VIP Natural Products

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The Total Synthesis of the Oxopolyene Macrolide RK-397**

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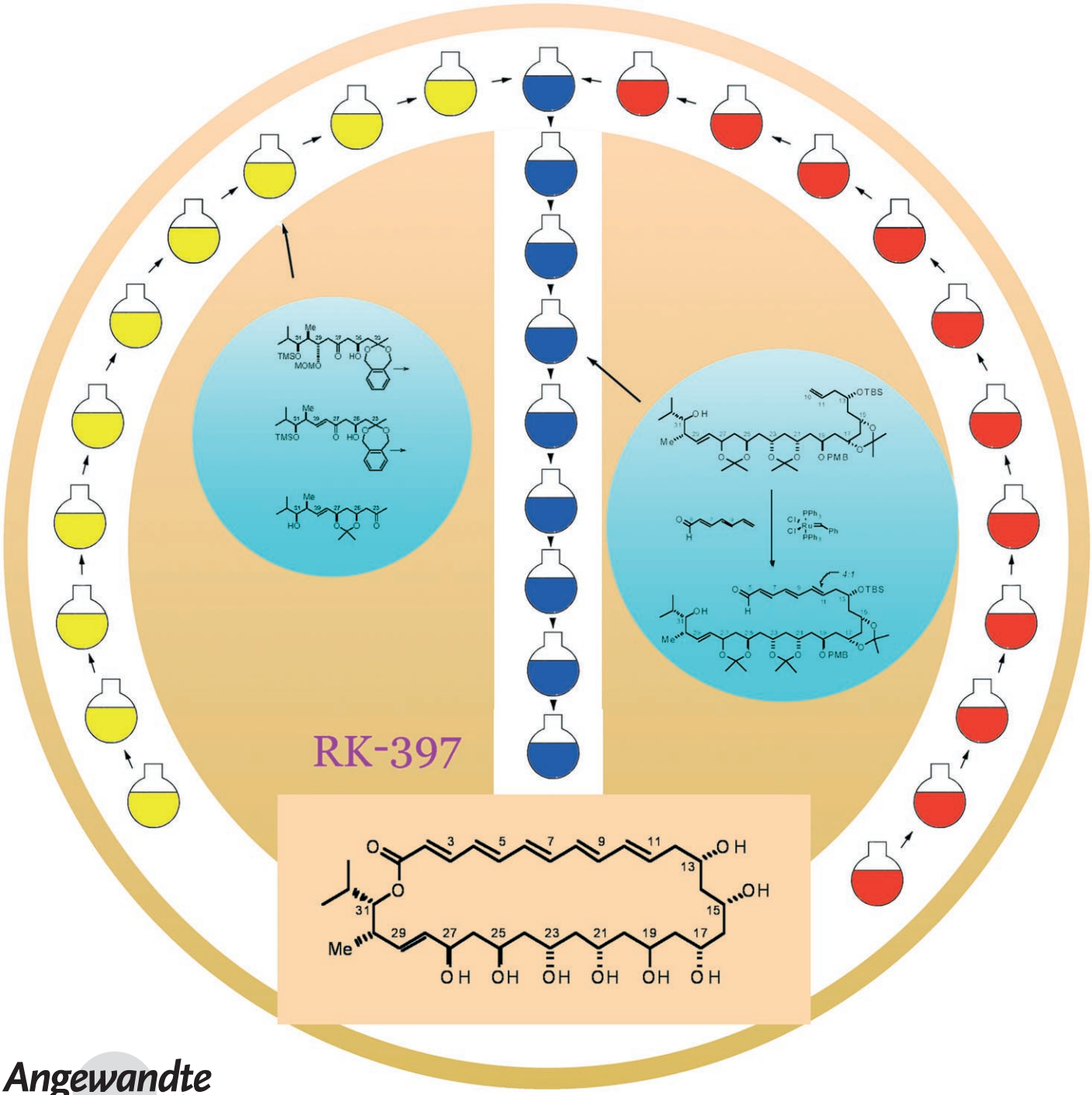
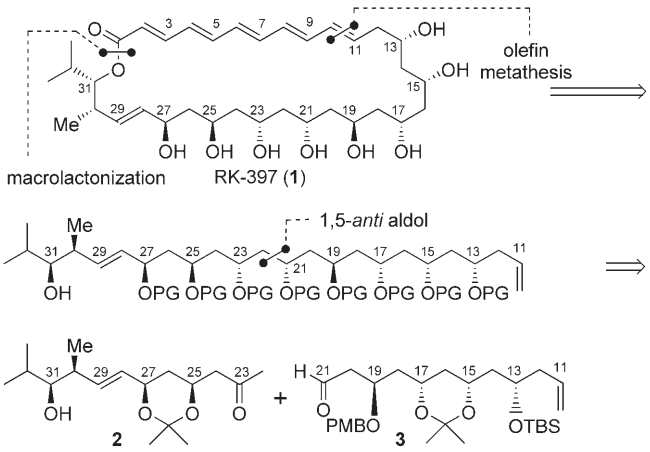


