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Aldol Reaction of 4-Trimethylsiloxy-6-methylene-1,3-dioxines with Chiral Aldehydes: Enantioselective Synthesis of 1,3-Dioxin-4-ones Having a 2,3-Dihydroxylated Alkyl Group at the 6-Position[1]

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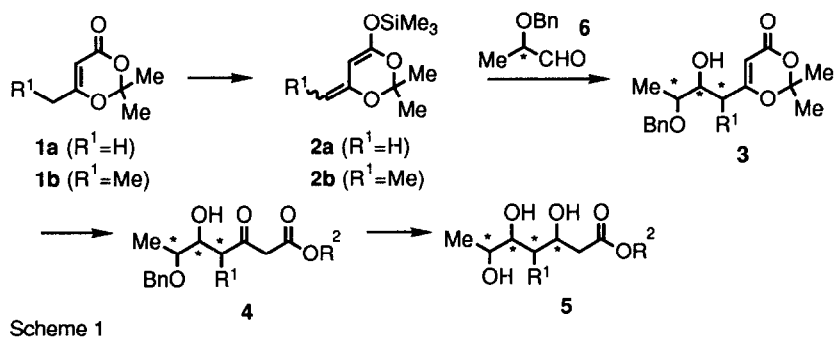
Abstract: A novel enantioselective synthesis of 1,3-dioxin-4-ones having a 2,3-dihydroxylated alkyl group at the 6-position has been accomplished by titanium tetrachloride-mediated aldol condensation of silyl enol ethers derived from the 6-alkylated dioxinones with chiral 2-benzyloxypropanal. The keto group of the corresponding β-keto esters obtained after cleavage of the acetal function affords, by 1,3-*syn* and/or *-anti* reduction, 3,5,6-trihydroxyheptanoic acids in highly enantioselective manner.

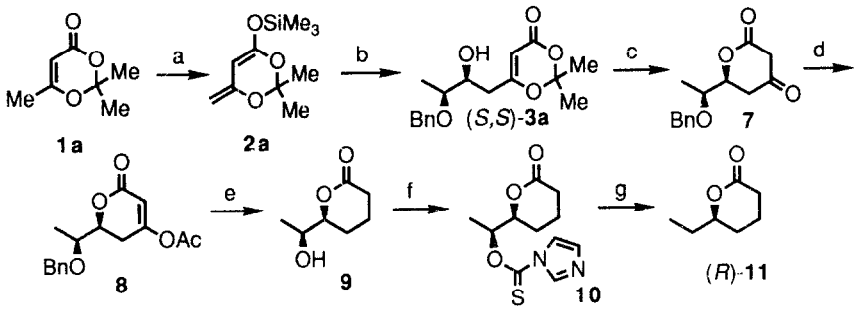
We have been interested in using chiral spirocyclic dioxinones as synthons of enantiomerically pure compounds (EPC).[2] In this communication, we will report highly enantioselective synthesis of 3,5,6-trihydroxyheptanoic acids (**5**) from the 6-alkylated dioxinones (**1**) *via* titanium tetrachloride mediated aldol condensations[3] of silyl enol ethers (**2**) derived from **1** with chiral 2-benzyloxypropanal (**6**),[4] cleavage of the acetal function of the products (**3**) to the dihydroxy-β-keto esters (**4**), and subsequent reduction. This strategy is on firm ground both from the recent synthesis of the silyl enol ether (**2a**: R^1=H),[5] the ready ring cleavage of the dioxinone ring to β-keto esters (**4**) (**3**→**4**)[6] and by the well-settled 1,3-*syn*[7] and *-anti* reductions[8] of β-hydroxyketones (e.g. **4**→**5**).



