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Erythroselective Aldol Condensation of Amine Free 2-t-Butyl-5-Methyl-2-Phenyl-1,3-Dioxolan-4-one Lithium Enolate Synthesis of the Ethyl Acetolactate Enantiomers

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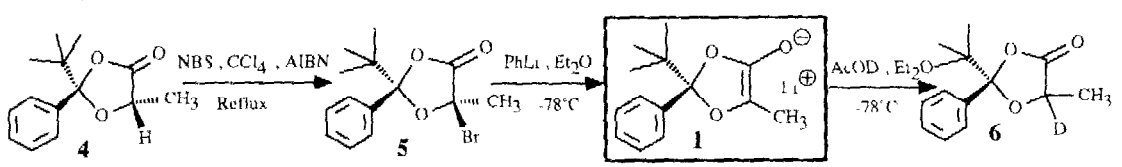
SUMMARY : Generated by halogen metal exchange, the sterically hindered 2-t-butyl-5-methyl-2-phenyl -1,3-dioxolan-4-one lithium enolate reacts in an erythroselective way with acetaldehyde Separation of the resulting diastereomers, followed by alcoholysis lead to the corresponding enantiomerically pure diols

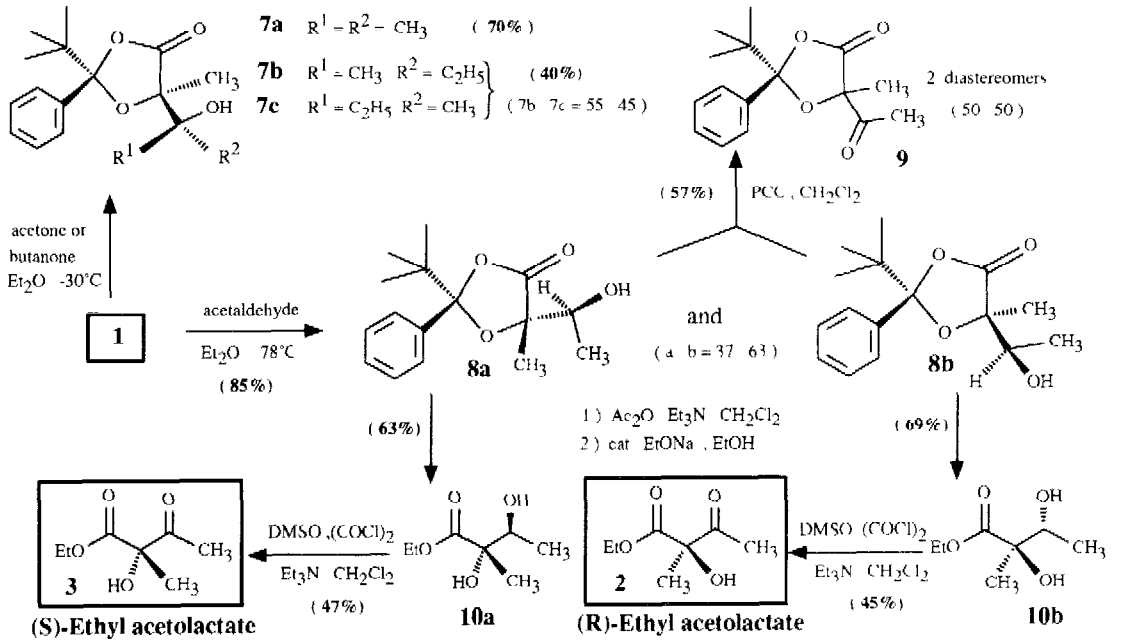
5-Monosubstituted-1,3-dioxolan-4-ones became very popular tools in diastereoselective synthesis in recent years.[1,2] Our previous efforts in the area of diastereoselective dioxolanone formation using an acetal exchange technique, allowed us to prepare with high selectivity, either in weakly or strongly acidic medium,[3] new sterically hindered 2,2-disubstituted-1,3-dioxolan-4-ones, leading in several instances to crystalline derivatives, easy to purify to an enantiomerically pure state We report here our preliminary results on the diastereoselective reactivity of 2-t-butyl-5-methyl-2-phenyl-1,3-dioxolan-4-one lithium enolate **1**, and its application to the preparation of both enantiomerically pure ethyl 2-hydroxy-2-methyl-3-oxo-butyrates **2** and **3** (R- and S- ethyl acetolactates) [4] Previously published synthesis of the corresponding methyl esters required a low yielding resolution step [5,6]

