

Synthesis of (–)-Octalactin A by a Strategic Vanadium-Catalyzed Oxidative Kinetic Resolution**

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The kinetic resolution of racemic material is a well-established approach used to prepare a wide range of enantiomerically enriched compounds.^[1] However, the overall efficiency of a standard kinetic resolution is limited to a maximum theoretical yield of 50% of the enriched chiron, with the balance of undesired material being discarded in most applications.^[2] As a result of this inherent overall efficiency,^[3] kinetic resolution is often deemed unacceptable on a preparative scale except for the most simple and inexpensive of substrates. Consequently, kinetic resolution methods, especially in the context of complex molecule synthesis, have largely been relegated to the preparation of small chiral building blocks at an early stage of the synthesis.

Having recently developed a vanadium-catalyzed asymmetric aerobic oxidation of α hydroxycarbonyl compounds,^[4] we became interested in exploring the potential of this kinetic resolution methodology, to move beyond the preparation of simple building blocks toward a more meaningful, strategic synthetic function. The observation that asymmetric oxidation of substrates bearing multiple stereocenters by catalytic amounts of [VO(OiPr)₃] and (*S*)-2-(3,5-di-*tert*-butylsalicylideneamino)-*tert*-butyl-1-ethanol (**1**) resulted in the isolation of both enantioenriched alcohol and ketone products motivated us to consider a synthetic strategy (Figure 1) wherein

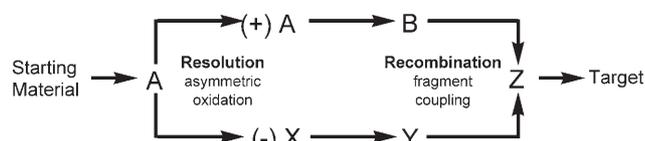
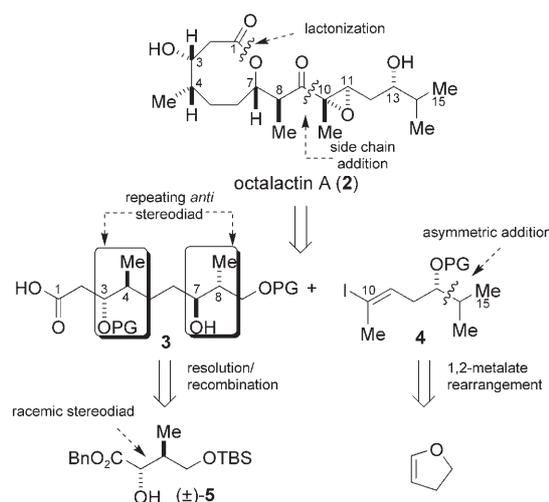


Figure 1. Resolution/recombination synthetic pathway.

both components of the resolution might be leveraged toward a single synthetic target. By doing so, the kinetic resolution serves as the key structural and stereochemical branching

point in the synthetic sequence and the overall efficiency of the resolution is improved beyond 50%. Herein, we report the successful implementation of this type of resolution/recombination synthetic strategy^[5] to the total synthesis of the bioactive marine metabolite octalactin A.^[6]

Octalactin A (**2**) belongs to a small class of medium-ring lactones isolated from marine microorganisms. In vitro bioassays have shown octalactin A to possess significant cytotoxicity toward B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines.^[6,7] As a result, numerous synthetic investigations, including several total syntheses,^[8] have been directed towards its preparation.^[9] Our approach to octalactin A begins in an antithetic sense with disconnection of the C10–C15 side chain and retrolactonization of the eight-membered core, thus leading to the simplified fragments **3** and **4** (Scheme 1). From here, the basis of our strategy



Scheme 1. Retrosynthetic analysis of octalactin A. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, PG = protecting group.