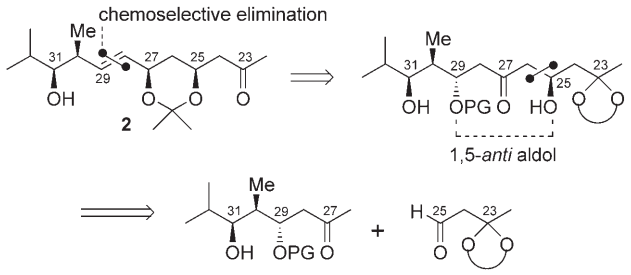
The stereochemically complex natural product RK-397 (**1**, Scheme 1) was isolated in 1993 from a strain of soil bacteria and was shown to possess antifungal, antitumor, and antibacterial activities.[1] RK-397 is an oxopolyene macrolide[2] whose structure[3] corresponds to that of C14-demethyl mycoticin A,[4] in which the stereocenters at C19 and C21 have the opposite configuration.[5] Members of this class of natural products have been popular targets for synthesis,[6] and Burova and McDonald,[7] as well as Denmark and Fujimori[8] have recently reported syntheses of RK-397. Herein, we describe our recently completed route to this molecule.



Scheme 1. Retrosynthesis of RK-397 (**1**). PG = protecting group, TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.

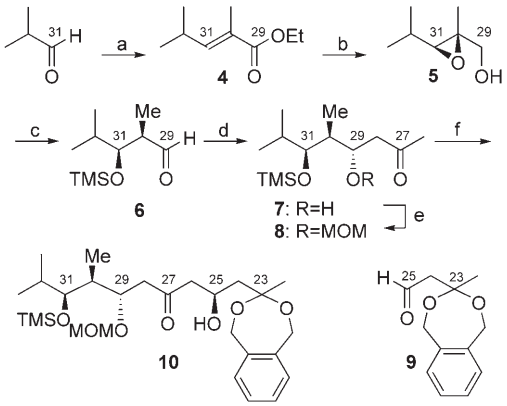
This molecule presents several synthetic challenges, including the efficient construction of the stereochemically complex polyol chain, the introduction of the sensitive polyene moiety, and the formation of the macrocycle. In analogy to previous oxopolyene macrolide syntheses, we planned to form the macrocycle through a macrolactonization.[9] The polyol was disconnected into two fragments of roughly equal complexity, namely methyl ketone **2** (C22–C33) and aldehyde **3** (C10–C21, Scheme 1). We envisioned an asymmetric catalysis approach with relay of stereochemistry across the alkene for the synthesis of **2**, a two-directional approach for the synthesis of **3**, and a late-stage cross-metathesis of an olefin to append the polyene chain.

Scheme 2 depicts our retrosynthetic analysis of methyl ketone **2**. From the outset, we wished to make use of the C30/C31 stereodiad to dictate the stereochemistry at C27 and C25 through remote asymmetric induction. We chose to accomplish this by using the method reported by the research groups of Evans and Paterson, in which a β-alkoxy methyl ketone undergoes an aldol reaction with relay of stereochemistry between the β-alkoxy group and the newly formed stereocenter (1,5 induction).[10] We therefore required an alkoxy group at C29 to relay asymmetric induction to C25 and then planned to subject this group to an elimination reaction in order to install the C28–C29 alkene.



