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An asymmetric synthesis of the polyol fragment of the polyene macrolide antibiotic RK-397

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ABSTRACT

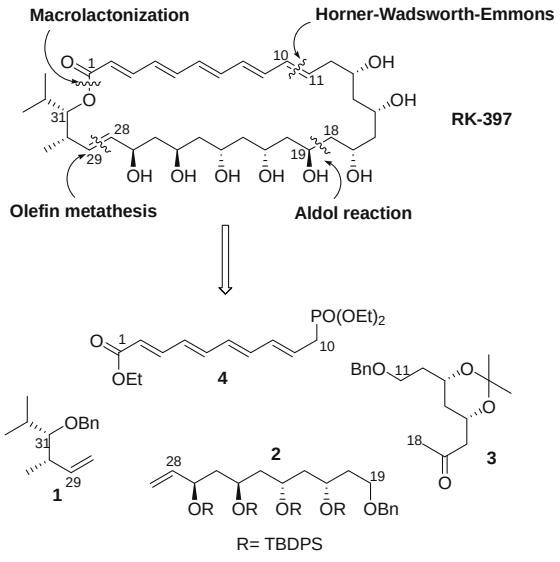
A highly convergent and asymmetric synthesis of the C11–C31 polyol fragment of RK-397 as a single isomer is accomplished via a catalytic enantioselective hetero-Diels–Alder reaction and an intermolecular olefin cross-metathesis as key steps.

The antibiotic RK-397, which is a member of a large family of polyene macrolides,[1] was isolated from a strain of soil bacteria *Streptomyces* sp. *87-397*, from a soil sample collected in Saku city, Nagano prefecture of Japan. RK-397 exhibits antifungal and antibacterial activities as well as promising anticancer activity. It was isolated and structurally characterized by Osada et al.[2] Due to its potent biological activity and structural complexity, several syntheses of this natural product have been reported.[3]

The main focus of the synthesis of RK-397 is on the absolute stereocontrol of the ten stereogenic centres in the polyol chain. We envisioned that the challenge could be resolved by synthetic methodologies developed in our laboratory on catalytic enantioselective allylation.[4] Moreover, an asymmetric hetero-Diels–Alder protocol using Jacobsen's catalyst and an intermolecular olefin cross metathesis strategy were employed for the asymmetric synthesis of the polyol fragment. Herein, we report an efficient, enantioselective synthesis of the C11–C31 polyol fragment of RK-397 utilizing these developed methods as key strategic steps.

Our retrosynthetic approach divides the natural product into four modules (Scheme 1). Disconnections at the lactone linkage and the C10–C11 double bond afforded the polyene phosphonate fragment **4**. Subsequent disconnections at the C18–C19 and C28–C29 bonds afforded fragments **1**, **2** and **3**. In the forward synthesis, a cross olefin metathesis step followed by a 1,5-*anti* aldol addition would connect fragments **1**, **2** and **3** together for the construction of the C11–C31 polyol chain.

This synthetic plan commenced with the preparation of homoallylic alcohol **1** synthesized from isobutyraldehyde using (+)-*B*-methoxy-diisopinocampheylborane and *cis*-but-2-ene. Asymmetric Brown crotylation[5] afforded the *syn*-γ-allylic alcohol **5** in 76% yield and 92% ee, which was further protected as the benzyl ether to give **1** in 90% yield (Scheme 2).



Scheme 1. Retrosynthetic analysis of RK-397.

The preparation of key building block **2** began with mono-benzyl ether protection of 1,3-propanediol followed by 2-iodoxybenzoic acid (IBX) oxidation[6] to afford 3-(benzyloxy)propanal **6** in an excellent yield of 95% (Scheme 3).

