Pergamon

Tetrahedron Letters, Vol. 36, No. 40, pp. 7189-7192, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01493-4

An Improved Synthesis of the Octalactins

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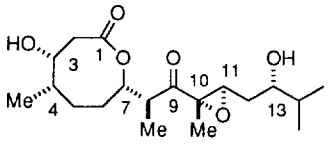
Abstract: A new and efficient synthesis of the key C.1-C.9 intermediate **5** of the octalactins has been achieved starting from L-ascorbic acid.

We recently described the first total synthesis and established the absolute configuration of both octalactin A (**1**) and B (**2**),[1,2] two novel, marine derived natural products whose isolation and relative configurations were



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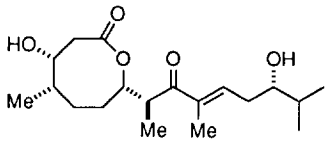

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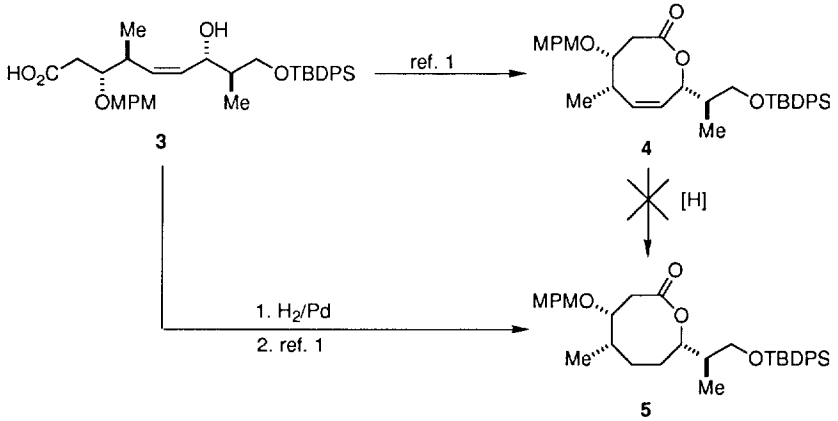
reported by Fenical and Clardy.[3] Octalactin A in particular has attracted special interest because of its very potent cytotoxicity toward murine melanoma and human colon tumor cell lines and its unknown mode of action.[3] Our original strategy for the construction of the saturated eight-membered lactone common to both structures involved a straightforward intramolecular esterification of the unsaturated hydroxy carboxylic acid **3**, prepared in 18 steps from (*S*)-(+)-3-hydroxy-2-methylpropionate, followed by an expected facile hydrogenation of the olefin. The first part of this approach proved unremarkable. However, it was not possible to reduce the double-

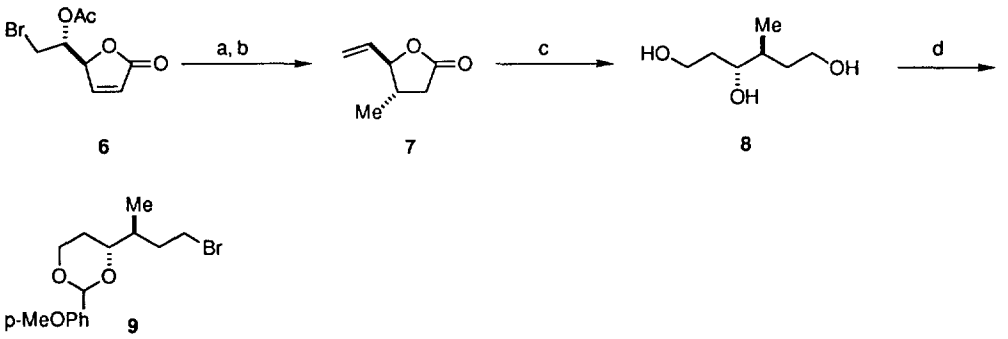


bond under the many conditions attempted. We subsequently discovered an unprecedented reaction manifold in which the desired lactone could be obtained directly from the *saturated* hydroxy carboxylic acid in excellent yield

using the Corey double activation lactonization protocol.[4] Since the olefin was no longer required for the synthesis, we identified a much simpler route to the saturated precursor. We now describe a very different and substantially improved synthesis of this key intermediate which has the potential to meet the demand for the octalactins.

The first part of this approach is outlined in Scheme 1. We recognized that the C.4 stereocenter of the butenolide **6**, which was easily obtained from L-ascorbic acid in three steps by a known route[5] and on a 100+ gram scale, corresponded to the C.3 configuration of the octalactins. The reaction of **6** with lithium dimethylcuprate in the presence of TMSCl in THF at -78°C afforded a single diastereomer in 78% yield (95% based on recovered starting material) and thereby introduced the C.4 methyl group with complete stereocontrol.[6]

Conversion of the bromo acetate into the olefin was accomplished with zinc dust in 50% aqueous acetic acid/acetone (1.6:1 v/v) to give **7**, $[\alpha]_D^{23}$ = +66.9° (c = 2.5, $CHCl_3$), in 94% yield.[7] Regioselective hydroboration of the alkene with 9-BBN in refluxing THF for 12 h, followed by the introduction of additional excess BH_3-THF complex to complete reduction of the lactone, gave after oxidation the triol **8**, $[\alpha]_D^{23}$ = +15.5° (c = 6.2, CH_3OH), in 71% yield. The 1,3-diol was protected as its anisylidene ketal (85%, single diastereomer) by treatment with a five-fold excess of *p*-methoxybenzaldehyde in the presence of catalytic concentrated aqueous HCl for 24 h. The remaining alcohol was brominated (91%) with PPh_3/NBS[8] in CH_2Cl_2 to furnish **9** which was used immediately in subsequent operations.

