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Synthesis of (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone

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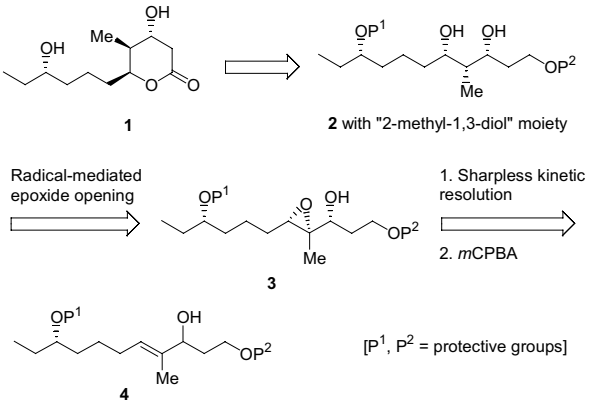
Abstract—Radical-mediated opening of a chiral trisubstituted epoxy alcohol using cp_2TiCl furnished the '2-methyl-1,3-diol' moiety with the desired stereochemistry, which led to a total synthesis of (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone **1**.

Biosynthetic engineering is emerging as a powerful tool to assemble rapidly analogues of natural products in the search for novel molecular structures,[1] which are increasingly in demand because of the alarming decline over the past decade in the number of new chemical entities introduced each year as drugs.[2] During the studies of the biosynthesis of spinosyns, a family of agriculturally important molecules,[3] a truncated version of the spinosyn polyketide synthase was expressed in the heterologous host *Saccharopolyspora erythraea* JC2.[4] This resulted in the formation of a novel pentaketide lactone that was identified as (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone **1**. The discovery of this molecule helped in understanding the crucial steps of spinosyn biosynthesis[4] and supported the widely accepted hypothesis of step-by-step functionalization of the growing polyketide chain in the biosynthesis of macrolides.[5] A general strategy for the synthesis of this type of lactone would help to prepare material for use as standards during mechanistic studies of polyketide synthases and related biological studies.[6] In this paper, we describe the total synthesis of lactone **1** following a convergent strategy. Retrosynthetically, compound **1** could be prepared from a suitably protected tetrol **2** having a '2-methyl-1,3-diol' moiety, ubiquitously present in polyketide natural products. The key feature in our synthesis is the application of a method developed by us[7] for the synthesis of chiral 2-methyl-1,3-diols by radical-mediated anti-Markovnikov opening of trisubstituted epoxy alcohol **3** at the more substituted carbon using cp_2TiCl to construct the three stereocentres of **1**. The trisubstituted *syn* epoxy alcohol **3**, in turn, could be synthesized by *m*CPBA epoxidation of the unreacted *R*-allylic alcohol obtained during a Sharpless kinetic resolution[8] of compound **4**.



The synthesis is outlined in Scheme 1. Starting with (*S*)-1,3-pentanediol **5**,[9] the C3-*O*-Bn protected compound **6** was prepared in three steps in 88% overall yield—protection of the primary OH as the TBDPS–ether, benzylation of the secondary hydroxyl group and finally desilylation using tetra-*n*-butylammonium fluoride.

Keywords: (3*R*,4*S*,5*S*,9*S*)-3,5,9-Trihydroxy-4-methylundecanoic acid; δ-Lactone; Sharpless kinetic resolution; Epoxide opening; 2-Methyl-1,3-diol.
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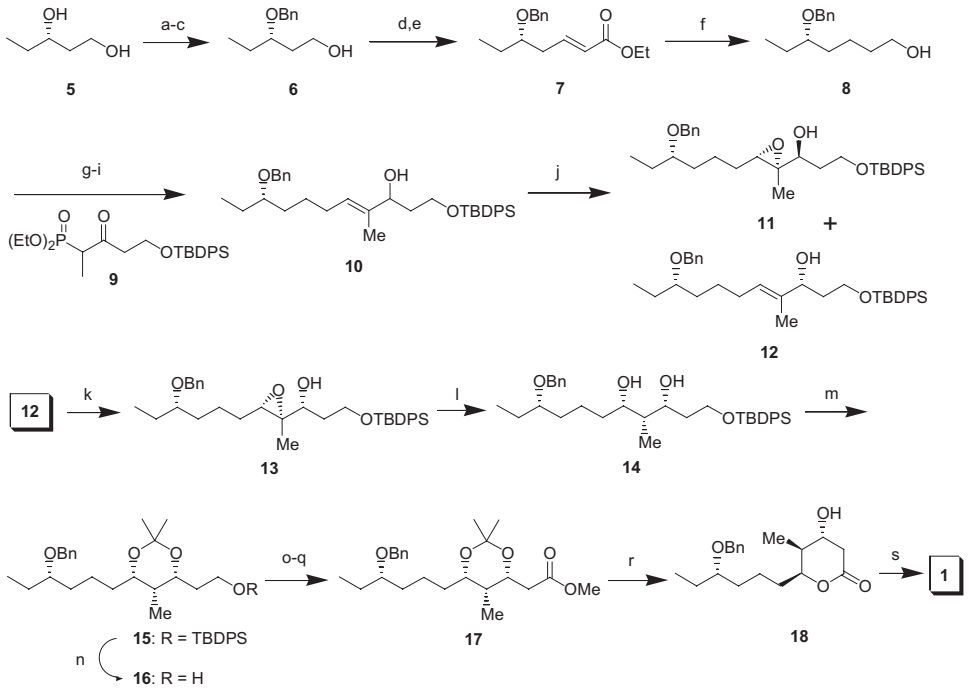

