Asymmetric Synthesis of the Polyol Portion of the Polyene Macrolide Antibiotic RK-397

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Abstract: A highly convergent and asymmetric synthesis of a fully functionalized polyol portion of the new polyene macrolide antibiotic RK-397 has been achieved taking advantage of a novel polyol synthesis.

Key words: RK-397, polyene macrolide antibiotics, total synthesis, aldol reaction, Cope rearrangement

The polyene macrolide antibiotic RK-397 (**1**) was isolated in 1993 from a streptomyces strain collected from a soil sample in Japan and was shown to display antitumor, antibacterial, and antifungal activity in preliminary screening studies (Figure 1).[1] The constitution of **1** was assigned based upon extensive spectroscopic measurements and was found to be identical to 14-demethyl mycoticin A.[2] The relative and absolute configuration of **1** was only recently established through degradation of the natural product to furnish smaller subunits, which were analyzed by special NMR methods and CD spectroscopy suggesting that the stereogenic centers at C(19) and C(21) have the opposite configuration compared to mycoticin A.[3]

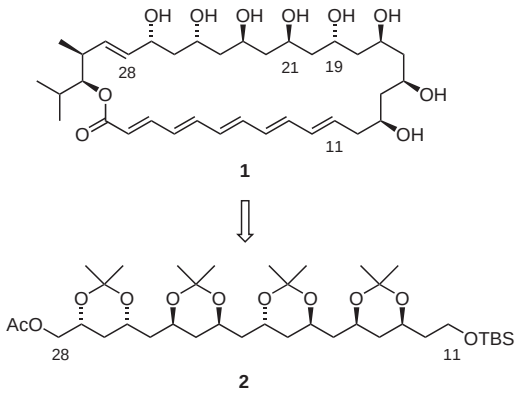
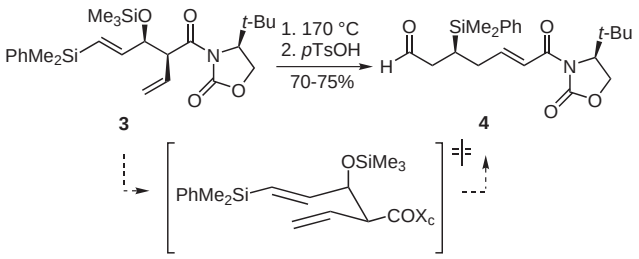


Figure 1

Some of the polyene macrolide antibiotics known to date such as amphotericin B are used clinically for the treatment of life-threatening fungal infections.[4] However, serious side effects on various organs continue to hamper the application of these drugs. On the search for better antifungal agents a great deal of effort has been undertaken to develop efficient and stereoselective syntheses of the polyol fragments of the natural products in particular.[5]

We report here a convergent asymmetric synthesis of a fully functionalized polyol fragment **2** of RK-397 (**1**), which may be used in a total synthesis of the natural product and is also amenable to the synthesis of other stereoisomers. In order to make the synthesis as convergent as possible the polyol fragment **2** was assembled from two triol building blocks of similar complexity (**7** and **8**), which in turn were derived from the same chiral key compound.

Our point of departure was the chiral 7-oxo-5-phenyldimethylsilyl-2-enimide **4** which was easily obtained in good yield and enantiopure state on a multigram-scale using the silyloxy-Cope rearrangement of aldol product **3** (Scheme 1).[6] This multifunctional compound does not contain any hydroxyl group yet but carries suitable functional groups in the required 1,3,5-orientation, which were to be traded for secondary hydroxy groups in a straightforward manner. Furthermore, two of these Cope products were intended to be used for the synthesis of the advanced intermediates **7** and **8**.



Scheme 1

We have previously shown that the Cope product **4** may be readily and stereoselectively converted to protected triols of any configuration.[7] Reagent-controlled allylboration of the aldehyde moiety in **4** with subsequent benzylation installed the first oxy substituent with either configuration depending on the borane reagent used (e.g. **7** vs **8**). Then auxiliary-directed conjugate addition of a phenyldimethylsilyl cuprate reagent to the enimide moiety and oxidative cleavage of the two carbon-silicon bonds introduced the second and third hydroxy groups with retention of configuration. These were protected as a 1,3-diol acetonide giving rise to the diastereomeric triol esters **5** and **6**, respectively (Scheme 2).