1a (R^1=H) **1b** (R^1=Me) **2a** (R^1=H) **2b** (R^1=Me) **3** **4** **5**

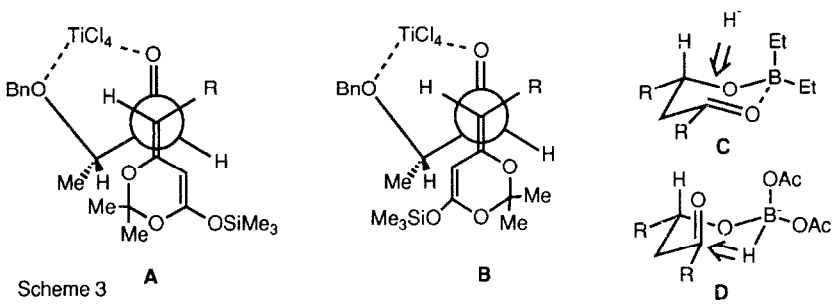
Scheme 1

We have already demonstrated that the silyl enol ether (**2a**) derived from the 6-methyldioxinone (**1a**) affords, when reacted with benzaldehyde or acrolein in the presence of $TiCl_4$, the expected aldol condensation products.[9] Thus, taking **2a** as the substrate, the $TiCl_4$-mediated aldol condensation of (*S*)-2-benzyloxypropanal [(*S*)-**6**] was carried out. As expected from the well-known chelation control, a single product [(*S,S*)-**3a**][10] was obtained in 75% yield as the sole product. In order to determine the absolute configuration unequivocally, the transformation depicted in Scheme 2 was carried out. The δ-lactone [**11**] {$[\alpha]_D^{25}$ +52.2 (c 1.02, THF)} thus



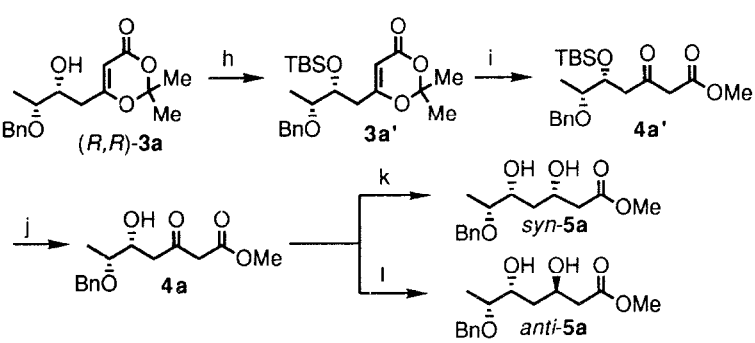
Scheme 2 *Conditions*: a) LDA, TMSCl, THF, -78 °C; b) (*S*)-**6**, $TiCl_4$, CH_2Cl_2, -78°C, 75% from **1a**; c) K_2CO_3, MeOH, 98%; d) AcCl, pyridine, CH_2Cl_2, 91%; e) H_2/Pd-C, HCl, AcOEt, 52%; f) $(imidazoyl)_2C{=}S$, CH_2Cl_2, 68%; g) Bu_3SnH, AIBN, benzene reflux, 68%

formed was determined by comparison with authentic specimen [(*R*)-**11**][11] as having *R*-configuration at the newly formed stereogenic center. This result fits well to the proposed mechanism for the chelation controlled aldol reactions in which **A** and **B** are the possible complexations.[3] Hence, irrespective of the mode of complexations, the newly formed stereogenic center of the aldol condensation product should have *S*-configuration.



Scheme 3

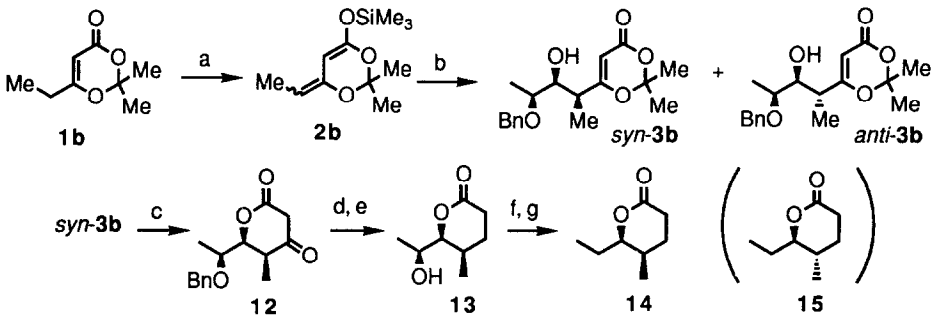
In order to utilize (*S,S*)-**3a** or its enantiomer [(*R,R*)-**3a**] as EPC synthesis of natural product, (*R,R*)-**3a** was synthesized by using (*R*)-**6** in the above aldol condensation. The silylated product (**3a'**) of (*R,R*)-**3a** was converted to the β-keto ester (**4a'**) by heating in toluene containing methanol.[6] Removal of the silyl group of