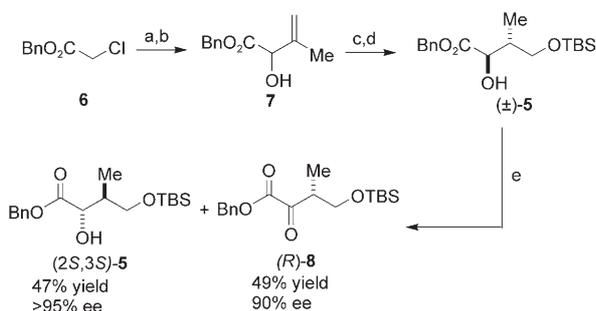
stems from the identification of an element of pseudosymmetry in the seco-acid component **3**. Specifically, we envisioned that the repeating *anti*-1,2-*vic*-hydroxymethyl stereodiad could be derived from the enantiomers of racemic *anti*-1,2-*vic*-hydroxymethyl stereoconstruct (±)-**5**. As such, oxidative resolution of (±)-**5** and subsequent head-to-tail recombination of elaborated fragments would allow rapid access to **3**. The C10–C15 side chain **4** could be obtained by asymmetric addition of an isopropyl group to a suitably functionalized aldehyde, wherein the trisubstituted olefin geometry might be secured by stereospecific cuprate-induced dyotropic rearrangement of 2,3-dihydrofuran.

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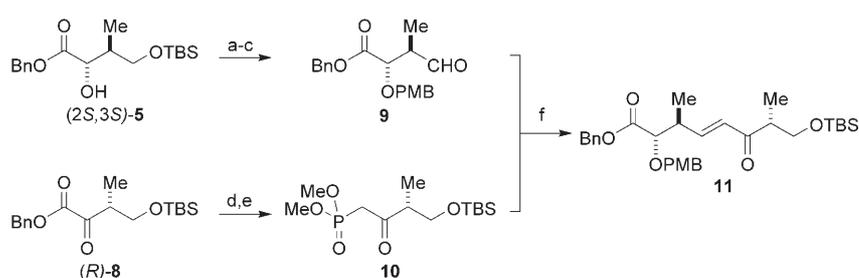
Preparation of (\pm)-**5** began with a Darzens condensation^[10] of benzyl chloroacetate (**6**) and acetone followed by an acid-catalyzed rearrangement of the intermediate glycidic ester to give hydroxy ester **7** in good yield (Scheme 2). Treatment of **7** with 9-BBN resulted in a diastereoselective (d.r. > 10:1) hydroboration of the double bond of **7** to afford the desired *anti* stereodiad, in accord with the model proposed by Still and Barrish.^[11,12] Following selective monosilylation of the unstable intermediate diol and chromatographic removal of the minor *syn* diastereomer, key building block (\pm)-**5** was obtained.



Scheme 2. Synthesis and resolution of (\pm)-**5**. Reagents and conditions: a) *t*BuOK, acetone, THF, -78°C , 95%; b) 10-camphorsulfonic acid, toluene, 110°C , 90%; c) 9-BBN, THF, RT; then *m*CPBA, 67%; d) TBSCl, imidazole, CH_2Cl_2 , 85%; e) 5.5 mol% (*R*)-**1**, 5 mol% [VO-(O*i*Pr)₃], 1 atm O₂, acetone, 35°C . 9-BBN = 9-borabicyclo[3.3.1]nonane, *m*CPBA = *meta*-chloroperbenzoic acid.

With multigram quantities of (\pm)-**5** in hand, the stage was set for the pivotal asymmetric oxidation. The use of a solution of ligand (*R*)-**1** in acetone at 40°C under one atmosphere of oxygen resulted in the asymmetric oxidation proceeding to approximately 50% conversion over the course of 24 h and gave high levels of enantiocontrol at all three stereocenters.^[13] Good mass recovery of optically active alcohol (*2S,3S*)-**5** and ketone (*R*)-**8** was obtained after column chromatography. The absolute configuration of the alcohol component (*2S,3S*)-**5** was readily determined by analysis of the Mosher ester derivative,^[14] which confirmed the configuration required for naturally occurring octalactin A.

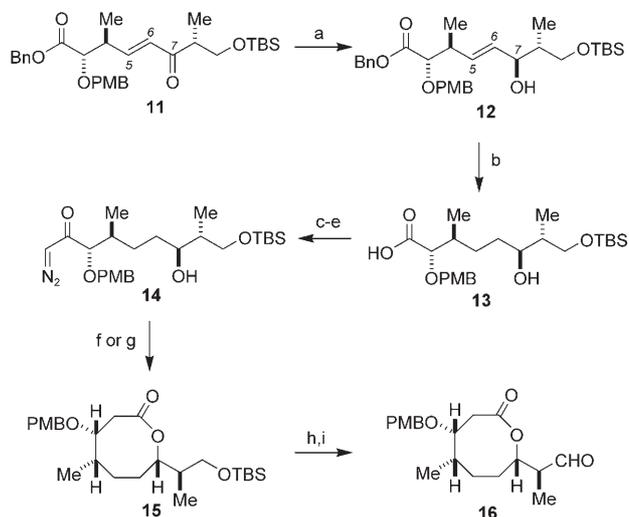
Both the alcohol ((*2S,3S*)-**5**) and the ketone ((*R*)-**8**) components could now be advanced independently along parallel paths toward fragment coupling partners **9** and **10** (Scheme 3). Specifically, (*2S,3S*)-**5** was subjected to a conventional three-step protection/oxidation sequence to provide the aldehyde **9** in good yield. With respect to (*R*)-**8**, after hydrogenolysis of the benzyl ester, conversion of the resulting keto acid into ketophosphonate **10** was effected by a one-pot procedure, which involved excision of the carboxylate by iodobenzene-promoted oxidative decarboxylation,^[15] formation of the ethyl chloroformate derived mixed anhydride, and addition of lithio dimethylmethanephosphonate.



