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Tetrahedron Letters 44 (2003) 7747–7751

TETRAHEDRON LETTERS

Formal total synthesis of altohyrtin C (spongistatin 2). Part 2: Construction of fully elaborated ABCD and EF fragments

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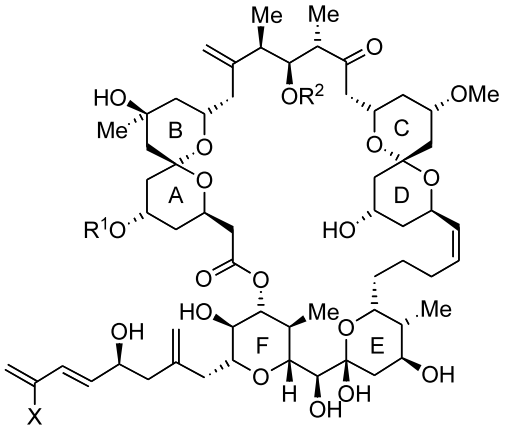
Received 5 August 2003; revised 19 August 2003; accepted 21 August 2003

Abstract—Coupling of the C1–C14 (AB) crotylstannane with the C15–C28 (CD) aldehyde followed by stereochemical arrangements gave the C1–C28 (ABCD) fragment of altohyrtin C. The C29–C44 (EF) fragment was also prepared. The syntheses of these two fragments, both of which were identical with those prepared by the Smith group, constitute a formal total synthesis of altohyrtin C.

The altohyrtins, spongistatins, and cinachyrolide A (**1**–**4**) were isolated from marine sponges by the Kitagawa, Pettit, and Fusetani groups, respectively (Fig. 1).[1] In the preceding communication,[2] we described an aldol coupling approach to construct the ABCD (C1–C28) fragment **5**[3] (Fig. 2). Since it was difficult in our hand to introduce the C13 exomethylene into **5**, we then pursued a second-generation strategy to combine the AB (C1–C14) and the CD (C15–C28) fragments. Among the many possible approaches, we chose a crotylstannane–aldehyde coupling because (i) it is not necessary to introduce the C13 exomethylene after the fragment assembly, and (ii) the stereoselectivity of the coupling reactions has been well studied[4] and it is known to be controlled by Lewis acids.[5] Based on this analysis, we envisioned that the subtarget **6** or **7** could be constructed by the coupling between the C1–C14 (AB) crotylstannane **8** and the C15–C28 (CD) aldehyde **9** or **10**, respectively.

Although crotylstannane **8** could be synthesized in six steps from aldehyde **11** (through **12**, Scheme 1), which was prepared in the preceding communication,[2] the synthesis needed a total of 32 steps from the starting 3,4,6-tri-*O*-acetyl-D-glucal.[6a] Therefore, we developed a more efficient synthesis of **8** as described below (Scheme 2). The synthesis started from the known ketone **13**[7] and aldehyde **14**.[8] Enantioselective aldol reaction of **13** with **14** by using (−)-diisopinocampheylboron chloride ((−)-Ipc$_2$BCl)[9] afforded β-hydroxyketone **15** in moder-



Altohyrtin A (Spongistatin 1) (**1**): X=Cl, R^1=R^2=Ac
Altohyrtin B (**2**): X=Br, R^1=R^2=Ac
Altohyrtin C (Spongistatin 2) (**3**): X=H, R^1=R^2=Ac
Cinachyrolide A (Spongistatin 4) (**4**): X=Cl, R^1=Ac, R^2=H

Figure 1.

Keywords: altohyrtins; spongistatins; stereoselective synthesis; crotylstannanes.

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doi:10.1016/j.tetlet.2003.08.083