Scheme 2. Retrosynthesis of methyl ketone **2**.

Our synthesis of **2** began with a crossed aldol condensation between ethyl propionate and isobutyraldehyde (Scheme 3). This modified literature procedure[11] provided enoate **4** in good yield, excellent *E* selectivity (64%, $E/Z >$ 50:1), and was readily conducted on a molar scale. Reduction of the enoate with $LiAlH_4$[12] was followed by a Sharpless asymmetric epoxidation[13] to afford the known epoxy alcohol **5** with good enantiocontrol (96% *ee*). Rearrangement of **5** to the β-silyloxyaldehyde **6** proceeded with good diastereose-



Scheme 3. Preparation of hydroxy ketone **10**. Reagents and conditions: a) ethyl propionate, NaH, EtOH (64%, $E/Z >$ 50:1); b) $LiAlH_4$, then (+)-DIPT, $Ti(OiPr)_4$, *t*BuOOH (96% *ee*); c) TMSOTf, iPr_2NEt (24:1 d.r.); d) acetone, LDA (40% from **4**, >10:1 d.r.); e) MOMCl, iPr_2NEt (73%); f) Bu_2BOTf, iPr_2NEt, then **9** (85%, *anti*/*syn* 4:1). TMS = trimethylsilyl, Tf = triflate = trifluoromethanesulfonyl, MOM = methoxymethyl; LDA = lithium diisopropylamide, DIPT = diisopropyl tartrate.

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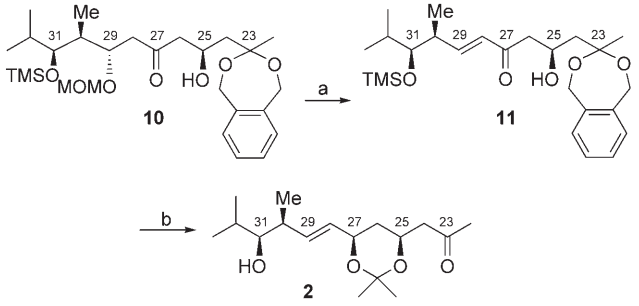
lectivity (24:1) on treatment with TMSOTf and *N*,*N*-diisopropylethylamine by using a procedure described by Jung and D'Amico for related systems.[14] Addition of the lithium enolate of acetone to **6** at −100 °C afforded the aldol adduct **7** with good selectivity and yield over the four-step sequence (40 % from **4**, >10:1 d.r.). Protection of the C29 hydroxy group as a MOM ether provided ketone **8** in 73 % yield. This compound was then subjected to the methyl ketone aldol reaction with 1,5-*anti* induction to set the stereochemistry at C25. By using the protocol described by Evans et al. (Bu_2BOTf, iPr_2NEt)[10b] with aldehyde **9**, compound **10** was produced in high yield with useful levels of diastereoselectivity (85 %, *anti*/*syn* 4:1).[15]

With compound **10** in hand, we now required a chemoselective elimination of the OMOM group at C29 in preference to the OH group at C25. We initially attempted this transformation using two equivalents of LDA at −78 °C; however, these conditions provided mixtures of the desired elimination product **11** and recovered **10**. After much experimentation, we were able to accomplish this transformation using K_2CO_3 (0.2 equiv) in 95 % ethanol at 0 °C in good yield and with excellent *E* selectivity (81 %, *E*/*Z* >50:1, Scheme 4). Conversion of **11** into **2** was then accomplished by

