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Enantiospecific Synthesis of Tetrasubstituted δ-Lactones

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Abstract

For investigations concerning the selectivity of polyketide synthases (PKSs) which have been rationally engineered through genetic techniques the synthesis of substituted δ-lactones is of great importance. An enantiospecific route towards eight of the possible sixteen stereoisomers was developed which is also readily adaptable for the introduction of alkyl modifications and isotopic labels.

Keywords: Aldol reaction; Asymmetric synthesis; Lactones; Polyketides; Combinatorial Biosynthesis.

Substituted δ-lactones are obtained from biological systems both as natural products (often produced as shunt metabolites from prematurely terminated polyketide biosynthesis)[1] and as 'non-natural' natural products from genetically modified organisms which express hybrid polyketide synthases (PKS) during so called 'Combinatorial Biosynthesis'.[2] During recent studies, enantiopure synthetic standards of substituted δ-lactones were required in order to aid the identification and isolation of novel polyketide products from hybrid PKSs.[3-6] The synthesis of some substituted δ-lactones with consecutive *syn* β-hydroxyl-α-alkyl relationships generated using iterative boron-enolate mediated aldol reactions have been reported previously.[4-6] We present here a general and efficient method for the synthesis of enantiopure substituted δ-lactones, which contain both *syn* and *anti* β-hydroxyl-α-alkyl relationships. The utility of this system is further developed through the demonstration that several alkyl group analogues can be prepared effectively.

In devising a straightforward strategy for the synthesis of δ-lactones **9a-e**, **12**, **19**, and **22** it was decided to use asymmetric boron-enolate chemistry. As the stereocentres at the newly formed α-methyl and β-hydroxyl carbon atoms are always *syn* to one another an Evans type aldol reaction[7] was the obvious choice for the

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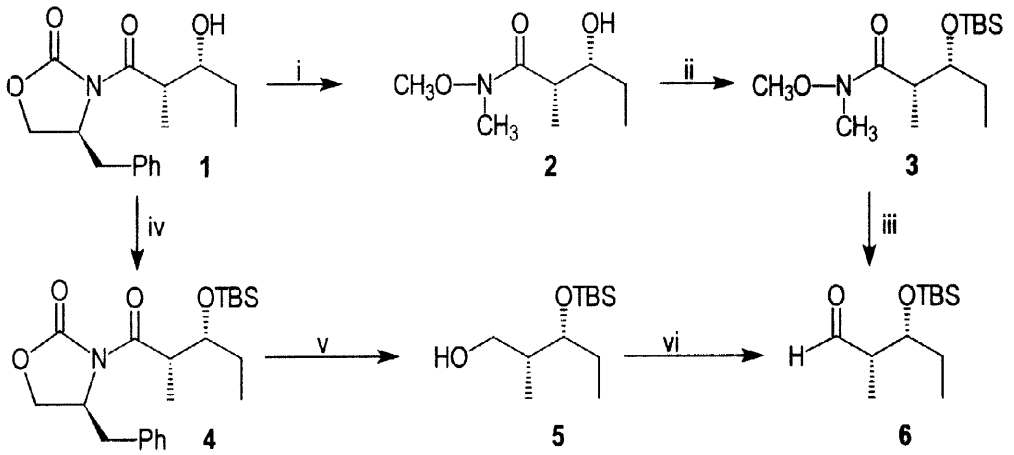
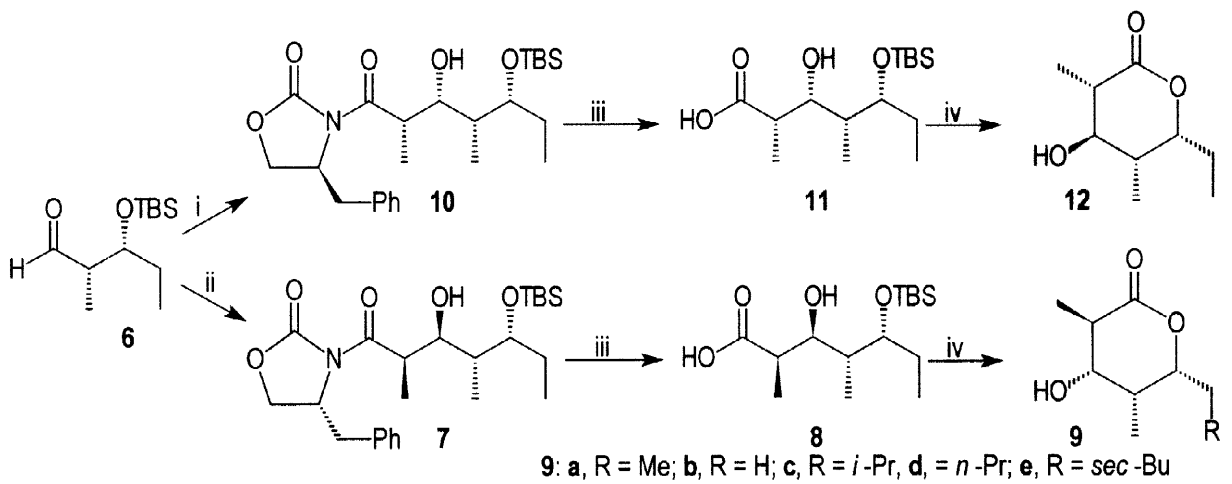
introduction of this structural feature. This holds true for the other chiral centres in lactones **9a-e** and **12**. In the case of the lactones **19** and **22** the relationship between the γ- and δ-stereocentres is *anti*. For the synthesis of these features an alternative approach which has been described by Heathcock[8] was utilised.