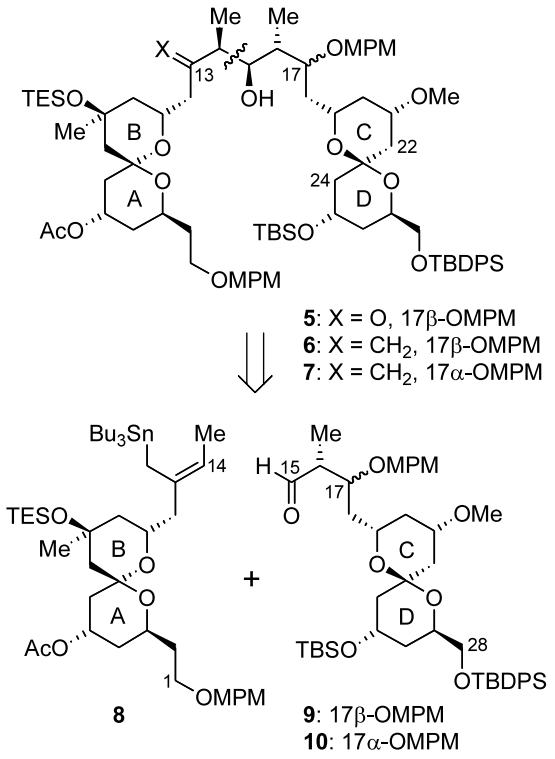
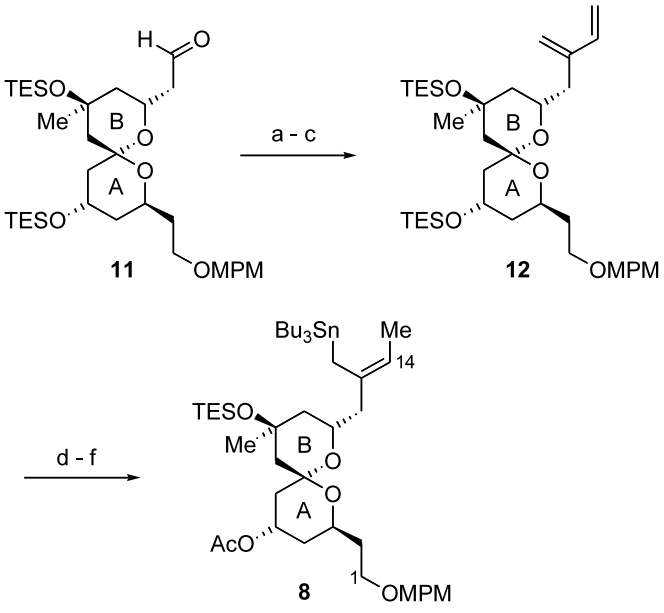


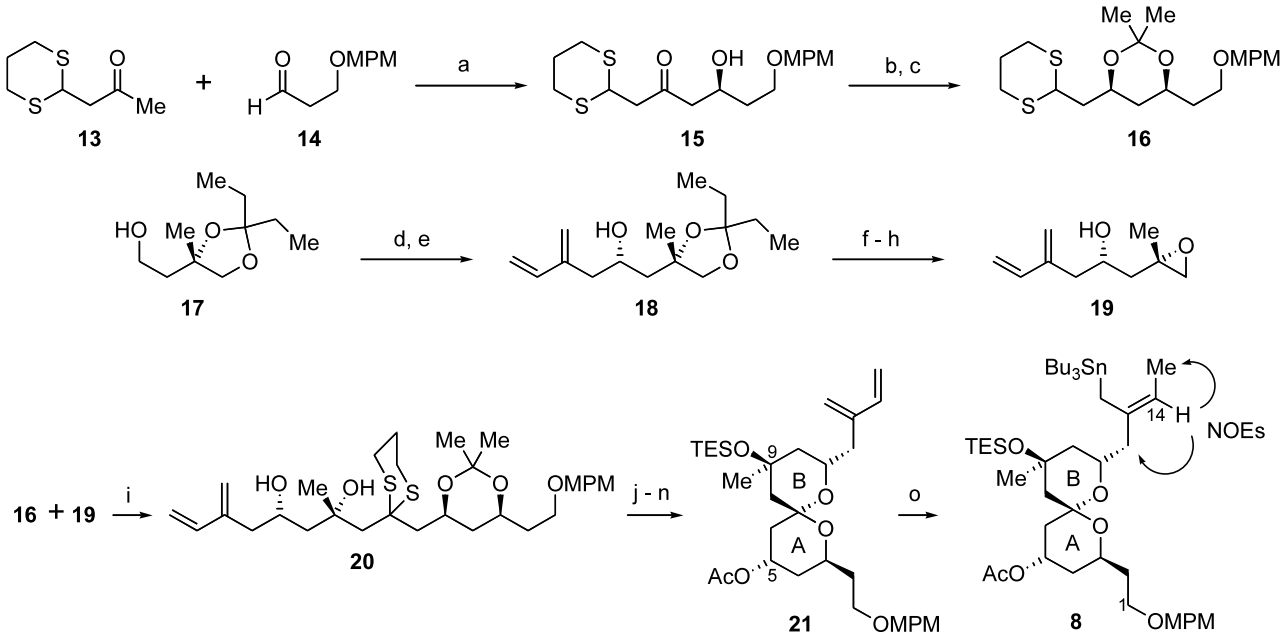
Figure 2.