Deprotonation of dioxolanones is usually achieved with strong base (LDA, LHMDS),[7,8] but has proven difficult in some circonstances [9] Deprotonation of **4** followed by quenching with deuterated acetic acid or benzyl bromide,[10] failed to give in good yield α-deuterated dioxolanone or alkylation product [11] Another method of enolate generation had to be devised, able to generate lithium enolate **1** :

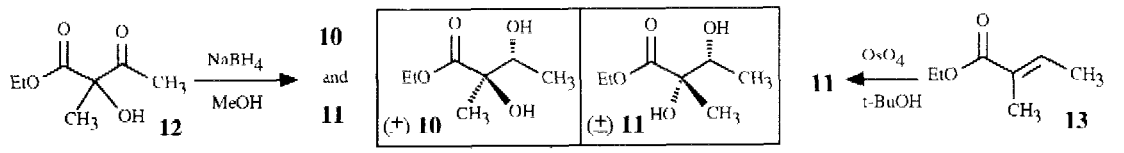


Organometallic reagents have been shown to reduce α-bromocarbonyl derivatives to the corresponding enolates, and these may then be reacted further [12,13] The α-bromodioxolanone **5** was easily obtained from **4** with NBS in CCl_4 at reflux, with AIBN initiation.[14] The radical stabilizing capto-dative[15] center α to the carbonyl facilitates this radical bromination Only one stereomer was observed, with the bromine entering on the least hindered side of the heterocycle, **5** underwent clean halogen metal exchange in ether at -78°C with phenyllithium. Lithium

enolate **1** is consequently generated free of any other reactive species [16,17] Aldol condensation was investigated with acetaldehyde, acetone and butanone.

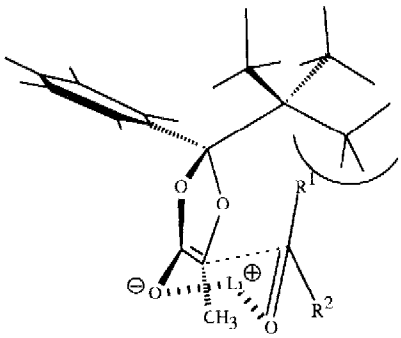


Acetone reacted in a stereoselective manner from the least hindered side to yield a single stereomer **7a** . 2-Butanone gave two diastereomers **7b** and **7c** in a 55·45 ratio,[18] both arising from a similar transition state **II** (R^1= CH_3 or C_2H_5, R^2= C_2H_5 or CH_3), with a small differentiation between methyl and ethyl [18] Acetaldehyde reacted easily to yield two out of four possible diastereomers in a 37·63 ratio [18] To establish the diastereofacial selectivity in this condensation, this isomeric mixture **8a** and **8b** was oxidized with PCC Surprisingly, a diastereomeric mixture of keto-derivatives **9** was obtained (50.50).[18,19] This suggests a stereochemical control of the center β to carbonyl, not α, as would be expected from similar cases[8] and the above results with acetone. This was unambiguously established by opening the diastereomeric mixture of dioxolanones **8a** and **8b** in refluxing ethanol containing a catalytic amount of sodium ethoxide, to a single product **10** (^{1}H and ^{13}C NMR), thus confirming two enantiotopic aldol fragments. A mixture of erythro and threo aldols **10** and **11** (40 60)[18] was prepared by $NaBH_4$ reduction of (±) ethyl 2-hydroxy- 2-methyl-3-oxo-butyrate **12** The racemic threo aldol **11** was selectively obtained by cis- hydroxylation of ethyl tiglate **13** with cat OsO_4/N-methylmorpholine N oxide [20] Comparison of NMR spectra unambiguously confirmed the erythro configuration for **10** . The



absolute configuration of the products was clear from the ^{1}H NMR spectra with the shielding/deshielding effect due to the phenyl and t-butyl substituents in **8** The major isomer **8b** is obtained by the aldehyde entering from the least hindered face (cis to phenyl)

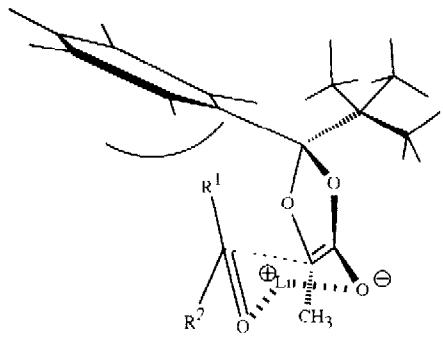
The analysis of the anticipated transition states rationalizes this fact·