The introduction of the first stereogenic centre was attempted using the chiral (*R*)-BINOL–$InCl_3$ complex and the chiral (*R,R*)-PYBOX–$In(OTf)_3$ complex developed in our laboratory[4] for the asymmetric allylation of 3-(benzyloxy)propanal **6**. The yields and enantioselectivities of the allylation product **7** obtained were 64% and 88% ee and 70% and 80% ee for the (*R*)-BINOL–$InCl_3$ and (*R,R*)-PYBOX–$In(OTf)_3$ complexes, respectively. Unfortunately, when we attempted the asymmetric allylation on a larger scale (10 mmol), the yield remained high, however, the enantioselectivity was reduced to 51% ee with the (*R*)-BINOL–$InCl_3$ complex. A

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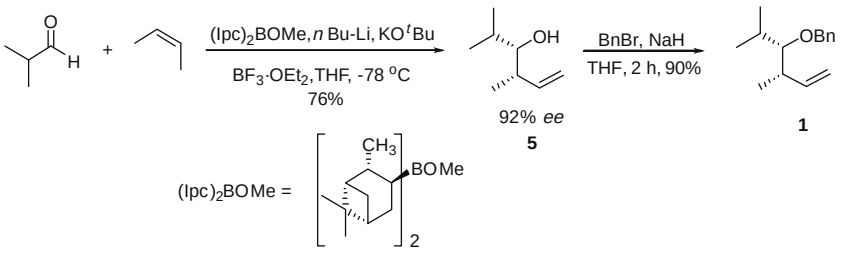
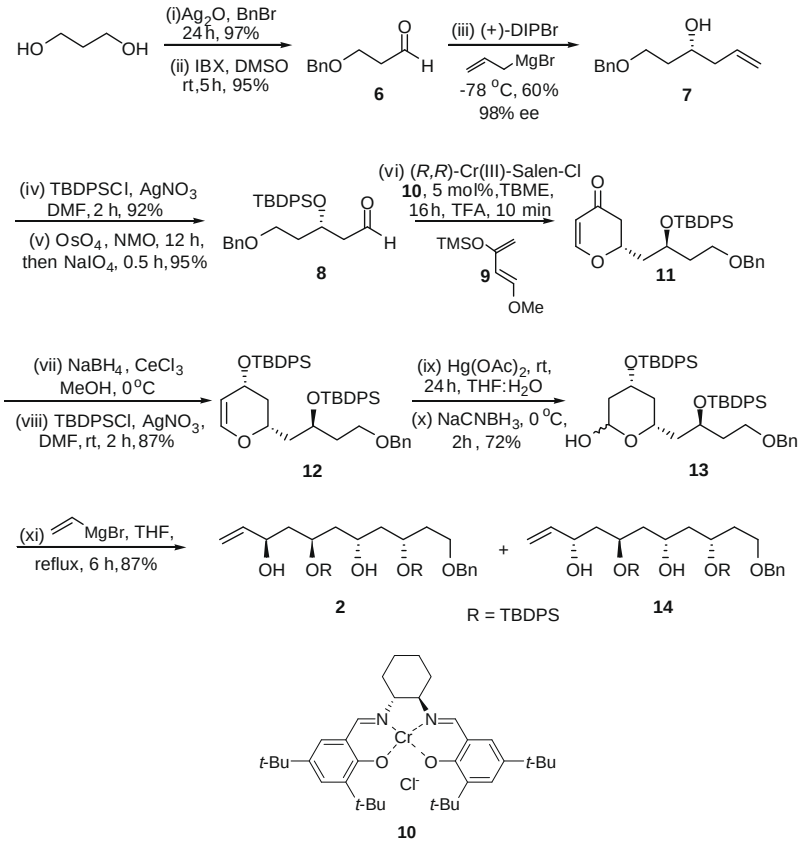


Scheme 2. Synthesis of fragment **1**.



Scheme 3. Synthesis of fragment **2**.

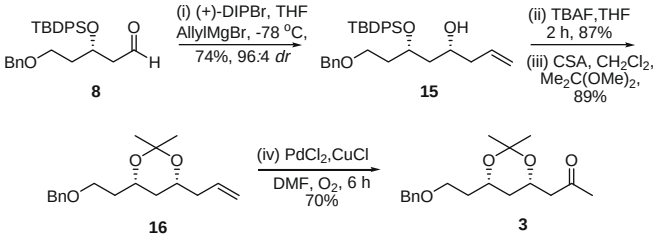
similar result was obtained with the (*R,R*)-PYBOX–In(OTf)$_3$ complex (46% ee). Eventually, we found Brown's allylation,[7] employing (+)-DIPBr to be the most desirable protocol, which yielded 60% of the homoallylic alcohol **7** with 98% ee. Moreover, the reaction could be carried out on a large scale (20 mmol).