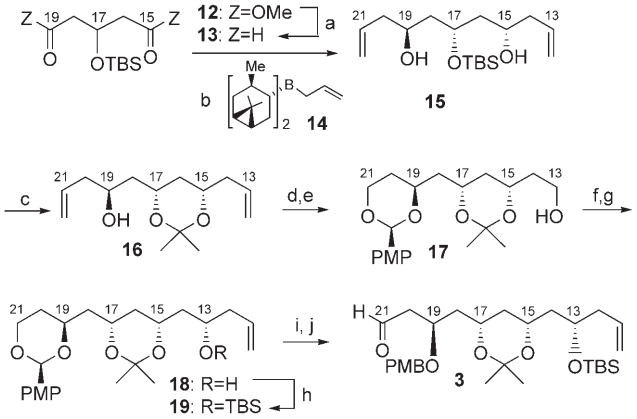


Scheme 4. Preparation of methyl ketone **2**. Reagents and conditions: a) K_2CO_3 (0.2 equiv), EtOH/H_2O 95:5 (81 %, *E*/*Z* >50:1); b) 1. Et_2BOMe, $NaBH_4$; 2. $FeCl_3$, acetone, Desispheres (68 %, 2 steps).

reduction by using a procedure reported by Prasad and coworkers[16] followed by treatment with $FeCl_3$[17] in dry acetone containing the alumina-based desiccant desispheres. This transformation removes the protecting groups at C23 and C31 and installs an acetonide between C25 and C27. This sequence provides compound **2** with remote asymmetric induction across the alkene in ten steps and proceeds in about 10 % overall yield from commercially available starting materials.

We designed the synthesis of compound **3** to take advantage of the symmetry within the molecule and employed a two-directional allylation approach.[18] We chose C17 as the central carbon atom because the hydroxy group at this site is *syn* to the hydroxy group at C15, and *anti* to that at C19. As such, this stereochemical triad could be synthesized from a 3-alkoxy glutaraldehyde derivative through a double asymmetric allylation with reagent control and subsequent terminus differentiation.

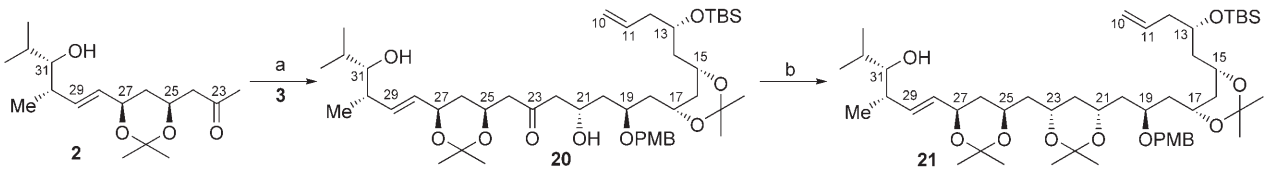
Our synthesis of **3** began with the reduction of glutarate ester **12** to the corresponding glutaraldehyde derivative **13**[19] (Scheme 5). Bisallylation of this species using the (+)-3-carene-derived allylboration reagent **14** reported by Brown