Scheme 3. Elaboration and recombination of resolution fragments (*2S,3S*)-**5** and (*R*)-**8**. Reagents and conditions: a) 2.5 equiv PMBO(C=NH)CCl₃, 1 mol% Ph₃CBF₄, Et₂O, 0°C , 87%; b) AcOH/THF/H₂O (3:1:1), RT, 97%; c) 1.5 equiv Dess–Martin periodinane, CH₂Cl₂, RT, 91%; d) 1 atm H₂, Pd/C, EtOAc, RT, quant.; e) 1. 1.1 equiv PhIO, THF, RT; 2. EtO(CO)Cl; then Et₃N, THF, RT; 3. LiCH₂P(O)(OMe)₂, 55% (over 3 steps); f) 0.6 equiv BaO, 1.2 equiv H₂O, Et₂O, 0°C , 82% (> 20:1 *E/Z*). PMB = *para*-methoxybenzyl.

At this juncture, our resolution/recombination strategy called for the merger of aldehyde **9** and ketophosphonate **10**. A modification of the barium hydroxide promoted method^[16] proved effective in promoting the olefination reaction without undesired saponification of the product benzyl ester. In this way, alkene **11** was obtained in 82% yield with high *E/Z* selectivity (> 20:1) and no observable epimerization of the stereocenters.

Having now recombined the resolution fragments, we set about advancing toward the lactone **16** (Scheme 4). A reagent controlled reduction (with (+)-Ipc₂BCl)^[17] of ketone **11** delivered the desired *anti* diastereomer **12** in good yield (80%) and diastereoselectivity (d.r. 83:17).^[18] Heterogeneous hydrogenation with an ethylenediamine-modified palladium

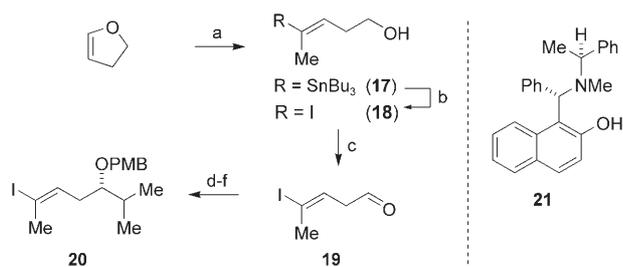


Scheme 4. Formation of lactone **16**. Reagents and conditions: a) (+)-Ipc₂BCl, Et₂O, -20°C , 80% (d.r. 83:17); b) 1 atm H₂, Pd/C(en), MeOH, quant.; c) TESCl, Et₃N, DMAP, CH₂Cl₂, RT, 84%; d) EtO(CO)Cl, Et₃N, CH₂Cl₂, -78°C ; then CH₂N₂, Et₂O, RT, 74%; e) AcOH, MeOH, RT, 87%; f) 5 equiv AgOBz, 10 equiv DMAP, THF (0.005 M), RT, 26%; g) 1. THF, H₂O, $h\nu = 254\text{ nm}$; 2. Bz₂O, DMAP, CH₂Cl₂ (0.002 M), RT, 67% (over 2 steps); h) TBAF, AcOH, THF, RT, 90%; i) Dess–Martin periodinane, CH₂Cl₂, RT, quant. Bz = benzoyl, DMAP = 4-dimethylaminopyridine, en = ethylenediamine, Ipc = isopinocampheyl, TBAF = *tetra-n*-butylammonium fluoride, TES = triethylsilyl.

catalyst^[19] resulted in clean saturation of the C5–C6 double bond with concomitant removal of the benzyl ester group and gave a quantitative yield.