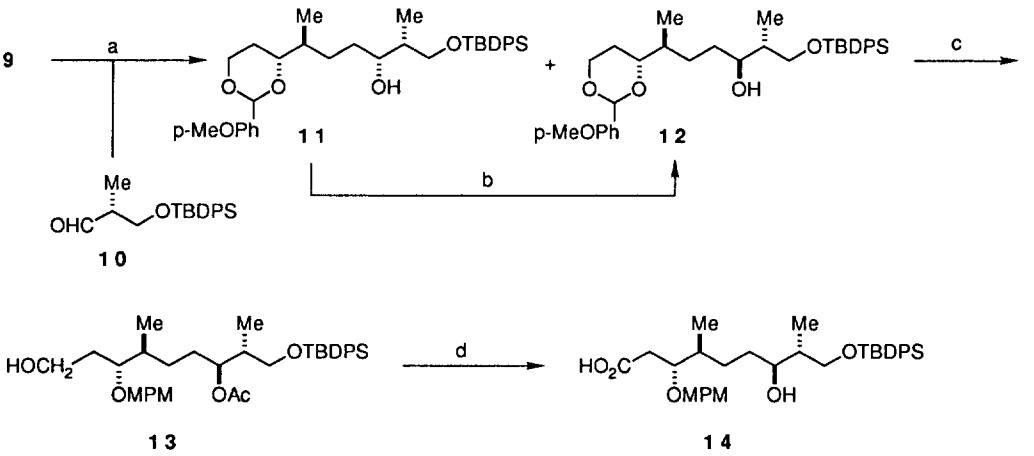


Scheme 1. Reagents and Reaction Conditions
(a) 1. Me_2CuLi/TMSCl/THF/-78°C ---> RT/12 h. (b) 1. Zn dust/50% aq HOAc:acetone (1.6:1 v/v)/RT/5 h. (c) 1. 9-BBN/THF/65°C/12 h, then excess BH_3/THF/65°C/12 h. 2. 30% H_2O_2/15% NaOH/0°C/1 h. (d) 1. *p*-MeO-C_6H_5CHO/cat. conc.HCl/RT/24 h. 2. PPh_3/NBS/cat. pyridine/CH_2Cl_2/RT/1 h.

We considered several options for coupling **9** with the aldehyde **10**. The addition of alkyllithium and alkyl Grignard reagents to β-alkoxyaldehydes generally proceed with poor stereocontrol. In contrast, lithium dialkylcuprates are reported to give superior results favoring the threo isomer.[9] Unfortunately, condensing the Gilman cuprate derived from the alkyl bromide with the aldehyde **10**[10] in ether at -78°C afforded only a disappointing 1:1 threo:erthyro ratio. Repeated reaction with the more desirable mixed ethynyl cuprate complexes[11] also gave no improvement in diastereoselectivity. The nature of the alkoxy protecting group did not significantly affect the stereochemical outcome. Thus, similar results were obtained with either benzyl- or THP-

ether protecting groups. Extensive efforts to improve the chelation-directed stereoselectivity of this step have met with only limited success thus far.[12]

The bromide was ultimately lithiated and added to the aldehyde in ether at -78°C to give in 75% yield a chromatographically separable 3:1 erythro:threo [1:1 if the solvent is changed to ether/pentane (1:1, v/v) and the reaction conducted at -90°C] mixture of diastereomers (Scheme 2).[13] The more polar compound was readily converted to the desired diastereomer (92%) by Mitsunobu inversion.[14] Routine protection of the combined threo products as the acetate (98%) was followed by regioselective hydrolysis of the anisylidene ketal with $NaBH_3CN$ and TMSCl in acetonitrile to afford in 84% yield the secondary MPM ether **13**.[15] Oxidation of the resulting primary alcohol was effected using a two-part procedure: initial Dess-Martin oxidation[16] gave the aldehyde which was treated further with buffered (pH 3.5/NaH_2PO_4) $NaClO_2$ in *t*-BuOH to yield the carboxylic acid (82% overall). Finally, removal of the acetate with K_2CO_3 in MeOH quantitatively afforded the key hydroxy carboxylic acid **14** which was identical in every respect to the material prepared by the original route.[1,17] Lactonization of **14** as described previously produced **5**.[17]