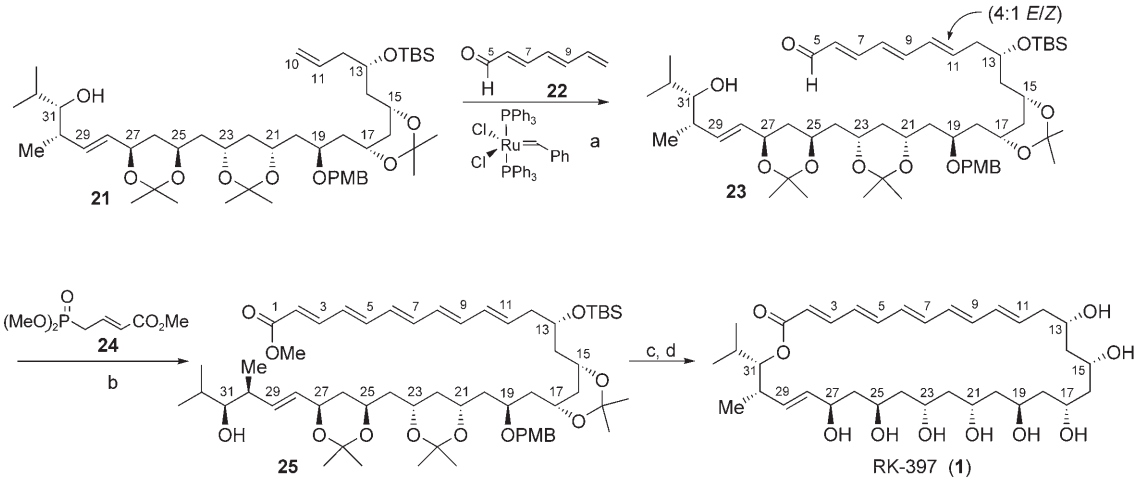
Scheme 5. Preparation of aldehyde **3**. Reagents and conditions: a) DIBAL-H, then 125 °C at 2 mmHg; b) **14**, then H_2O_2/NaOH (53 % over two steps, >98 % *ee*, 10:1 d.r.); c) 1. amberlyst-15, MeOH; 2. acetone, $CuSO_4$, PPTS (cat.); d) ozone, then $NaBH_4$; e) *p*-anisaldehyde dimethyl acetal, PPTS (cat.) (73 % over 4 steps); f) oxalyl chloride, DMSO, Et_3N (94 %); g) **14**, then H_2O_2/NaOH (87 %, >30:1 d.r.); h) TBSCl, imidazole (98 %); i) DIBAL-H (81 %); j) oxalyl chloride, DMSO, Et_3N (85 %). PMP = *p*-methoxyphenyl; PPTS = pyridinium *p*-toluene sulfonate; DIBAL-H = diisobutylaluminum hydride.

and co-workers[20] provided diol **15** in good yield and high selectivity (53 % from **12**, >98 % *ee*, 10:1 d.r.). Differentiation of the diastereotopic termini of this substrate began with removal of the TBS group at C17 by using amberlyst-15. Subsequent formation of the thermodynamically more favored *syn* acetonide between the C15 and C17 hydroxy groups (as compared to the *anti* acetonide which would be formed between the C17 and C19 hydroxy groups) with acetone and a catalytic amount of PPTS provided compound **16** (*syn* acetonide/*anti* acetonide >20:1). While this sequence provides internal differentiation, it does not discriminate between the two terminal alkenes. This was accomplished through ozonolytic cleavage of the alkene with a reductive ($NaBH_4$) workup to provide the corresponding triol. Subsequent treatment of this triol with catalytic PPTS and *p*-anisaldehyde dimethyl acetal provided **17** in 73 % yield over the four-step sequence. The use of mild conditions and a reactive acetal precursor avoids acetonide migration in this reaction. Compound **17** was then subjected to Swern oxidation and a second asymmetric allylation, again with the (+)-3-carene-derived reagent, to provide **18** (>30:1 d.r.). The hydroxy group of **18** was next protected as the TBS ether to provide **19** (80 % from **17**). Reduction of the *p*-methoxybenzylidene acetal group of **19** using DIBAL-H (0 °C to RT) provided the hydroxy group at C21, which was oxidized to provide **3** in 11 steps and 21 % overall yield for the sequence.

Having assembled methyl ketone **2** and aldehyde **3**, these fragments were coupled by using the Paterson variant of the 1,5-*anti* aldol procedure to provide **20** in good yield and selectivity (83 %, >10:1 d.r., Scheme 6).[21] The hydroxy



Scheme 6. Preparation of protected polyol chain **21**. Reagents and conditions: a) Cy_2BCl, Et_3N, then **3** (83%, *anti/syn* > 10:1); b) 1. Et_2BOMe, $NaBH_4$; 2. 2-methoxypropene, PPTS (cat.) (84% over 2 steps, *syn/anti* > 10:1). Cy = cyclohexyl.