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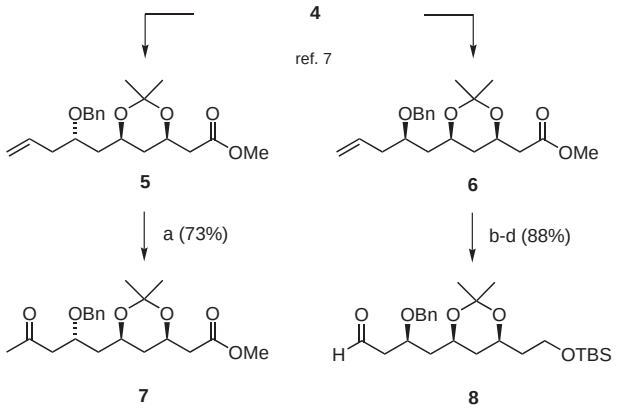
For the coupling of the two subunits **5** and **6** we took advantage of their terminal double bond. Thus, a Wacker oxidation furnished the methyl ketone **7** from **5** in good yield with only traces of the aldehyde being formed. Secondly, compound **6** was converted to the corresponding silyl ether through a reduction-silylation sequence upon which the terminal double bond was easily oxidized to aldehyde **8**.

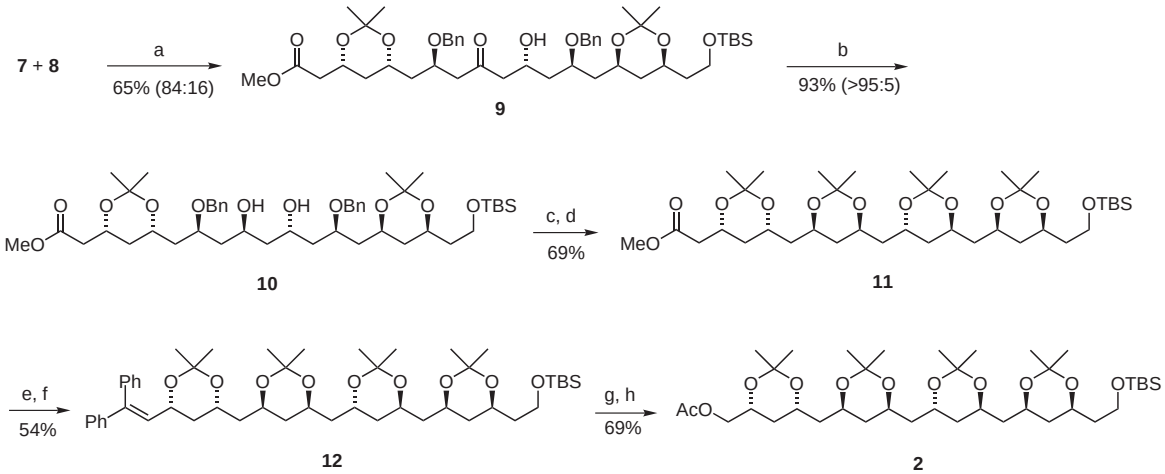


Scheme 2 a) $PdCl_2$ (cat.), $CuCl_2 \cdot 2H_2O$, DMF/H_2O, 70 °C; b) $LiAlH_4$, THF, –78 °C; c) TBSCl, imidazol, DMF, 0 °C; d) *N*-methylmorpholine-*N*-oxide, OsO_4 (cat.), acetone/H_2O, r.t., then $NaIO_4$, r.t.

