Me_2SiH)_2NH$, 100 °C; (c) cat. Pt(DVDS), THF. (d) 30% aq H_2O_2, $KHCO_3$, KF, MeOH/THF (65% yield, three steps); (e) Et_2BOMe, THF/MeOH, $NaBH_4$, −78 °C; (f) K_2CO_3, MeOH; (g) $Me_2C(OMe)_2$, cat. TsOH, 3Å MS (80% yield, three steps).

II. Coupling of C17−C22 and C23−C31 Modules and Hydration of the Internal Alkyne. Cross-coupling of the lithium acetylide from **23** with either electrophilic epoxides **29** or **30** could be accomplished with BF_3−OEt_2[22] to provide the corresponding homopropargylic alcohols **38** or **39** (Scheme 4). Care was taken to avoid using more than 1 equiv of *n*-BuLi for deprotonation of **23**, as deprotonation on the aromatic ring of the PMBn protective group resulted in diminished yields of coupling products.

Several approaches were explored for hydration of the C23−C24 alkyne including iodocyclization of a carbonate derivative of **38**,[10,23,24] before we settled on hydroxyl-directed hydrosilylation/Si−C bond oxidation, which had been reported by Tamao and more recently Marshall.[25] As our initial studies indicated that TBS ether protective groups were incompatible with siloxane carbon−silicon bond oxidation, we began by forming the hydrodimethylsilyl ether substrate **40** (Scheme 5) from *p*-methoxybenzyl ether-protected alkynyl alcohol **39**. The

Scheme 7. Coupling of C10−C31 to Polyene and Completion of RK-397 Synthesis[a]



[a] Reagents and conditions: (a) Cp_2ZrCl_2, $LiEt_3BH$, THF; then I_2 (90% yield); (b) DDQ, CH_2Cl_2 (61% yield); (c) 2,2-dimethoxypropane, TsOH (0.8 equiv), H_2O (1.5 equiv), 3 d (86% yield); (d) $HO_2CCH_2P(O)(OEt)_2$, BOP, DMAP, CH_2Cl_2 (91% yield); (e) *all-trans*-7-(tributylstannyl)-2,4,6-heptatrien-1-ol, cat. $Pd_2(dba)_3$−$CHCl_3$, Ph_3As, *i*-Pr_2NEt, THF (32% yield + 27% recovered iodide); (f) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2; (g) LiCl, DBU, MeCN, 2 d (29% yield, two steps); (h) Dowex 50W acidic resin, MeOH (73% yield).

organic soluble catalyst complex Pt(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex (Pt(DVDS))[26] completely converted **40** to the cyclic siloxane **41**,[27] which was directly oxidized with aqueous hydrogen peroxide in the presence of KF to furnish *β*-hydroxyketones as a mixture of TMS-protected alkyne **42** and its unprotected counterpart **43** in 56% yield for three steps starting from alcohol **39**. Hydroxyl-directed reduction of the mixture of *β*-hydroxyketones **42** and **43** with $NaBH_4$/Et_2BOMe,[9b] and sequential acetylenic TMS deprotection and acetonide formation, gave product **44** in good yield.

(22) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(23) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798.
(24) Iodocyclization of the *tert*-butyl carbonate derivative of the alcohol of **38** was successful. However radical deiodination resulted in a product attributed to radical cyclization onto the C28−C29 alkene. Please see Supporting Information for more discussion.
(25) Tamao, K.; Maeda, K.; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 6955. (b) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173.
(26) Denmark, S. E.; Wang, Z. *Org. Lett.* **2001**, *3*, 1073.
(27) Incomplete conversion of **40** to cyclic siloxane intermediate **41** was observed during intramolecular hydrosilylation of **40** catalyzed by chloroplatinic acid (H_2PtCl_6) even after extended reaction time. Cyclic siloxane **41** suffered significant decomposition upon prolonged exposure to silica gel; therefore, it was taken to the next step without purification.