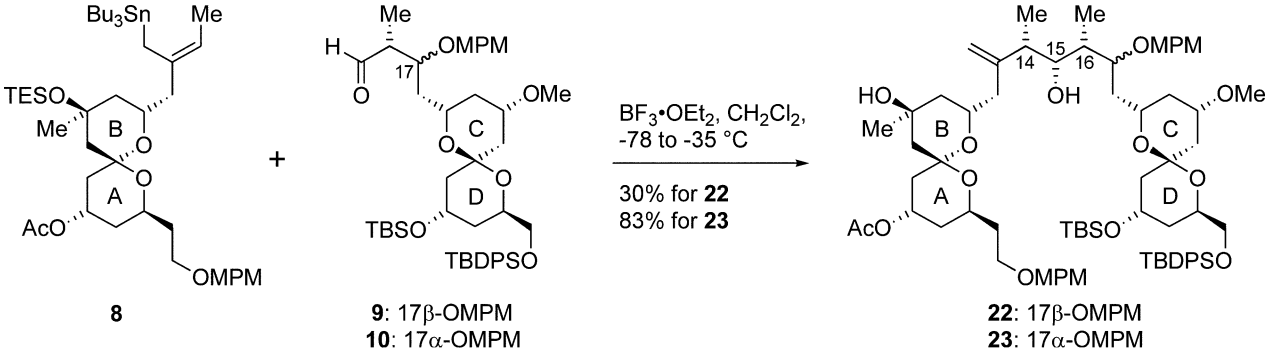
Scheme 1. Synthesis of the AB fragment **8**. *Reagents and conditions*: (a) vinylmagnesium bromide, ether, –40°C; (b) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt (73% for two steps); (c) Cp_2ZrCl_2, Zn, CH_2I_2, THF, rt (75%); (d) PPTS, CH_2Cl_2–MeOH, 0°C (70%); (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (84%); (f) *n*-Bu_3SnH, $Pd(PPh_3)_4$, benzene, rt (58%).

ate yield (45%) and moderate enantiomeric excess (60%). 1,3-*syn*-Selective reduction of **15** with DIBALH[10] followed by acetonide formation led to acetonide **16** in 78% yield. The coupling partner **19** was prepared in five steps from the known alcohol **17**.[11] That is, *o*-iodoxybenzoic acid (IBX) oxidation[12] followed by the Brown's diastereoselective isoprenylation[13] produced alcohol **18** in high diastereomeric excess (>98%). Epoxide formation smoothly proceeded using the usual three-step sequence to furnish **19** in 35% overall yield from **17**. Treatment of **19** with lithiated **16** produced the coupling product **20** in 84% yield based on the recovered **19** (62%). A longer reaction time and/or higher temperature caused the decomposition of **20** in the coupling reaction. Removal of acetonide and dithioacetal followed by acid-catalyzed spiroacetallization proceeded in 34% yield. Sequential protection of the C5 and C9 hydroxy groups gave the fully protected spiroacetal **21** in 82% yield. Finally, the palladium(0)-catalyzed hydrostannation[14] of **21** furnished crotylstannane **8** in 58% yield, which was identical with the sample prepared by the method in Scheme 1. The stereochemistry of the trisubstituted olefin in **8** was determined to be *Z* based on the NOE studies. The synthesis of **8** was thus achieved in 21 total steps. Although there is still room for improvement of this synthesis, we believe that the synthetic route described herein is straightforward.