With the two coupling partners in hand we next focused on combining them. Studies by the groups of Paterson[8] and Evans[9] have revealed that methyl ketone-aldehyde aldol additions may be stereoselectively executed with boron enolates and the proper protecting group on the β-oxy substituent in the enolate component. This resulted in typically good levels of 1,5-*anti*-stereoselectivity with the β-oxy-substitutent exerting the dominant stereocontrolling effect. Accordingly, aldol reaction of the dibutylboron enolate of **7** with the aldehyde **8** furnished the aldol product **9** in 65% yield and with 84:16 diastereoselectivity (Scheme 3).[10] Substantial amounts of the aldehyde and ketone components were, however, recovered and could be used for the aldol reaction again. Attempts to increase the diastereoselectivity of the aldol reaction by modifying the boron substitutents were met with limited success. In particular, the use of the (+)- and (–)-diisopinocampheyl boron enolates of **7** gave rise to **9** with 80:20 and 60:40 diastereoselectivity, respectively.[8] Also, performing the aldol condensation under Mukaiyama conditions, e.g. BF_3-catalysed addition of the trimethylsilyl enolate of **7** to aldehyde **8**, did not increase the diastereoselectivity.[11]

Aldol product **9** was reduced to *anti*-diol **10** with $(Me_4N)BH(OAc)_3$ in good yield and selectivity (Scheme 3).[12] At this stage a reliable proof of configuration was possible using Rychnovsky's ^{13}C NMR method.[13,14] The two benzyl protecting groups were subsequently taken off through hydrogenolysis and the resulting tetraol was protected as the tetraacetonide **11**. This compound already comprised the complete polyol fragment of RK-397 but had one carbon atom too many at the left side. Therefore, a Barbier–Wieland degradation[15] was chosen to complete the synthesis of **2**. Phenyl lithium addition to ester **11** and Burgess elimination[16] yielded the 1,1-diphenylalkene **12** which was subjected to ozonolysis to furnish the fully protected and functionalized polyol portion of RK-397. For the purpose of safe storage the intermediate aldehyde was converted to acetate **2** through a reduction-acetylation sequence.[17]

In conclusion, we have synthesized the complete polyol fragment of the new polyene macrolide antibiotic RK-397 in a highly convergent manner. The underlying synthetic strategy also permits the stereoselective preparation of virtually every other stereosisomer. The functional groups at the termini of the polyol chain should allow for efficient coupling to the polyene and aldol fragments.



Scheme 3 a) Bu_2BOTf, Et_3N, CH_2Cl_2, –100 °C; b) $(Me_4N)BH(OAc)_3$, CH_3CN, CH_3COOH, –20 °C; c) Pd/C, NH_4HCO_2, MeOH, 64 °C; d) 2-methoxypropene, PPTS (cat.), CH_2Cl_2, r.t.; e) PhLi, THF, 0 °C; f) $MeO_2CNSO_2NEt_3$, toluene, 55 °C; g) ozone, MeOH/CH_2Cl_2, –78 °C, then $NaBH_4$; h) Ac_2O, pyridine, CH_2Cl_2, 0 °C.