Scheme 2. Reagents and Reaction Conditions
(a) 1. *t*-BuLi/Et_2O/-78°C/1 h, then add **10** at -78°C/0.5 h yielding a 3:1 mixture of **11**:**12** followed by silica gel flash chromatography (5% Et_2O/CH_2Cl_2). (b) 1. PPh_3/*p*-NO_2-$C_6H_5CO_2H$/Et_2O-PhMe (2:1)/RT/1 h, followed by $EtO_2CN{=}NCO_2Et$. 2. K_2CO_3/MeOH/RT/1 h. (c) 1. Ac_2O/pyridine/DMAP/CH_2Cl_2/RT/2 h. 2. $NaBH_3CN$/TMSCl/3 Å molecular sieves/MeCN/0°C ---> RT/12 h. (d) 1. Dess-Martin periodinane/CH_2Cl_2/RT/ 1 h, then $NaClO_2$ (in pH 3.5 buffer)/2-methyl-2-butene/*t*-BuOH/RT/ 1 h. 2. K_2CO_3/MeOH/RT/1 h.

In summary, a highly efficient synthesis, adaptable to large scale, of the key C1.-C.9 lactone intermediate of the octalactins has been achieved in 12 steps starting from readily obtained material derived from inexpensive L-ascorbic acid. The foregoing synthesis provides much easier access to the octalactins and their analogues.

Acknowledgment. Financial support from the American Cancer Society (DHP-87) is gratefully acknowledged.

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10. Derived in three steps in 77% overall yield from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate: (i) TBDPSCl/imidazole/CH_2Cl_2/RT; (ii) DIBAL/Et_2O/-78°C; (iii) Dess-Martin periodinane/CH_2Cl_2/RT.

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12. We have made further efforts to increase the proportion of the threo diastereomer. For example, oxidation of the diastereomers **11** and **12** to the corresponding ketone, followed by hydride reduction with a wide range of reducing agents and conditions, gave variable results. Once again, the choice of the alkoxy protecting group made little difference. Either L- or N-Selectride® in THF at -78°C, gave **11** with at least 5:1 selectivity. However, removing the TBDPS group and reducing the resulting hydroxy ketone with L-Selectride® under the same conditions afforded, after silylation, **11** exclusively by ^1H NMR analysis.

13. ^1H NMR ($CDCl_3$) of **12**: δ 0.82 (3 H, d, *J* = 6.9 Hz), 0.96 (3 H, d, *J* = 6.7 Hz), 1.07 (9 H, s), 1.43 - 1.85 (8 H, m), 3.60 - 3.68 (4 H, m), 3.77 (1 H, dd, *J* = 4.1, 10.2 Hz), 3.80 (3 H, s), 3.94 (1 H, dt, *J* = 2.4, 11.6 Hz), 4.29 (1 H, dd, *J* = 3.7, 11.4 Hz), 5.47 (1 H, s), 6.89 (2 H, d, *J* = 8.9 Hz), 7.39 - 7.47 (8 H, m), 7.69 (4 H, dd, *J* = 1.6, 7.8 Hz); $[\alpha]_D^{23}$ = -23.1° (c = 2.05, $CHCl_3$).

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17. ^1H NMR ($CDCl_3$) of **14**: δ 0.81 (3 H, d, *J* = 6.9 Hz), 0.94 (3 H, d, *J* = 6.8 Hz), 1.07 (9 H, s), 1.39 - 1.91 (7 H, m), 2.54 (2 H, m), 3.60 - 3.65 (2 H, m), 3.76 - 3.82 (2 H, m), 3.79 (3 H, s), 4.52 (2 H, ABq, *J* = 10.9 Hz), 6.86 (2 H, *J* = 8.6 Hz), 7.26 (2 H, *J* = 8.6 Hz), 7.39 - 7.47 (6 H, m), 7.68 (4 H, dd, *J* = 1.5, 7.8 Hz), 13.2 (1 H, bs); ^1H NMR ($CDCl_3$) of **5**: δ 0.96 (3 H, d, *J* = 6.8 Hz), 1.04 (9 H, s), 1.05 (3 H, obscured d), 1.16 (1 H, m), 1.63 (3 H, m), 1.93 (2 H, m), 2.46 (1 H, d, *J* = 13.2 Hz), 2.98 (1 H, dd, *J* = 6.2, 13.2 Hz), 3.51 (1 H, dd, *J* = 4.4, 10.0 Hz), 3.58 (1 H, d, *J* = 6.2 Hz), 3.78 (3 H, s), 3.85 (1 H, dd, *J* = 4.0, 10.0 Hz), 4.36, (1 H, d, *J* = 12.0 Hz), 4.56 (1 H, m), 4.84 (1 H, d, *J* = 12.0 Hz), 6.85 (2 H, d, *J* = 8.4 Hz), 7.29 (2 H, d, *J* = 8.4 Hz), 7.32 - 7.39 (6 H, m), 7.61 - 7.65 (4 H, m); $[\alpha]_D^{23}$ = -65.4° (c = 1.3, $CHCl_3$).

(*Received in USA* 27 *June* 1995; *revised* 1 *August* 1995; *accepted* 4 *August* 1995)