The crucial fragment assembly was achieved via the crotylstannane–aldehyde coupling of **8** with **9**[2] in the presence of $BF_3{\cdot}OEt_2$ to furnish bis-spiroacetal **22** in 30% yield as a single adduct (Scheme 3). On the other hand, the coupling of **8** with **10**,[6b,15] which has the α-OMPM group at C17, yielded **23** in 83% yield as a single adduct. In order to unambiguously confirm the stereochemistry, we tried to transform the coupling product **22** into the Smith's ABCD fragment **25**,[16] the intermediate of the total synthesis of altohyrtin C, through keto-aldehyde **24** in several steps (Scheme 4). Unfortunately, the obtained product was not identical with **25** based on the ^1H NMR spectrum. Moreover, the coupling product **23** led to **24**, indicating that **23** also had the undesired configurations. On the basis of these results and the general rule for crotylstannane–aldehyde couplings,[4,5] the stereochemical consequence of **22** and **23** was supposed to be C14,15-*syn* and C15,16-*syn*. We tried to use Bu_2SnCl_2 and $MgBr_2$[5] to obtain the correct stereochemistry, and found that the desired coupling reaction did not proceed and only the protodestannylation of **8** occurred in these cases. Therefore, it was necessary to isomerize both the C14 and C15 stereocenters. After Dess–Martin oxidation[17] of the C15 hydroxy group in **23**, the resultant ketone **26** was treated with excess K_2CO_3 in MeOH–H_2O. Fortunately, the desired epimerization at C14 did occur under these conditions to give a 1:1 inseparable mixture of C5-de-*O*-acetyl **26**[18] and **27**. It is noteworthy that no C16 epimerization[18] and olefin isomerizaiton (i.e. C13–C15 enone formation) were observed. DIBALH reduction of the mixture proceeded with high stereoselectivity and the resultant mixture was subjected to the four-step sequence (acetylation of the C5 and C15 hydroxy groups, protection of the C9 hydroxy group as TES ether, oxidative removal of the C1 and C17 MPM ethers, and Dess–Martin oxidation of the resultant diol) to afford a 1:1 separable mixture of **28**[18] and **29**. Since