In preparation for installation of the final C2 methylene unit of the octalactin lactone core by way of an Arndt–Eistert homologation,^[20] acid **13** was converted into the α diazoketone **14** by a conventional three-step sequence. With the homologation precursor in hand, we considered that the Wolff rearrangement^[21] of diazoketone **14** might be conveniently coupled to the lactonization process if the transient ketene intermediate were directly engaged by the free C7 hydroxy group. Indeed, treatment of diazoketone **14** with silver benzoate and DMAP in dilute tetrahydrofuran afforded lactone **15** directly, albeit in a modest 26% yield. Alternatively, the transformation (**14**→**15**) can be efficiently accomplished in two synthetic steps: photolytic Wolff rearrangement of **14** in aqueous tetrahydrofuran provided ready access to seco-acid **3**, which can then be treated with benzoic anhydride to induce lactonization.^[8e,22] Desilylation and oxidation of lactone **15** gave aldehyde **16**, the functionalized octalactin core.

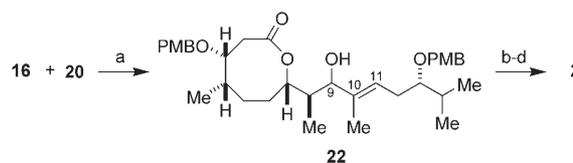
With respect to the C10–C15 side chain, iodoaldehyde **19**^[23] (prepared in three steps from dihydrofuran by using 1,2-metalate rearrangement methodology;^[24] Scheme 5) was



Scheme 5. Synthesis of side chain **20**. Reagents and conditions: a) 1. *t*BuLi; 2. $\text{Li}_2[\text{Bu}_3\text{Sn}(\text{Bu})\text{CuCN}]$; 3. MeI, THF, 69%; b) I_2 , Et_2O , RT, 97%; c) Dess–Martin periodinane, CH_2Cl_2 , RT, 94%; d) 0.75 equiv diisopropenylzinc, 1.5 equiv Et_2Zn , 15 mol% **21**, toluene, -40°C , 68% (83% ee); e) 1000 psi H_2 , $[\text{RhCl}(\text{Ph}_3\text{P})_3]$, toluene, 75%; f) PMBO(C=NH) CCl_3 , 15 mol% CSA, CH_2Cl_2 , 70%. CSA = camphorsulfonic acid.

identified as a suitably functionalized intermediate. Installation of the terminal asymmetric isopropyl unit was achieved by catalytic isopropenylation of **19** with diisopropenylzinc^[25] and ligand **21**,^[26] followed by chemoselective hydrogenation of the newly installed 1,1-disubstituted olefin with Wilkinson's catalyst. Protection of the free alcohol set the stage for subsequent manipulation.

In accord with previous synthetic reports,^[8a,d] we effected the union of aldehyde **16** and vinyl iodide **20** by using Nozaki–Hiyama–Kishi coupling (Scheme 6). Although the diastereoselectivity of this reaction was disappointing, the diastereomeric alcohols could readily be separated by chromatography on silica gel. Vanadium-catalyzed diastereoselective epoxidation of **22** secured the desired C10–C11 configuration. Final oxidation of the C9 alcohol and cleavage of the PMB ether groups completed the total synthesis to yield (–)-octalactin A (**2**).^[27]



Scheme 6. Completion of the (–)-octalactin A synthesis. Reagents and conditions: a) CrCl_2 , NiCl_2 , DMSO, RT, 70% (d.r. 1.05:1); b) 25 mol% $[\text{VO}(\text{acac})_2]$, *t*BuOOH, benzene, RT, 84%; c) Dess–Martin periodinane, CH_2Cl_2 , RT, 69%; d) DDQ, CH_2Cl_2 , H_2O , RT, quant. acac = acetylacetonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethyl sulfoxide.

This report illustrates the application of vanadium-catalyzed oxidative kinetic resolution to the total synthesis of octalactin A. Contrary to the typical application of kinetic resolution at the early stages of total syntheses, the vanadium-catalyzed methodology plays a significant strategic role in the overall design and execution of this synthesis. Moreover, whereas standard kinetic resolutions are limited to a 50% yield of the enriched chiron, the resolution/recombination strategy employed here effectively uses both products of the asymmetric operation. We note that insofar as any asymmetric operation performed on racemic starting material might serve a similar function, this resolution/recombination approach could in principle be applicable to a wide range of synthetic targets.

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