Scheme 4 *Conditions*: h) *tert*-butyldimethylchlorosilane (TBSCl), imidazole, DMF, 98%; i) MeOH, toluene, reflux, 91%; j) Bu_4NF, THF, 73%; k) $NaBH_4$, Et_2BOMe, THF-MeOH, 86%; l) $Me_4NHB(OAc)_3$, AcOH, 85%

4a' led to the methyl ester (**4a**). Based on the configuration of the C_5-hydroxyl group, two alcohols epimeric to each other at C_3-position were synthesized. Thus, reduction of **4a** with diethylmethoxyborane-$NaBH_4$[7] gave the 3,5-*syn* diol (*syn*-**5a**) as the sole product in 86% yield, while that with tetramethylammonium triacetoxyborohydride[8] afforded a mixture of the *anti* diol (*anti*-**5a**) and the *syn*-diol (*syn*-**5a**) in 85% yield (ratio of *anti*/*syn* = *ca.* 10). It is obvious that the former reaction proceeded by intermolecular sodium borohydride reduction of the borane complex (**C**), while in the latter reaction the hydride shift from the reagent itself in the corresponding complex (**D**) gave directly the final product. Two heptanoates (*syn*- and *anti*-**5a**) thus obtained have been utilized as C7-building blocks for EPC synthesis of amphotericin B and bryostatins 1 and 11, respectively.[12]

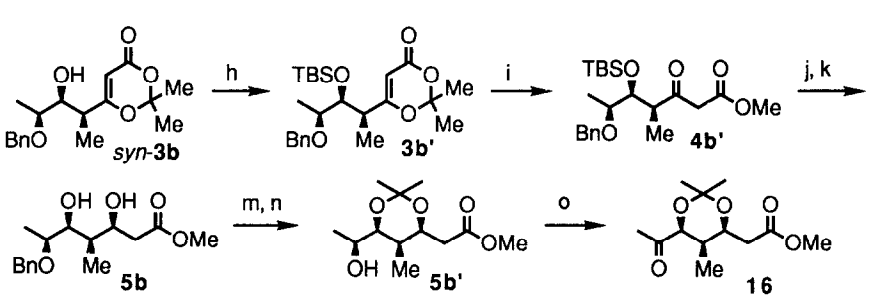
In order to extend this methodology to the synthesis of branched diol side-chain derivatives, we then prepared the silyl enol derivative (**2b**) of the 6-ethyldioxinone (**1b**). The expected silyl enol ether (**2b**) was obtained as a mixture of *E*- and *Z*-isomers in a combined yield of 87%. Though the separation of both isomers had failed due to instability, the same aldol condensation of the mixture (*ca.* 3:1 ratio) with (*S*)-**6** gave *syn*- and *anti*-**3b** in 57% and 9% yields, respectively. It is obvious that the predominant formation of the *syn* adduct is the result of the chelation control (C-2', C-3' *syn*) and *syn* stereoselection between C-1' and C-2' groups (cf. **A** and **B**). The absolute configuration of the newly formed stereogenic centers of the major product (*syn*-**3b**) was



Scheme 5 *Conditions:* c) 77%; d, e) 40% from **12**; f) 73%; g) 83%

determined unequivocally by the transformation to the corresponding δ-lactones (**14**).[13,14] In the same manner, the minor product (*anti*-**3b**) was converted to the *trans* δ-lactone (**15**).[13]