Transition State I

disfavored approach

if $R^1 \neq H$



Transition State II

kinetically disfavored approach

if $R^1 \neq H$ and $R^2 = H$

Ketones react only through T.S **II** ($R^1 \neq H$, $R^2 \neq H$) The aldehydic hydrogen, much smaller than methyl, does not interact severely with the bulky t-butyl or phenyl groups (T.S. **I** and **II**, $R^1 = H$), thus allowing aldehydes to approach from both sides of the enolate, but preferably with this hydrogen oriented towards the acetal center. Reaction involving the transition state in which the methyl group is oriented towards the phenyl (T S. **II**, $R^1 = CH_3$, $R^2 = H$), similar to the ketone transition state, is kinetically disfavored, due to steric interaction The consequence of these arrangements is generation of two enantiotopic erythro aldol fragments, the acetal center of the dioxolanone leading to diastereomers.

To obtain both enantiomeric aldols **10a**, **10b**, the diastereomeric mixture of dioxolanones **8a** and **8b** was converted to the acetates (Ac_2O/Et_3N), the resulting diastereomers separated by chromatography on silicagel, and recrystallized (heptane) to purity. Sodium ethoxide catalyzed ethanolysis afforded separately the two erythro aldols **10a**, **10b** and final oxidation (DMSO/oxalyl chloride/Et_3N)[21,22] yielded the (R) and (S) enantiomers **2** and **3**. The enantiomeric purity, investigated with the $Eu(hfc)_3$ shift reagent, was shown to be better than 99% for both enantiomers [23]

Thus, our new methodology for enolate generation from sterically hindered dioxolanones gives access to enantiomeric erythro aldol fragments[24] from aldehydes and chiral α-hydroxy acids. It appears complementary to previously known methods which allow to control the α-center chirality only Further application of this selectivity to the synthesis of biologically important compounds is currently under investigation.

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10. A 86:14 mixture of alkylation products was obtained with a 38% conversion
11. All labile protons may be removed from the reaction medium by adding an extra equivalent of n-butyl lithium Thus technique has also failed in our case See Laube, T., Dunitz, J.D ; Seebach, D. *Helv chim Acta* **1985**, *68*, 1373
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14 Several authors have recently used this technique independently:
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Mattay, J ; Mertes, J ; Maas, G *Chem Ber* **1989**, *122*, 327
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16 Secondary amines present in the reaction medium by basic proton abstraction, strongly coordinate lithium cations and may be involved in the reaction transition states
17. Bromobenzene is in this case the only by-product n-Butyl bromide generated by using n-butyl lithium may act as an alkylating agent. t-Butyl lithium generates one equivalent of LiBr.
18. Ratios are determined by ^{1}H NMR at 250MHz The identity of aldol condensation adducts and the stereofacial selectivity of the reaction was deduced from NOE experiments.
19. The diastereomers underwent this oxidation with different rates.
20 Ray, R ; Matteson, D S. *Tetrahedron Lett* **1980**, *21*, 449
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22 A stoichiometric amount of oxalyl chloride gave a partial conversion, whereas an excess lead to methylthiomethylation of the tertiary alcohol.
23. Racemic ethyl acetolactate was prepared by $KMnO_4$ oxidation of ethyl tiglate according to Crout, D.H G.; Rathbone, D.L. *Synthesis* **1989**, 40. No enantiomer could be detected by NMR in **2** and **3** . Enantiomeric contamination was detected down to 1%
24. Physical data of products ($[\alpha]_D$ ($CHCl_3$); ^{1}H NMR (250MHz, $CDCl_3$); ^{13}C NMR (50MHz, $CDCl_3$); dioxolanones configuration assigned by NOE)

5 (2S) Mp= 160°C, $[\alpha]_D^{21}$ = +80 (c=2), ^{1}H NMR; δ(ppm): 7.48-7.36 (m,5H), 2.27 (s,3H,C$\underline{H}_3$), 0.99 (s,9H,tBu). ^{13}C NMR; δ(ppm): 167.60(4-C); 133 45; 129 20; 127.83; 127 24; 115 81(2-C); 85.91(5-C), 39.60(C(CH$_3$)$_3$), 28 70(5-CH$_3$), 24 15(C(CH$_3$)$_3$),