Protection of homoallylic alcohol **7** proceeded smoothly with $AgNO_3$ and TBDPSCl, followed by one-pot osmium tetraoxide-catalyzed dihydroxylation and oxidative cleavage with sodium periodate to afford aldehyde **8** in 95% yield.

With the desired aldehyde **8** in hand, the second chiral alcohol was introduced via an asymmetric hetero-Diels–Alder reaction between Danishefsky's diene **9** and aldehyde **8** catalyzed by Jacobsen's (*R,R*)-(Salen)–Cr(III)–Cl complex[8] **10** to afford the 2, 3-dihydropyran-4-one **11** in 89% yield and an excellent diastereomeric ratio of 97:3 as determined by HPLC analysis.

Luche reduction[9] with $CeCl_3$ is known to be efficient for the regioselective 1,2-instead of 1,4-reduction of α-enones with $NaBH_4$ in methanol. As excellent stereo-control was achieved in the hetero-Diels–Alder step, the *syn* isomer was obtained exclusively in the reduction step. The reaction mixture was quenched and the crude alcohol was immediately subjected to protection with TBDPSCl to afford dihydropyran **12** in 87% yield. Oxymercuration of the functionalized dihydropyran **12** in THF:H_2O (1:1) with mercury(II) acetate proceeded smoothly and the intermediate was subsequently demercurated with sodium cyanoborohydride via a radical process to afford the corresponding lactol **13** in 72% yield. Immediate reaction with the vinyl Grignard reagent afforded the corresponding allylic alcohol in 87% yield[10] as a 1:1 mixture of the desired fragment **2** and the undesired isomer **14**. The two isomers were separated via flash chromatography and the undesired isomer **14** could be converted to the desired isomer **2** via allylic oxidation with MnO_2 into the α,β-unsaturated ketone and subsequent regioselective 1,2-Luche reduction back to the alcohol **2**.[11]

Similarly, an excellent diastereomeric ratio of 96:4 was achieved when aldehyde **8** was subjected to Brown's allylation with (+)-DIPBr-allyl magnesium bromide. The homoallylic alcohol **15** was subjected to TBAF for removal of the TBDPS-protecting group. The resulting 1,3-diol was subsequently protected as



Scheme 4. Synthesis of fragment **3**.

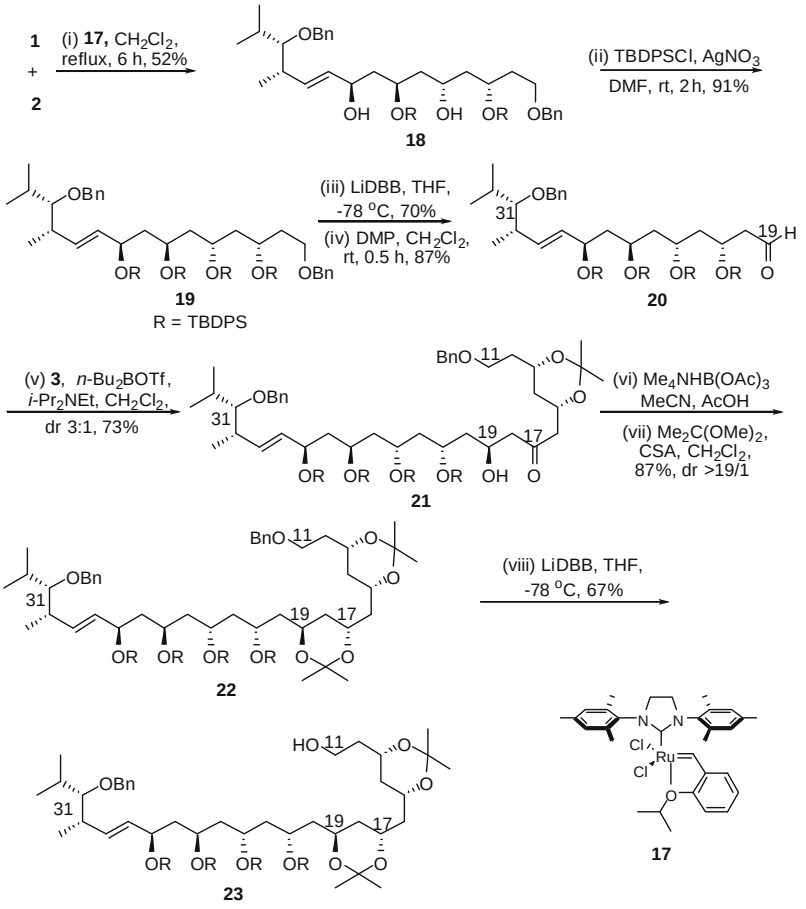
acetonide **16** in 89% yield. Wacker oxidation[12] of **16** gave the desired fragment **3** in 70% yield as a single diastereoisomer (Scheme 4).