Reagents: i 3 eq. MeO(Me)NH·HCl, 3 eq. $AlMe_3$; ii 3.5 eq.TBDMSCl, 0.5 eq. DMAP, 7 eq. imidazole, 95% over 2 steps; iii 2.5 eq. DIBAL-H, 84%; iv 2 eq. Hunig's base, 1.5 eq. TBDMSTf, 100%; v 1.1 eq. H_2O, 1.1.eq. $LiBH_4$, 84%; vi 1.1 eq. Dess-Martin reagent, 97%.

Scheme 1



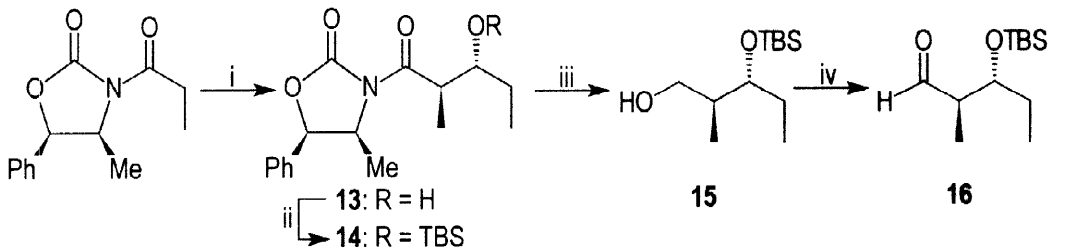
9: **a**, R = Me; **b**, R = H; **c**, R = *i*-Pr, **d**, = *n*-Pr; **e**, R = *sec*-Bu

Reagents: i acylated 4(*S*)-auxiliary, 1.2 eq. Bu_2BOTf, 1.25 eq. Et_3N, 68%; ii acylated 4(*R*)-auxiliary, 1.17 eq. Bu_2BOTf, 1.12 eq. Et_3N, 78%; iii LiOH, H_2O_2; iv 1M HCl, THF, **9a** 74% over 2 steps, **12** 89% over 2 steps .

Scheme 2

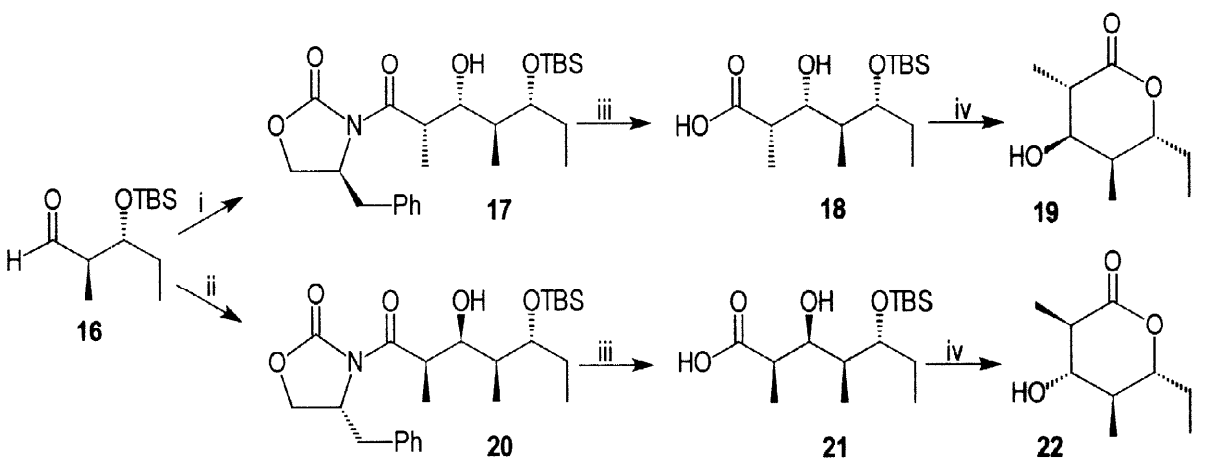
In order to obtain the *syn-syn* lactones **9a-c** and **12** the following procedure was used. The yields given are representative for all lactones **9a-e**. The Evans type aldol product **1** was converted into its Weinreb amide **2** and the crude reaction mixture was then directly protected with *t*-butyldimethylsilyl chloride (TBDMS-chloride) in the presence of imidazole (95%) (Scheme 1, i-iii). Subsequent DIBAL-H reduction gave the unstable aldehyde **6** (84%).[5] Alternatively **1** can be converted into **6** *via* protection,[9] selective reduction[10] and subsequent Dess-Martin oxidation[11] (81% overall yield) (Scheme 1, iv-vi). The aldehyde was then used in a second aldol step with *N*-propionylated (*R*)-4-phenylmethyl-2-oxazolidinone to yield the desired carbon chain **7** in 78% yield with the required stereochemistry (Scheme 2). For the remaining stages of auxiliary

