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Synthesis of Octalactin Lactone and Side Chain

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abstract: Two key intermediates of (+)-octalactin A, a potent new cytotoxic natural product, have been synthesized in a direct, and efficient manner. Lactone **1** was made using a substrate controlled lactonization reaction using the carbodiimide EDCI and two crotylborane additions were used to access the precursor hydroxyacid. The importance of proper substitution in the hydroxyacid tether is noted for successful medium-ring lactonization. Synthesis of the side chain vinyl iodide **2** employed an asymmetric allenylboronate addition. Copyright © 1996 Elsevier Science Ltd

Ring formation is a major synthetic challenge of the medium-sized lactone class of natural products due to destabilizing non-bonded interactions.[1] An important new member of this class is the eight-membered lactone octalactin-A. It was isolated from a marine actinomycete and shown to possess potent cytotoxicity to B-16-F10 murine melanoma (IC_{50} $7.2x10^{-3}\mu g/mL$) and human colon tumor cells HCT-116 (IC_{50} $0.5\mu g/mL$).[2] The epoxyketone functionality suggests that the mechanism of activity may involve covalent bond formation in that octalactin-B, a co-isolate which lacks the epoxide, is inactive. Synthetic material will help establish the mode of action by allowing for alkylation studies with model cellular nucleophiles. Total syntheses by Buszek and Clardy established the key disconnection between aldehyde **1** and the side chain vinyl iodide **2** (scheme 1).[3] In addition it was demonstrated that the substituted eight-ring lactone could be made using a hydroxyacid lactonization. Recently, a new approach for the attachment of the side chain has also appeared.[4] The new synthesis of the lactone **1** reported in this paper employs a direct carbodiimide mediated macrolactonization reaction. The enforcing effect of the ring substituents is clearly demonstrated from results with less substituted hydroxyacids. The *anti, anti*-substituted seco-acid **3**, the precursor to octactin lactone **1**, was made using two asymmetric *E*-crotylborane additions. Allenylboronate addition was used to provide the side chain vinyl iodide

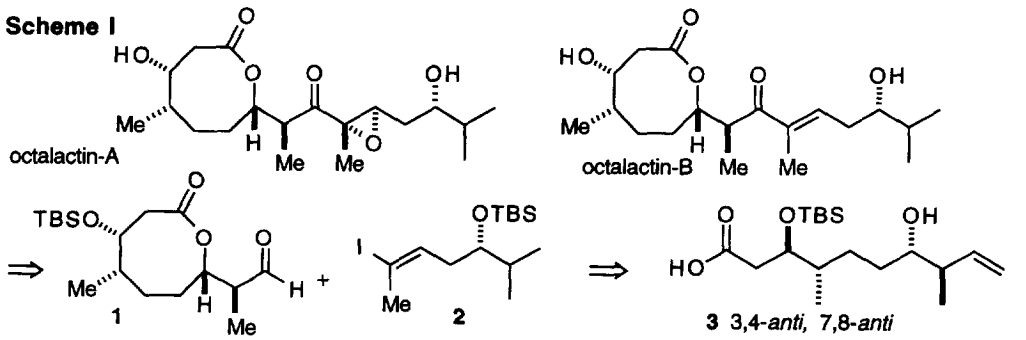
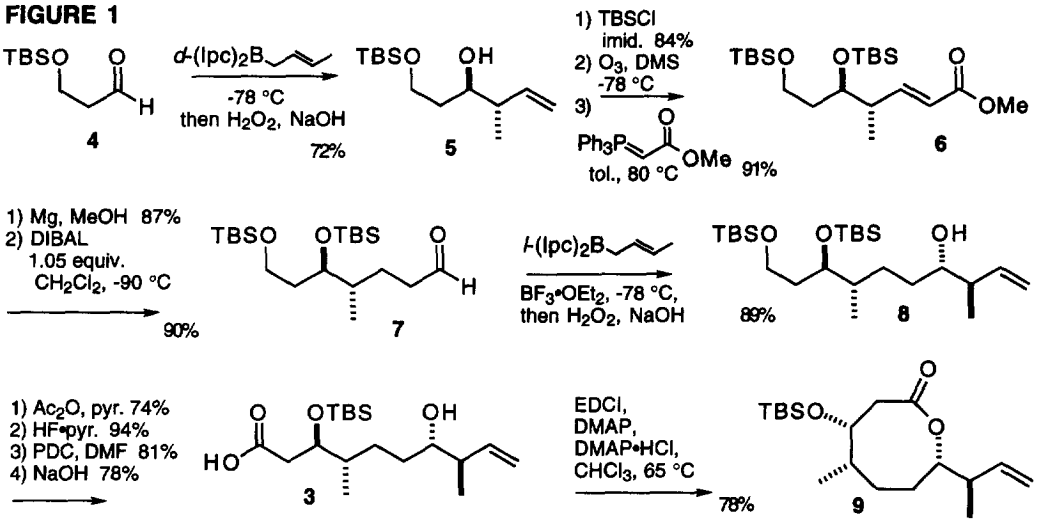