In order to utilize *syn*-**3b** for the EPC synthesis of natural products, its conversion to multifunction-



Scheme 6 *Conditions*: h) 98%; i) 78%; j) 75%; k) 73%; m) $(MeO)_2CMe_2$, $HClO_4$, acetone, 74%; n) H_2/Pd-C, MeOH, quant.; o) $(COCl)_2$, DMSO, Et_3N, 80%

alized heptanoic acid [**16**: the seven-carbon segment (C_{22}~C_{27}) of FK 506[15]] was carried out. Thus, the silylated product (**3b'**) was converted to the β-keto ester (**4b'**). Removal of the silyl group of the latter and subsequent *syn*-reduction afforded the 3,5-diol in 73% yield as a mixture of *syn*-**5b** and its 3-epimer (*syn*/*anti* = 40). Acetonide formation, debenzylation and subsequent oxidation led to the desired heptanoate (**16**).

The present method for the synthesis of enantiomerically pure 3,5,6-trihydroxyheptanoates (**5**) from the readily available dioxinones (**1**) has the following three advantageous features: 1) high d.e. for the aldol condensation step and hence high d.e. of the keto esters (**4**), 2) stereocontrol of the reduction of the keto group of **4** can readily be regulated based on the C-5 hydroxyl group, and 3) it could provide a general diastereo- and/or enantioselective method for the synthesis of alkanoic acids having 3,5,6-trihydroxyl groups as well as their 2-substituted derivatives.

Acknowledgments

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10. All new compounds exhibited satisfactory spectroscopic (NMR, IR) and combustion or high-resolution mass spectral data; Specific rotations were measured in $CHCl_3$. (*S,S*)-**3a**: $[\alpha]_D^{23}$ +4.9 (*c* 2.06); (*R,R*)-**3a**: $[\alpha]_D^{26}$ -5.0 (*c* 1.92); **3a'**: $[\alpha]_D^{22}$ +22.8 (*c* 1.92); *syn*-**3b**: $[\alpha]_D^{21}$ +58.6 (*c* 1.90); *anti*-**3b**: $[\alpha]_D^{23}$ -26.0 (*c* 0.80); **3b'**: $[\alpha]_D^{24}$ -1.9 (*c* 1.87); **4a**: $[\alpha]_D^{23}$ -6.9 (*c* 1.48); **4a'**: $[\alpha]_D^{24}$ +24.9 (*c* 1.53); **4b'**: $[\alpha]_D^{22}$ +6.6 (*c* 1.83); *syn*-**5a**: $[\alpha]_D^{22}$ -19.5 (*c* 1.28); *anti*-**5a**: {80% d.e., $[\alpha]_D^{25}$ -27.7 (*c* 1.93)}; **5b**: {95% d.e., $[\alpha]_D^{20}$ +25.5 (*c* 1.37)}; **5b'**: {95% d.e., $[\alpha]_D^{20}$ -3.1 (*c* 1.36)}; **7**: $[\alpha]_D^{22}$ +14.0 (*c* 1.16); **8**: $[\alpha]_D^{26}$ -75.4 (*c* 1.65); **9**: $[\alpha]_D^{20}$ +34.7 (*c* 1.56); **10**: $[\alpha]_D^{23}$ -26.3 (*c* 1.21); **12**: $[\alpha]_D^{23}$ +61.7 (*c* 1.56); **13**: $[\alpha]_D^{20}$ +70.4 (*c* 1.10); **14**: $[\alpha]_D^{20}$ +62.4 (*c* 1.10), lit.[13]; (5*S*,6*S*) derivertive $[\alpha]_D^{24}$ -65.8 (*c* 1.024); **15**: $[\alpha]_D^{20}$ +43.0 (*c* 1.32), lit.[13]; $[\alpha]_D^{24}$ +49.3 (*c* 1.034); **16**: $[\alpha]_D^{21}$ -47.4 (*c* 1.06).
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