III. Coupling to the C10−16 Module and Completion of the Synthesis of RK-397. The coupling of terminal alkyne **44** and the C10−C16 epoxyalkyne module **36** proceeded smoothly to afford diyne **45**, which underwent the identical sequence of hydrosilylation−oxidation to **46** and chelation-controlled reduction to provide regio- and stereoselective introduction of the C17-alcohol, protected as the acetonide **47** (Scheme 6).

From this stage, we sought to validate our methodology by completing the total synthesis of RK-397, introducing the polyene and closing the macrocycle following the strategy previously demonstrated for dermostatin by Sinz and Rychnovsky.[8k−l] The terminal alkyne of **47** underwent hydrozirconation−iodination[28] to the *trans*-vinyl iodide **48** in excellent yield (Scheme 7). Subsequent deprotection of the PMBn ethers to **49** and protective group equilibration with wet 2,2-dimethoxypropane and catalytic TsOH provided the desired tetracetonide **50** in good yield, with only the C31 alcohol unprotected. After esterification with diethylphosphonoacetic acid, Stille coupling with *all-trans*-7-(tributylstannyl)-2,4,6-heptatrien-1-ol[29] to **51** and oxidation of the primary alcohol provided the corresponding aldehyde which successfully underwent Horner−Emmons macrocyclization under Masamune−Roush conditions[12b] to provide the known tetraacetonide derivative **52**[2c] of RK-397. Acidic methanolysis of the acetonide protective groups provided synthetic RK-397 (**4**). Our synthetic RK-397 and tetraacetonide **52** were both identical with natural RK-397 and the derived tetraacetonide **52** with regard to proton NMR spectra in CD_3OD, and UV-spectroscopy.[30] Thus the unambiguous nature of our synthesis with regard to setting stereocenters confirms Nakata's assignment of stereochemistry for RK-397.

(28) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257. $Cp_2Zr(H)Cl$ has a poor shelf life. In our hands, commercial samples of this reagent gave mostly or only the terminal alkene, probably from disproportion to Cp_2ZrH_2 and inactive Cp_2ZrCl_2. (b) Review: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.

(29) Prepared in two steps from known *all-trans*-5-(tributylstannyl)-2,4-pentadienal (Dominguez, B.; Iglesias, B.; Lera, A. R. *Tetrahedron* **1999**, *55*, 15071): (a) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2 (95% yield); (b) DIBAL, CH_2Cl_2, −78 °C (75% yield).

(30) ^1H NMR spectra and ultraviolet spectra of natural RK-397 (**4**) and its tetraacetonide derivative **52** were generously provided by Dr. Tadashi Nakata and Dr. Hiroyuki Koshino from The Institute of Physical and Chemical Research (RIKEN), Japan.

Conclusions

The first synthesis of RK-397 (**4**) also demonstrates the merit of our modular synthesis approach to this natural product, via the advanced intermediate **47** bearing all 10 chiral centers. Although all three β-hydroxyketones (precursor to **22**, compounds **42** and **46**) were reduced to *syn*-1,3-diols by chelation-controlled reductions, the option of obtaining 1,3-*anti*-diols[9c] by hydroxyl-directed reduction at any of these stages and the availability of any isomer of **23** (four chiral centers, 16 isomers), **30** (four isomers) and **36** (four isomers) makes it not unrealistic to consider that any of the 2^{10} (1024) isomers of advanced intermediate **47** can be prepared, and barring possible conformational restrictions on the polyene macrocyclization, perhaps any isomer of RK-397 can be prepared. Thus more efficient conversions of the hydroxyalkynes **39** and **45** to β-hydroxyketones **42** and **46**, respectively, might enable practical parallel synthesis of a library of RK-397 stereoisomers. Extensions of this strategy to the synthesis of polypropionates are also in progress.

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Supporting Information Available: Complete experimental details and compound characterizations, crystallographic data for a derivative of compound **23** (includes cif data), discussion of attempted hydration from iodocyclization of the *tert*-butyl carbonate derivative of **38**, and comparison of spectral data of synthetic and natural RK-397 (**4**) and tetraacetonide derivative **52**. This material is available free of charge via the Internet at http://pubs.acs.org.

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