FIGURE 1



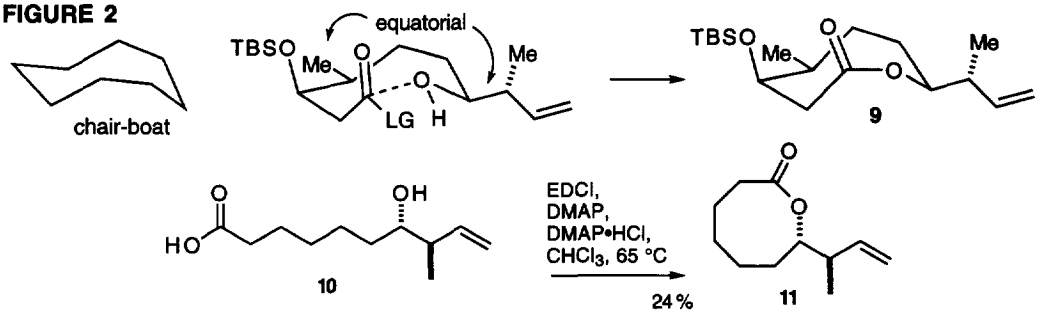
2 to complete the formal synthesis.

To begin the lactone synthesis, TBS(*tert*-butyldimethylsilyl) protected 3-hydroxypropanal **4**,[5] was added to *E*-(*d*)-(Ipc)$_2$crotylborane (1.5 equiv., Ipc = isopenocampheyl, *d* = from *d*-(+)-pinene) to obtain (4*R*,3*S*)-*anti*-homoallylic alcohol **5** (72%, 95% ee, 20:1 *anti:syn*) according to the procedure of Brown (Figure 1).[6] Scale up of this reaction was conveniently performed when 2% acetone-hexanes was used as the chromatography solvent.[7] The ee of the reaction was determined using the bis-TBS-ether by chiral GC analysis after protection.[8] Ozonolysis, followed by treatment with carbethoxymethylidene triphenylphosphorane, generated enoate **6** in 91% combined yield.[9] The double bond was then reduced using magnesium in dry methanol[10] followed by half reduction with one equivalent of DIBAL (1.5 M in toluene) at -90 °C to provide aldehyde **7**.[11] Reaction with the enantiomeric *E*-(*l*-)-(Ipc)$_2$crotylborane (derived from *l*-(-)-pinene) gave the (4*S*,3*R*)-homoallylic alcohol **8** after chromatography in 89% yield with >95% de.[12] The alcohol was acetylated and the primary silylether was removed by treatment with 70% HF•pyridine (THF, MeOH, pyridine) for 3 h.[13] PDC oxidation in DMF[14] was then used followed by sodium hydroxide hydrolysis to provide the seco-acid **3**.