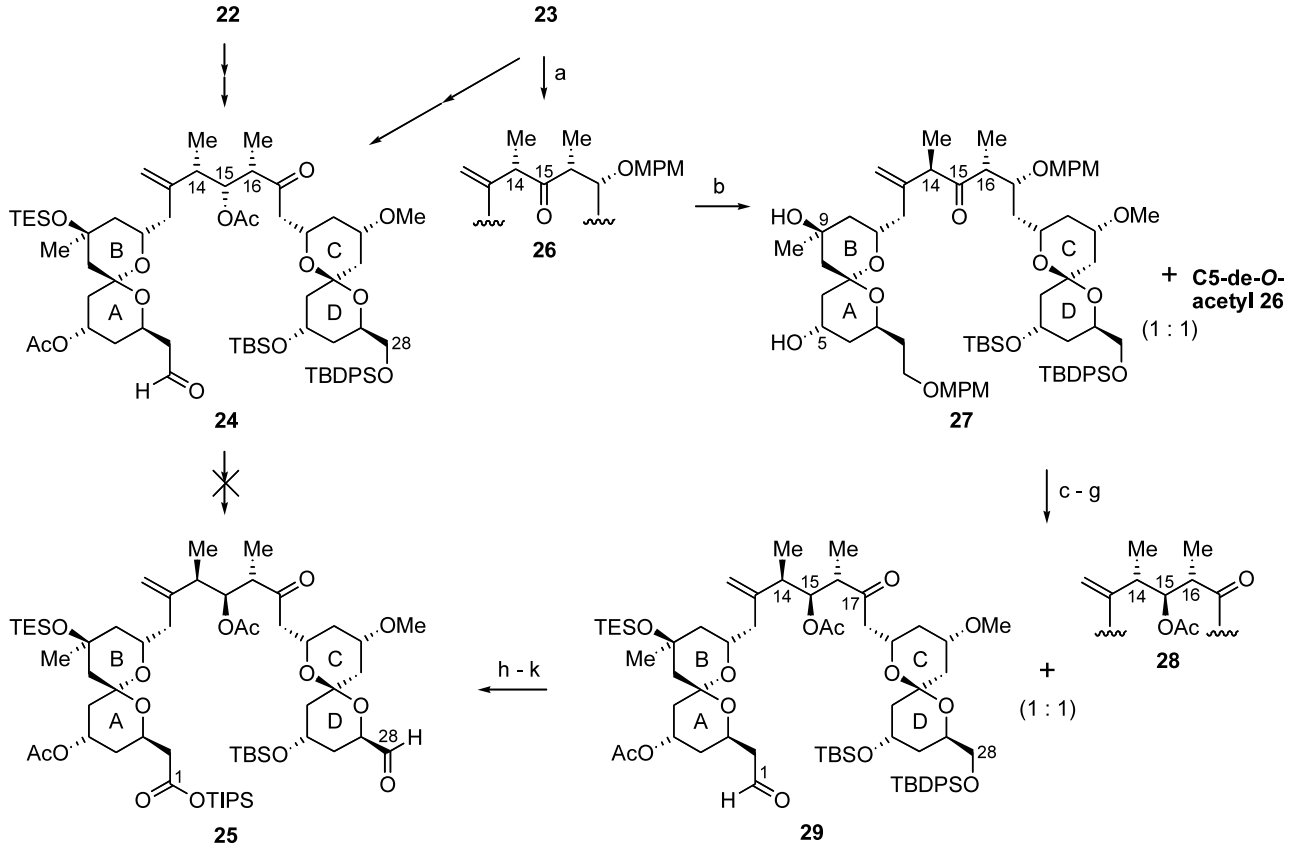
Scheme 2. New synthesis of the AB fragment **8**. *Reagents and conditions*: (a) **13**, (–)-Ipc$_2$BCl, Et$_3$N, CH$_2$Cl$_2$, –78°C to rt, then **14** (45%, 60% ee); (b) DIBALH, THF, –78 to –20°C (85%, >96% de); (c) 2,2-dimethoxypropane, PPTS, rt (92%); (d) IBX, DMSO–THF, rt (82%); (e) isoprene, TMP, *n*-BuLi, *t*-BuOK, (–)-Ipc$_2$BOMe, BF$_3$·OEt$_2$, THF, –78°C, then aldehyde, –78 to –20°C; (f) HCl, MeOH, rt (72% for two steps, >98% de); (g) TsCl, Et$_3$N, CH$_2$Cl$_2$, rt; (h) NaOH, Et$_2$O, rt (60% for two steps); (i) **16**, *n*-BuLi, HMPA, Et$_2$O, –40°C, then **19**, THF, –40°C (84% based on recovered **19** (62%)); (j) 80% aq. AcOH, rt; (k) MeI, CaCO$_3$, acetone–H$_2$O, 60°C; (l) PPTS, CH$_2$Cl$_2$, rt (34% for three steps); (m) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt (89%); (n) TESOTf, 2,6-lutidine, CH$_2$Cl$_2$, rt (92%); (o) *n*-Bu$_3$SnH, Pd(PPh$_3$)$_4$, benzene, rt (58%). TMP = 2,2,6,6-tetramethylpiperidine, TES = triethylsilyl.



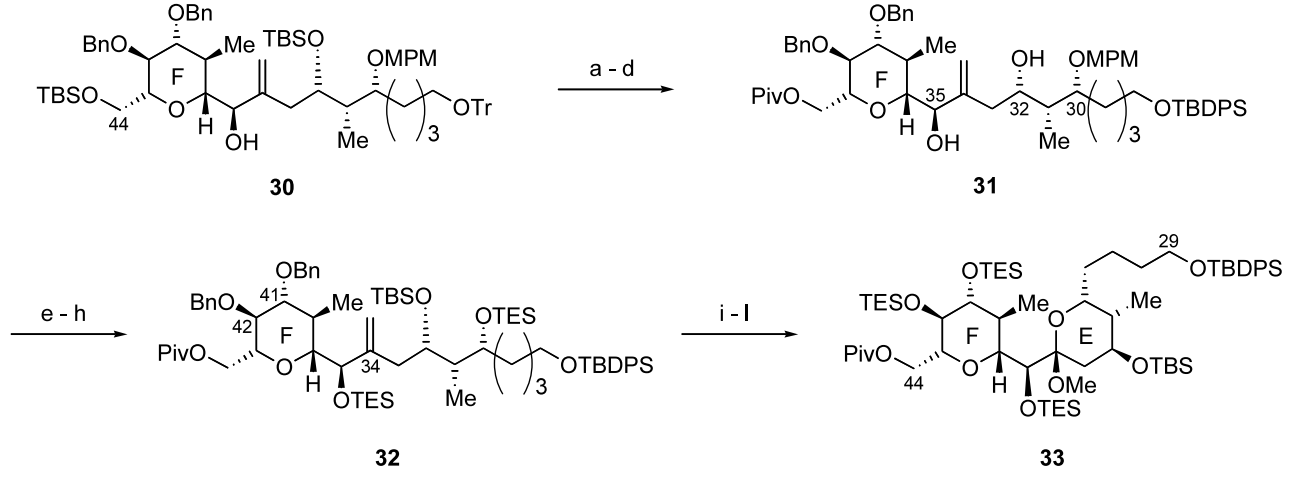
Scheme 3. Coupling of crotylstannane **8** and aldehyde **9** or **10**.