Scheme 1. Stereoselective synthesis of δ-lactone **1**. Reagents and conditions: (a) TBDPSCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 2 h, 98%; (b) BnBr, NaHMDS, THF–DMF (2:1), 0 °C, 1.5 h, 92%; (c) TBAF, THF, 0 °C to rt, 4 h, 98%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 1 h; (e) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 0 °C to rt, 3 h, 96% from **6**; (f) LiCl, $NaBH_4$, EtOH–THF (1:1), rt, 3 d, 62%; (g) same as in step d; (h) compound **9**, *n*-BuLi, THF, −78 °C, 0.5 h, then aldehyde from step g, −78 to 0 °C, 1 h, 95% from **8**; (i) $NaBH_4$, MeOH, 0 °C to rt, 2 h, 62%; (j) $Ti(O^iPr)_4$, (+)-DIPT, TBHP, 4 Å MS (20% w/w), CH_2Cl_2, −23 °C, 40 min, 45% of **12**; (k) *m*CPBA, CH_2Cl_2, 0 °C to rt, 45 min, 53%; (l) cp_2TiCl_2, Zn dust, $ZnCl_2$ (freshly fused), THF, −20 °C to rt, 6 h, 60%; (m) $Me_2C(OMe)_2$, CSA (cat.), CH_2Cl_2, 0 °C to rt, 45 min, 94%; (n) same as in step c, 93%; (o) SO_3–py, Et_3N, DMSO, 0 °C to rt, 1 h; (p) $NaClO_2$, NaH_2PO_4, ^{t}BuOH-2-methyl-2-butene (2:1), rt, 1.5 h; (q) CH_2N_2, ether, 0 °C, 15 min, 84% from **16**; (r) AcOH–H_2O (4:1), 0 °C to rt, 12 h, 76%; (s) H_2, Pd–C (10%), EtOAc, 2 h, 78%.

Swern oxidation[10] of the primary hydroxyl group of **6** furnished an aldehyde, which was reacted with the stabilized ylide $Ph_3P{=}CHCO_2Et$ to give α,β-unsaturated ester **7** (96% from **6**). Ester **7** was reduced using $LiBH_4$, prepared in situ from $NaBH_4$ and LiCl, to the saturated alcohol **8** in 62% yield. Oxidation of **8** to an aldehyde and subsequent the Horner–Wadsworth–Emmons olefination of the resulting aldehyde with the Li-anion of ketophosphonate **9**[11] furnished the trisubstituted *E*-enone (95% from **8**) with complete selectivity and no *Z*-olefin was detected. Next the intermediate enone was reduced with $NaBH_4$ to give the allylic alcohol **10** in 62% yield.

Sharpless kinetic resolution[8] of **10** furnished the chiral unreacted allylic alcohol **12** in 45% yield (92% ee, by the Mosher's ester method[12]). Diastereoselective epoxidation of **12** using *m*-chloroperbenzoic acid (*m*CPBA) gave the *syn* product **13** as the major product in 53% yield and the minor *anti*-isomer could be separated easily by column chromatography.[13] The stereochemistry of **13** was confirmed at a later stage, after opening of the epoxide ring and subsequent protection of the resulting diol, in the acetonide-protected stage. With the trisubstituted epoxy alcohol in hand, the stage was now set to carry out the crucial Ti(III)-mediated epoxide opening step. Treatment of **13** with cp_2TiCl, generated in situ from cp_2TiCl_2 according to the procedure described earlier,[7] provided the expected all-*syn* '2-methyl-1,3-diol'-containing intermediate **14** in 60% yield as the only isolable product.

Protection of the diol in **14** as an acetonide gave compound **15** in 94% yield. The ^{13}C NMR spectrum of **15** showed signals due to the acetonide methyls at 30.08 and 19.21 ppm and the ketal carbon at 98.8 ppm supporting the assigned '1,3-*syn*' stereochemistry of the diol moiety in **15**.[14] Furthermore, the ^3J couplings of 5.0 Hz of $CH(CH_3)$ with adjacent protons on both sides proved the '1,2- and 2,3-*syn*' relationships. Desilylation of **15** furnished the alcohol **16** in 93% yield. Oxidation of the primary hydroxyl of **16** in two steps gave the acid, which was esterified with CH_2N_2 to provide the methyl ester **17** in 84% yield from **16**. Treatment of **17** with acid led to deprotection of the acetonide group with concomitant cyclization to furnish the six-membered lactone **18** in 76% yield. Finally, hydrogenation of **18**, using Pd–C as catalyst, removed the benzyl-protection resulting in the successful completion of the first total synthesis of the target lactone **1** in 78% yield.[15] Our synthetic lactone **1** was identical in all respects with that isolated by Martin et al.[4] While the ^1H NMR is consistent with the reported values, the matching ^{13}C data[15] provides strong evidence that the two materials are the same.

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9. Compound **5** was prepared from the corresponding chiral (2*S*,3*S*)-epoxy alcohol (Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857) by hydride opening with Red-Al and subjecting the mixture of products to an oxidative cleavage reaction using $NaIO_4$ to remove the minor 1,2-diol product.
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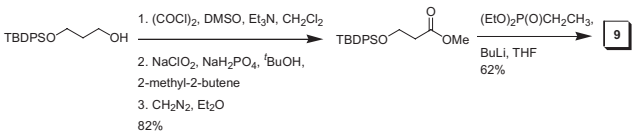

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15. Selected physical data of **1**. $R_f = 0.3$ (silica, 8% MeOH in $CHCl_3$); $[\alpha]_D^{27}$ −35 (*c* 2.5, $CHCl_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 78.0, 73.0, 68.7, 37.4, 36.4, 35.8, 31.7, 30.2, 21.6, 10.2, 9.8; MS (LSIMS) *m/z* (%) 231 (20) $[M+H]^+$, 213 (5) $[M+H-H_2O]^+$, 195 (5) $[M+H-2H_2O]^+$.