With the three individual fragments **1**, **2** and **3** in hand, we next coupled the modules together (Scheme 5).

The first step involved coupling of fragment **1** (2 equiv) with **2** (1 equiv) via an intermolecular cross-metathesis with the Hoveyda–Grubbs 2nd generation catalyst **17**[13] which afforded **18** in 52% yield (*trans:cis* 9:1). The catalyst was dissolved in dichloromethane and added dropwise to the refluxing reaction mixture over 30 min. Prior to the succeeding aldol coupling, it was necessary to selectively deprotect the primary *O*-benzyl ether at C19 instead of the secondary benzyl ether at C31, to enable Dess–Martin oxidation to the aldehyde at C19. The cross metathesis product **18** was therefore subjected to alcohol protection with *tert*-butyldiphenylsilyl chloride followed by careful treatment with lithium 4,4′-di(*t*-butyl)biphenyl[14] and subsequent Dess–Martin oxidation to afford the desired aldehyde **20** in an excellent yield of 87%.

The aldol product **21** from aldehyde **20** and ketone **3** was obtained in 73% yield with moderate selectivity of 3:1 (dr) for 1,5-anti-stereoinduction.[15] The *S* configuration at C19 was established by comparing the results of other chiral boron enolates where the aldol product from (−)-DIPBr[16] corresponded to the major diastereomer **21** obtained from the reaction with *n*-Bu_2BOTf. Stereochemical outcomes of similar systems have also been confirmed by Evans et al.[17] The carbonyl group at C17 was reduced with tetramethylammonium triacetoxyborohydride, and the resulting *anti*-diol was protected as acetonide[18] **22** in 87% yield (dr >19/1). Selective deprotection of the primary benzyl ether at C11 with LiDBB[19] afforded the target C11–C31 polyol fragment of RK-397 **23** in 67% yield.

In conclusion, the C11–C31 polyol fragment of RK-397 was synthesized via a convergent synthetic strategy that features Brown's asymmetric allylation and crotylation, a catalytic enantioselective hetero-Diels–Alder protocol employing Jacobsen's (*R,R*)-Cr(III)–Salen complex, and a 1,5-*anti*-stereo-induction by substrate-controlled dibutylboron enolate aldol addition for absolute control of the ten stereogenic centres in the polyol chain. The synthetic strategy described herein allows the stereoselective construction of practically every other stereoisomer by employment of either enantiomeric form of chiral reagent and catalyst. The synthesis also demonstrated a successful intermolecular cross-metathesis between two elaborate molecular fragments. As excellent enantio- and diastereocontrol was achieved during the synthesis, including isolation of the desired diastereoisomer via column chromatography, a single diastereoisomer of the target polyol chain **23** was prepared.



Scheme 5. Synthesis of polyol fragment C11–C31 of RK-397.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.019.

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10. 87% yield refers to the combined yield of a 1:1 mixture of **2** and **14**.
11. The Luche reduction affords a 1:1 mixture of **2** and **14**. Attempts to improve the stereoselectivity via substrate-controlled reduction with $LiAlH_4$ and DIBAL were made, however, no selectivity was obtained (1:1 mixture).
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19. A single isomer was detected after purification via column chromatography.