7a (2R,5R) Mp.92°C, $[\alpha]_D^{21}$ = 0 (c=2); ^{1}H NMR, δ(ppm) 7.53-7 34 (m,5H), 1.59 (s,3H), 1.26 (s,3H), 1.20 (s,3H); 1 05 (s,9H,tBu). ^{13}C NMR; δ(ppm): 173 86(4-C); 140 84; 129 17; 128 36; 113.92(2-C); 86 90, 75 12, 40 37; 25.44, 25.37; 24 91, 20.94

8a ^{1}H NMR, δ(ppm): 7.47-7 41 (m,2H), 7 37-7 32 (m,3H), 4 05 (q,J=6,4 Hz,1H,CH$_3$C$\underline{H}$); 2 98 (s,broad,1H,OH), 1 31 (d,J=6,4 Hz,3H,C$\underline{H}_3$CH); 0 99 (s,9H,tbu), 0.96 (s,3H,5-C$\underline{H}_3$) ^{13}C NMR, δ(ppm) 174 61(4-C); 139 49; 128.94-127.00, 114 13(2-C); 82 23(5-C), 69.75(C$\underline{H}$), 39.26(C(CH$_3$)$_3$); 24.69(C(CH$_3$)$_3$), 17.30, 15.79.

8b ^{1}H NMR; δ(ppm): 7 47-7.41 (m,2H), 7 37-7.32 (m,3H); 3 46 (q,J=6.3 Hz,1H,CH$_3$C$\underline{H}$), 1 96 (s,broad,1H,OH); 1.51 (s,3H,5-C$\underline{H}_3$), 1 11 (d,J=6,3 Hz,3H,C$\underline{H}_3$CH); 0 99 (s,9H,tBu). ^{13}C NMR, δ(ppm). 176 08(4-C), 138 81, 128 94-127.00; 114 13(2-C), 80 36(5-C), 69 82(CH); 39 00(C(CH$_3$)$_3$), 24.68(C(CH$_3$)$_3$), 15 67; 15 46

10 ^{1}H NMR; δ(ppm). 4 25 (q,J=7,2 Hz,2H,C$\underline{H}_2$CH$_3$), 3 80 (s,broad,1H, with TFA added:q,J=6.5 Hz, 1H,C$\underline{H}$CH$_3$), 3 54 (s,1H,OH); 2 45 (s,broad,1H,OH); 1 43 (s,3H,CH$_3$-2), 1.30 (t,J=7,2Hz,3H,CH$_2$CH$_3$); 1 15 (d,J=6.5 Hz,3H,CHC$\underline{H}_3$). ^{13}C NMR; δ(ppm). 175.37(ester), 76.94(C-2), 72.07, 62.01, 22.21, 17.54; 14.04. ^{13}C NMR (50MHz, CD_3SOCD_3); δ(ppm): 174 60(ester); 76 48(2-C), 70 23; 59 75, 20 31, 17.18; 13 81.

11 ^{1}H NMR, δ(ppm): 4.24 (q,J=7,1Hz,2H,C$\underline{H}_2$CH$_3$), 3.92 (s,broad,1H,C$\underline{H}$CH$_3$), 3.51 (s,broad,1H), 2.38 (s,broad,1H); 1.29 (s,3H,2-CH$_3$); 1 28 (t,J=7,1Hz,3H,CH$_2$C$\underline{H}_3$); 1 20 (d,J=6,4 Hz,3H,CH$_3$CH) ^{13}C NMR; δ(ppm) 176.13(ester), 77.06(2-C); 71.50, 61.97; 21.49, 16.49, 13.97.

3 (2S) $Bp_{0.5}$= 55°C (Kugelrohr); $[\alpha]_D^{22.5}$ = +44 (c=0 2), ^{1}H NMR; δ(ppm): 4 25 (q,J=7,1Hz,2H,C$\underline{H}_2$CH$_3$), 4.18 (s,broad,1H,OH); 2.27 (s,3H,C$\underline{H}_3$CO), 1.59 (s,3H,2-C$\underline{H}_3$); 1.29 (t,J=7,1Hz,3H,CH$_3$C$\underline{H}_3$) ^{13}C NMR, δ(ppm). 204 89(ketone); 171 37(ester), 81.00(2-C), 62 65(C$\underline{H}_2$), 24 20, 21.82, 14 03

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