the coupling constants (J = 10.2, 2.8 Hz) of the C14–C16 region in the ^{1}H NMR spectrum of **29** were close to those of the Smith's ABCD fragment **25** (J = 9.1, 3.4 Hz), we decided to convert **29** to **25**. NaClO$_2$ oxidation of **29** followed by the three-step sequence (removal of TBDPS ether in the presence of TBS ether,[19] oxidation of the resultant C28 hydroxy group, and the silyl ester formation) produced **25** in 31% overall yield. All the spectroscopic data of **25** were identical with those kindly provided by Professor Smith.[16]

We then prepared the C29–C44 (EF) fragment **33**, the intermediate[20] that was also employed in the Smith's total synthesis of altohyrtin C, from our previously prepared allyl alcohol **30**[6c] (Scheme 5). Deprotection of the silyl ether (TBAF) followed by the three-step sequence (selective protection of the C44 hydroxy group, removal of trityl group, and protection of the resultant hydroxy group as TBDPS ether) gave diol **31** in 76% overall yield. Sequential silyl ether formation at the C35 and C32 hydroxy groups smoothly proceeded. Oxidative removal of the C30 MPM group followed by silyl ether formation led to compound **32** in 71% overall yield. Ozonolysis of the C34 exomethylene was followed by the three-step sequence (methylacetal formation, removal of the benzyl groups using the Iadonisi conditions,[21] and silylation of the C41 and C42 hydroxy groups) to produce the fully elaborated C29–C44 fragment **33** in 21% overall yield. Compound **33** was identi-



Scheme 4. Synthesis of the ABCD fragment **25**. *Reagents and conditions*: (a) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt (88%); (b) K_2CO_3, MeOH–H_2O, rt; (c) DIBALH, CH_2Cl_2–hexane, −40°C; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C (83% for four steps); (f) DDQ, CH_2Cl_2–pH 7 phosphate buffer, rt; (g) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt (25% for **28**, 25% for **29**); (h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–H_2O, rt; (i) TBAF, AcOH, THF, rt; (j) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt; (k) TIPSCl, Et_3N, THF, rt (31% for four steps). TIPS = triisopropylsilyl.



Scheme 5. Synthesis of the EF fragment **33**. *Reagents and conditions*: (a) TBAF, THF, 60°C (98%); (b) PivCl, DMAP, CH_2Cl_2, 0°C (96%); (c) HCO_2H–Et_2O (3:2), 0°C (81%); (d) TBDPSCl, imidazole, CH_2Cl_2, rt (100%); (e) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0°C (72%); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt (100%); (g) DDQ, CH_2Cl_2–pH 7 phosphate buffer, rt (98%); (h) TESOTf, 2,6-lutidine, CH_2Cl_2, rt (100%); (i) O_3, CH_2Cl_2–MeOH, −78°C, then Me_2S (95%); (j) PPTS, MeOH–THF, rt (72%); (k) $KBrO_3$, $Na_2S_2O_4$, EtOAc–H_2O, rt (30%); (l) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C (100%). Piv = 2,2-dimethylpropionyl.

cal in all respects with that prepared by Smith and his co-workers.[20] Thus the syntheses of **25** and **33** constitute a formal total synthesis of altohyrtin C.

Acknowledgements

We thank Professor A. B. Smith, III for kindly providing comparison data of **25** and **33**.

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