Macrolactonization of 7-hydroxyheptanoic acid under a variety of conditions has been found to be impossible or at best very low yielding.[1,15] Buszek's result, using the dipyridyldisulfide conditions of Corey-Nicolaou,[16] demonstrated to the contrary that in the case of octalactin a substituted hydroxyacid cyclization is feasible.[3a] Now, using a modification of the conditions of Keck-Boden,[17] it was found that adding the hydroxyacid **3** as a 0.1 M ethanol-free[18] chloroform solution to DCC (dicyclohexylcarbodiimide, 5 equiv.), DMAP (4-N,N-dimethyl aminopyridine, 5 equiv.), and DMAP•HCl (5 equiv.) in refluxing chloroform (0.01 M, 12 h addition time, 24 h total reaction time) gave, after work up and careful removal of the urea by-product, the lactone **9** in 73% yield. Substituting the water soluble carbodiimide EDCI (ethyldimethylaminopropyl-carbodiimide hydrochloride)for DCC greatly simplified the reaction giving the product **9** in 81% isolated yield after chromatography. The key to success with this substituted substrate **3**, as opposed to the failure of the simple hydroxyacid to cyclize, seems to be due to the conformational constraint imposed by the substituents

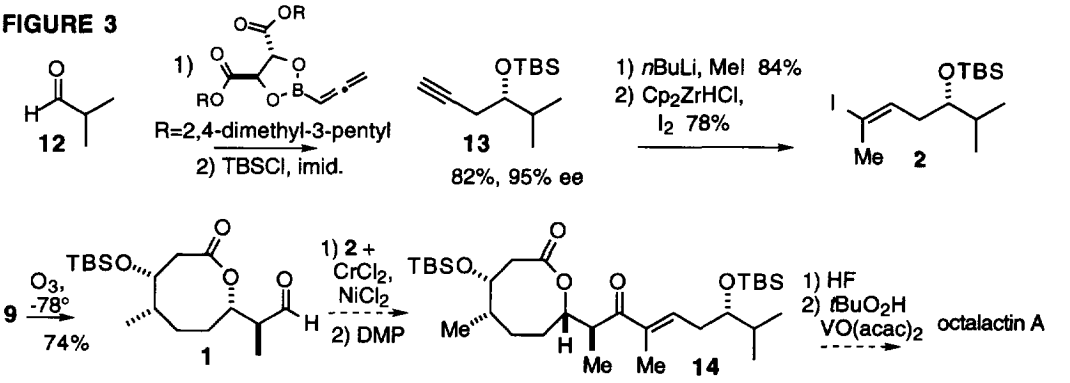
(fig. 2, LG= the uronium leaving group). The chair-boat conformation in the transition state leading to product places the methyl and 3-butenyl groups in pseudo-equatorial positions on the forming eight-membered ring. This has been shown to be the lowest energy conformation for many eight-membered ring compounds including the x-ray crystal structure of octalactin A.[2,15b] To confirm the idea, simplified analogs of **3** were prepared and reacted using the new EDCI conditions as before for 24 h (fig. 2).[19] Hydroxyacid **10**, which contains only the butenyl side chain and lacks the methyl and TBS-ether groups of **3**, gave the 8-ring lactone product in a much lower 24% yield. The unsubstituted 7-hydroxy heptanoic acid was also investigated and, not unexpectedly, gave 0% yield of lactone. In all cases, no dimer formation was observed.[20]

FIGURE 2



The synthesis of the vinyl iodide **2** shown in figure 3 began with allenyl(bis-2,4-dimethylpentyl-*d*-tartrate)boronate addition to isobutryaldehyde **12** according to the procedure of Yamamoto.[21] Protection as the TBS ether gave **13** in 82% overall yield and 95% ee.[8] Treatment with *n*-butyllithium (THF 1 M, 0 °C) and 4 equivalents of methyl iodide (in HMPT 0.2 M, -40 °C to 0°) provided the methylalkyne in 84% yield. Hydrozirconation with zirconacene hydride chloride (3 equiv.) at 40 °C in benzene (1 M, 4 h) followed by trapping with iodine generated **2** in 78% yield.[22] Vinyl iodide **2** was found to be identical in all respects to the previously reported material.[3a] To complete the formal total synthesis, ozonolysis of lactone **9** (-78 °C, in CH_2Cl_2 and MeOH 1:1, Me_2S quench) gave aldehyde **1**, again identical to the reported material,[3b] in 74% yield. The final four published steps[3] previously used to complete the synthesis of octalactin from lactone-aldehyde **1** and iodide **2** include coupling using chromous chloride and nickel(II) chloride to provide the allyl