Scheme 7. Synthesis of RK-397. Reagents and conditions: a) CH_2Cl_2 reflux (72%, *E*/*Z* 4:1); b) **24**, LDA, then **23** (82%); c) 1. LiOH, THF/H_2O/MeOH (quant.); 2. 2,4,6-trichlorobenzoyl chloride, Et_3N; 3. DMAP, toluene; d) HCl (12 M, 100 equiv)/MeOH (70% from **25**). DMAP = *N*,*N*-dimethylaminopyridine.

group at C31 did not prove problematic in the reaction using 2.4 and 3 equivalents of Cy_2BCl and NEt_3, respectively. Prasad reduction of **20** and protection of the resulting diol as the acetonide provided the fully functionalized and appropriately protected C10–C33 polyol domain of RK-397 (**21**, 84% from **20**, > 10:1 d.r.). This synthesis proceeds with a longest linear sequence of 14 steps and has allowed us to prepare multigram quantities of the protected polyol chain.

The terminal alkene of **21** can serve as a handle for the installation of the polyene through an olefin cross-metathesis reaction, and after much experimentation we found that treatment of **21** and 2,4,6-hexatrienal (**22**) with Grubbs first generation catalyst[22] in refluxing dichloromethane provided compound **23** in 72% yield as a 4:1 mixture of isomers at the C10–C11 alkene (Scheme 7). Conversion of this material into RK-397 was accomplished by a Horner–Wadsworth–Emmons reaction with **24**[23] (82% yield), followed by saponification and Yamaguchi macrolactonization,[24] and subsequent global deprotection with concentrated HCl in methanol (70% over four steps).[8,25] While milder acidic conditions such as Dowex 50W-X8 resin were capable of removing all the protecting groups on model systems, the PMB ether at C19 resisted cleavage under these conditions on the real system.

In summary, this route takes advantage of a streamlined strategy for the synthesis of the polyol segment which features a two-directional approach to the right half and a remote asymmetric induction approach to the left. The polyene was appended to the polyol by using a novel cross-metathesis reaction as another convergent step in the synthesis. The final steps, including the macrocyclization and deprotection, proceeded in high yield and provided RK-397 with a longest linear sequence of 20 steps.

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[1] K. Kobinata, H. Koshino, T. Kudo, K. Isono, H. Osada, *J. Antibiot.* **1993**, *46*, 1616–1618.
[2] For a review, see: S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021–2040.
[3] H. Koshino, K. Kobinata, K. Isono, H. Osada, *J. Antibiot.* **1993**, *46*, 1619–1621.
[4] S. L. Schreiber, M. T. Goulet, *J. Am. Chem. Soc.* **1987**, *109*, 8120–8122.
[5] T. Suenaga, H. Nakamura, H. Koshino, K. Kobinata, H. Osada, T. Nakata, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1997**, *39*, 607–612.
[6] For partial syntheses of RK-397, see: a) S. A. Burova, F. E. McDonald, *J. Am. Chem. Soc.* **2002**, *124*, 8188–8189; b) C. Schneider, F. Tolksdorf, M. Rehfeuter, *Synlett* **2002**, 2098–2100; c) S. Gerber-Lemaire, A. T. Carmona, K. T. Meilert, P. Vogel, *Eur. J. Org. Chem.* **2006**, 891–900.
[7] S. A. Burova, F. E. McDonald, *J. Am. Chem. Soc.* **2004**, *126*, 2495–2500.