removal, hydroxyl deprotection and cyclisation, several approaches were examined. In a previously reported synthesis the newly formed hydroxyl group at the β-position was protected as the TBDMS ether, the auxiliary removed using LiOH-H_2O_2 and the resulting acid thioesterified. The product was then deprotected and cyclised *in situ* using 49% aqueous HF.[4] This approach contains several apparently unnecessary steps, and while most reactions are described as proceeding smoothly, no yield is given for the second silyl protection reaction which in our hands proceeds exceptionally poorly. Attempts at a one-pot cleavage of the protecting group and auxiliary with concomitant cyclisation were unsuccessful under a variety of conditions. Removal of the auxiliary with LiOH-H_2O_2 followed by sodium sulphite work up and subsequent acidification, to both remove the protecting group and cause cyclisation, was also ineffective. After further detailed investigations we concluded that sodium and lithium salts were one major reason for poor yielding reactions. Our final route required initial cleavage of the auxiliary followed by removal of the volatiles and adjustment of the aqueous layer to pH 1. After extraction with ether and removal of solvent, the extracts were stirred in a (5:1) mixture of 1 M HCl and THF at 40°C. After work up and purification the product δ-lactone **9a** was isolated in 74% yield from **7**. Utilising (*S*)-*N*-propionylated chiral auxiliary, **10** was obtained in 68% yield. Deprotection and cyclisation as above gave the lactone **12** (89%).



Reagents: i 2 eq. Bu_2BOTf, 1.2 eq. Hunig's base, propanal, 64%, ii 2 eq. Hunig's base, 1.5 eq. TBDMSTf, 85%; iii 1.1eq. H_2O, 1.1 eq. $LiBH_4$, 88%; iv 1.1 eq. Dess-Martin reagent, 91%.

Scheme 3



Reagents: i acylated 4(*S*)-auxiliary, 1.25 eq. NEt_3, 1.2 eq. Bu_2BOTf, 55%; ii acylated 4(*R*)-auxiliary, 1.25 eq. NEt_3, 1.2 eq. Bu_2BOTf, 47%; iii LiOH, H_2O_2; iv 1 M HCl, THF, **19** 74%over 2 steps, **22** 70.5% over 2 steps.

Scheme 4

For the lactones **19** and **22** which display an *anti* stereochemistry between the γ- and δ-carbon atoms, Heathcock's approach was chosen.[8] Using two equivalents of dibutylboron triflate the acylated oxazolidinone gave the desired *anti* product **13** in 64% yield (Scheme 3). Following protection of the

hydroxyl group with TBDMS triflate[9] as indicated above, the amide was selectively reduced to the corresponding alcohol using lithium borohydride and one equivalent of water.[10] Subsequent oxidation with Dess-Martin reagent gave the unstable aldehyde **16** in 68% overall yield.[11] **16** was then converted in a *syn* (Evans type) aldol step with acylated (*R*)- or (*S*)-4-phenylmethyl-2-oxazolidinone respectively. Thus the carbon chains **17** and **20** with the stereochemistry of the target lactones were obtained (55 & 47%). After removal of the chiral auxiliary and the TBDMS group and cyclisation as described above, the lactones **19** and **22** were obtained in 74% and 71% yields respectively.

Using the established and highly effective chemistry described above it is possible to access the enantiopure substituted δ-lactones **9a**, **12**, **19**, and **22** in good overall yields. Furthermore, the use of varied aldehydes in the initial aldol step, leading to lactones **9b-e**, [12] in comparable yields, demonstrating the generality of this route.[13] This procedure can be simply modified for synthesis of the enantiomers of **9, 12, 19 and 22** which makes eight of the sixteen stereoisomers of the tetrasubstituted δ-lactones readily accessible. The use of appropriately acylated chiral auxiliaries allows the regiospecific incorporation of isotopic labels and alternative alkyl groups at the C-2 and C-4 positions.

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