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(10) **Experimental Procedure:** An amount of 149 mg (0.39 mmol) of methyl ketone **7** was dissolved in 4 mL diethyl ether and cooled to –78 °C. For enolization 0.59 mL (0.59 mmol) of a 1 M solution of dibutylboron triflate in dichloromethane were added and subsequently 92 μL (0.66 mmol) triethyl-amine and the resulting solution was stirred for 30 min at –78 °C and for 30 min at 0 °C. Then the solution was cooled to –100 °C and 122 mg (0.27 mmmol) of aldehyde **8**, dissolved in 1 mL diethyl ether, were added with a syringe. Stirring was continued for 3 h at –100 °C and 3 h at –78 °C after which the reaction was quenched with pH 7 buffer. After separation of the phases the aq phase was repeatedly extracted with diethyl ether, the combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the crude mixture through flash chromatography with diethyl ether/pentane (1:2) as eluent yielded 145 mg (65%) of the desired aldol product **9** as a colourless oil (84:16 mixture of stereoisomers) along with 34 mg (27%) of unreacted aldehyde **8** and 44 mg (30%) of methyl ketone **7** both of which were used again in the aldol reaction. $[\alpha]_D^{20}$ +19.7 (*c* 0.58, $CHCl_3$); IR(film): ν = 3471 (OH), 2992, 2949, 2857 (CH), 1741 (C=O), 1712 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, *t*-Bu), 1.07–1.33 (m, 2 H), 1.36, 1.40, 1.41 [3 s, 12 H, 2 × $C(CH_3)_2$], 1.50–1.97 (m, 10 H), 2.37 (dd, *J* = 15.5, 6.0 Hz, 1 H, 2-H), 2.43–2.65 (m, 4 H) 2.73 (dd, *J* = 15.5, 7.0 Hz, 1 H, 2-H), 3.68 (s, 3 H, OMe), 3.65–4.29 (m, 9 H), 4.45, 4.48, 4.55, 4.56 (4 × d, *J* = 11.5 Hz, 4 H, 2 × OBn), 7.25–7.36 (m, 10 H, 2 × Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.35, 18.30, 19.81, 19.84, 25.94, 30.11, 30.26, 36.86, 37.41, 39.45, 40.20, 40.47, 41.18, 42.39, 49.29, 50.81, 51.60, 58.77, 65.28, 65.48, 65.76, 65.87, 66.49, 70.36, 72.44, 71.93, 74.63, 98.36, 98.81, 127.70, 127.80, 128.00, 128.10, 128.40, 138.10, 138.30, 171.30, 209.40; MS (200 eV, DCI/NH_3): *m*/*z* (%) = 847(100) [M + NH_4^+]; calcd for $C_{46}H_{72}O_{11}Si$ (829.15): C, 66.63; H, 8.75. Found: C, 66.82; H, 8.50.
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(14) (a) Direct acetonide formation on diol **10** furnished a triacetonide with two *syn*- and one *anti*-stereochemical relationships. When the reduction of aldol product **9** was performed in a *syn*-selective manner with $NaBH_4$ and Et_2BOMe according to Narasaka[14b] with subsequent debenzylation and tetraacetonide formation the major stereoisomer contained two *syn*- and two *anti*-stereochemical relationships in agreement with the assigned configurations. (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.
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(17) **Spectroscopic Data of 2:** $[\alpha]_D^{20}$ 0 (*c* 0.2, $CHCl_3$); IR(film): ν = 2990, 2938, 2857 (CH), 1745 (C=O) cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ = 0.06, 0.08 (2 × s, 6 H, $SiMe_2$), 0.98 (s, 9 H, *t*-Bu), 1.10–1.60 (m, 14 H), 1.32, 1.37, 1.47, 1.49, 1.50, 1.54, 1.55 [7 s, 24 H, 8 × $C(CH_3)_2$], 1.67 (s, 3 H, OAc), 1.73–1.82 (m, 1 H), 2.06 (quint, *J* = 7.0 Hz, 1 H), 3.68 (dt, *J* = 10.0, 5.0 Hz, 1 H, CH_2OTBS), 3.82 (ddd, *J* = 10.0, 8.5, 5.0 Hz, 1 H, CH_2OTBS), 3.83–3.89 (m, 1 H), 3.96–4.34 (m, 9 H); ^{13}C NMR (150 MHz, C_6D_6): δ = –5.38, 18.49, 19.82, 19.92, 19.97, 20.42, 24.86, 26.13, 30.39, 30.63, 30.67, 37.60, 37.80, 39.46, 40.16, 42.80, 43.08, 43.59, 59.20, 62.55, 62.69, 64.86, 65.34, 65.60, 65.71, 65.76, 67.38, 67.70, 98.54, 98.59, 98.80, 100.50, 170.10; MS (200 eV, EI): *m*/*z* (%) = 715(34) [$M^+ - CH_3$], 414(4), 380(5), 337(10), 256(18), 149(21), 57(100) [C_4H_9]; HRMS calcd for $C_{38}H_{70}O_{11}Si$: for [$M^+ - CH_3$] 715.4453. Found: 715.4531.