[8] S. E. Denmark, S. Fujimori, *J. Am. Chem. Soc.* **2005**, *127*, 8971 – 8973.
[9] For related macrolactonization approaches to oxopolyene macrolides, see: a) Y. Mori, M. Asai, J-i. Kawade, A. Okumura, H. Furukawa, *Tetrahedron Lett.* **1994**, *35*, 6503 – 6506; b) D. A. Evans, B. T. Connell, *J. Am. Chem. Soc.* **2003**, *125*, 10899 – 10905; c) C. S. Poss, S. D. Rychnovsky, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 3360 – 3361; and also see Ref. [8].
[10] a) I. Paterson, K. R. Gibson, R. M. Oballa, *Tetrahedron Lett.* **1996**, *37*, 8585 – 8588; b) D. A. Evans, P. J. Coleman, B. Côté, *J. Org. Chem.* **1997**, *62*, 788 – 789; for syntheses utilizing these methods, see: c) Ref. [9b]; d) Ref. [8]; e) Ref. [6b]; f) I. Paterson, L. A. Collett, *Tetrahedron Lett.* **2001**, *42*, 1187 – 1191.
[11] C. S. Marvel, W. B. King, *Organic Syntheses Collective*, *Vol. 1* (Ed.: H. Gilman), Wiley, New York, **1941**, p. 252.
[12] V. J. Lee, A. R. Branfman, T. R. Herrin, K. L. Rinehart, *J. Am. Chem. Soc.* **1978**, *100*, 4225 – 4236.
[13] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974 – 5976; b) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765 – 5780; c) R. Göttlich, U. Schopfer, M. Stahl, R. W. Hoffmann, *Liebigs Ann.* **1997**, 1757 – 1764; d) S. H. Kang, H.-S. Jun, J.-H. Youn, *Synlett* **1998**, 1045 – 1046.
[14] M. E. Jung, D. C. D'Amico, *J. Am. Chem. Soc.* **1993**, *115*, 12208 – 12209.
[15] Despite extensive experimentation, which included variations of protecting groups at C29 and C31, we saw no significant increase in selectivity. Moreover, the use of the conditions reported by Paterson et al. (Cy_2BCl, Et_3N, see Ref. [10a]) on similar substrates provided lower selectivity (< 2:1).
[16] K. M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155 – 158. Reduction of hydroxyenone **11** using conditions reported in the reference above (Et_2BOMe, $NaBH_4$) gave the 1,3-*syn* diol as a single diastereomer on a small scale. On larger scales, this transformation was accompanied by partial cleavage of the C23 and C31 protecting groups during workup. Fortunately, both of these groups must be removed in the next step to give our desired C22–C33 ketone intermediate **2**. In practice, treatment of the mixture of partially deprotected compounds with $FeCl_3$ in dry acetone containing desispheres resulted in complete desilylation, benzodioxepine removal, and acetonide installation to afford **2** in good yield (68%, 2 steps).
[17] a) S. E. Sen, S. L. Roach, J. K. Boggs, G. J. Ewing, J. Magrath, *J. Org. Chem.* **1997**, *62*, 6684 – 6686; b) P. P. Singh, M. M. Gharia, F. Dasgupta, H. C. Srivastava, *Tetrahedron Lett.* **1977**, 439 – 440.
[18] a) C. S. Poss, S. L. Schreiber, *Acc. Chem. Res.* **1994**, *27*, 9 – 17; b) S. R. Magnuson, *Tetrahedron* **1995**, *51*, 2167 – 2213; c) R. W. Hoffmann, *Angew. Chem.* **2003**, *115*, 1128 – 1142; *Angew. Chem. Int. Ed.* **2003**, *42*, 1096 – 1109.
[19] Compound **13** is prone to hydration and polymerization. We have found this polymerization to be reversible and that the bisaldehyde can be obtained by dehydration (see the Supporting Information for details). For a similar observation and transformation, reported while this work was in progress, see: J. N. Shepherd, D. C. Myles, *Org. Lett.* **2003**, *5*, 1027 – 1030. For a related reaction, see: Z. Wang, D. Deschênes, *J. Am. Chem. Soc.* **1992**, *114*, 1090 – 1091.
[20] P. K. Jadhav, K. S. Bhat, T. Perumal, H. C. Brown, *J. Org. Chem.* **1986**, *51*, 432 – 439. For other reagent-controlled asymmetric allylations and crotylations, see: C. H. Burgos, E. Canales, K. Matos, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 8044 – 8049, and references therein.
[21] See Ref. [10a]. In this case, the Paterson conditions proved superior to the Evans conditions because of a greater preference for enolization at C22.
[22] a) *Handbook of Metathesis* (Ed.: R. H. Grubbs) Wiley-VCH, Weinheim, **2003**; b) T. W. Funk, J. Efskind, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 187.
[23] M. Kinoshita, H. Takami, M. Taniguchi, T. Tamai, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2151 – 2162.
[24] J. H. K. Inanaga, H. Saeki, T. Katsuki, M. Yamaguchi *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993.
[25] This material was purified by reverse-phase HPLC to provide a sample for characterization (see the Supporting Information for details).