FIGURE 3



alcohol, oxidization to enone **14**, and deprotection with HF to give octalactin B. Finally epoxidation rendered (-)-octalactin A.

In summary, efficient and direct syntheses of two key pieces of octalactin have been achieved. The lactone **1** required 13 steps from protected 1,3-propane diol and vinyl iodide **2** was made in only 4 steps starting with isobutyraldehyde. Hydroxyacid lactonization using EDCI gave octalactin lactone in 81% yield again demonstrating that the direct macrolactonization route to medium-sized rings is viable provided that the proper functionality is arrayed in the tether. Simplified substrates were shown to give greatly diminished yields. Alternatives to the existing coupling strategy for octalactin that requires excess vinyl iodide **2**,[3a] and the unselective enone epoxidation[3] can now be pursued in order to complete an improved total synthesis.

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References

1. Rousseau, G. *Tetrahedron*, **1995**, *51*, 2777.
2. Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682.
3. (a) Buszek, K.R.; Sato, N.; Jeong,Y. *J. Am. Chem. Soc.* **1994**, *116*, 5510-5512. (b) McWilliams, J.C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378-8379.
4. Bach, J.; Berenguer, R.; Garcia, J.; Villarrasa, J. *Tetrahedron Lett.* **1995**, *36*, 3425.
5. 1,3-propanediol was monosilylated (NaH, TBSCl, THF) according to McDougal, P. G.; Rico, J. G.; Oh, Y.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388, and was oxidized with PCC (NaOAc, 4Å mol. sieves, CH_2Cl_2), Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647, to give aldehyde **4** in 77% overall yield. All compounds were purified by silica gel chromatography and characterized by ^1H and ^{13}C NMR, IR, MS, and optical rotation.
6. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
7. Compound **5**, $[\alpha]_D$ -1.9 (c 0.22, CH_2Cl_2), chromatography using EtOAc/hexanes failed to remove the 3-pinanol by-product.
8. The ee of the TBS-ethers **5** and **13** were determined by capillary GC (chiradex-β, 100 °C, isothermal).
9. Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109. Bergelson, L. D.; Shemyakin, M. M. *Tetrahedron Lett.* **1963**, *19*, 149.
10. Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287.
11. Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3121.
12. The selectivity was determined by ^{13}C NMR peak height averaged differences.
13. Masamune, S.; Lu, L. D. -L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523.
14. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
15. (a) Funk, R. *J. Org. Chem.* **1986**, 3247. (b) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697-7705.
16. Corey, E. J.; Nicolaou, K. C.; Melvin, L. S. Jr. *J. Am. Chem. Soc.* **1975**, *97*, 653.
17. Boden, P. B.; Keck, G. E.; *J. Org. Chem.* **1985**, *50*, 2394. Keck, G. E. Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606.
18. Ethanol free chloroform was obtained by washing three times with water, drying over $MgSO_4$, followed by distillation from P_2O_5.
19. The substrates were synthesized following a modified route starting with 1,7-heptane diol, similar in manner to hydroxy acid **3** shown in figure 1.
20. No ion was observed in the Mx2 region of the mass spectrum.
21. The (*S*)-propargyl alcohol, $[\alpha]_D$ +72.9 (c 0.07, CH_2Cl_2), was isolated by distillation (53 °C, 20 mmHg). Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.
22. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. Cp_2ZrHCl was prepared according to: Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, M. *Tetrahedron Lett.* **1987**, *28*, 3895.

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