



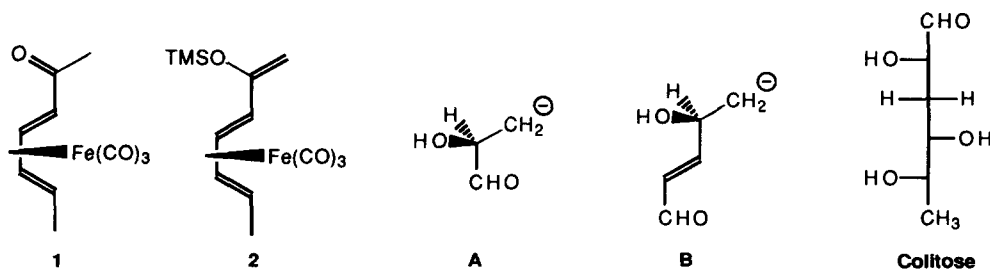
Aldol Condensation Reactions of (Dienone) Tricarbonyliron Complexes. 3¹. Enantioselective Total Synthesis of 3,6-Dideoxyhexoses from Lactaldehyde.

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Abstract: The trimethylsilyl enol ether **2** of racemic (3,5-heptadien-2-one) tricarbonyliron **1** undergoes a completely stereoselective cross aldol reaction with TiCl₄-coordinated (S)-(-)-benzyloxylactaldehyde (-)-**3**, yielding two separable diastereomeric ketols, differing only in the configuration of the metal-ligand attachment (resolution). Both were converted into protected 3,6-dideoxyhexoses [(+)-**16** (R,S,S) and (-)-**17** (S,S,S)] by successive stereoselective reduction into 1,3-diols, transformation into diacetates, decomplexation and ozonolysis. The same dideoxyhexoses, as well as the enantiomeric series, can be obtained from the racemic lactaldehyde and the pure enantiomers of **2**. © 1997 Elsevier Science Ltd.

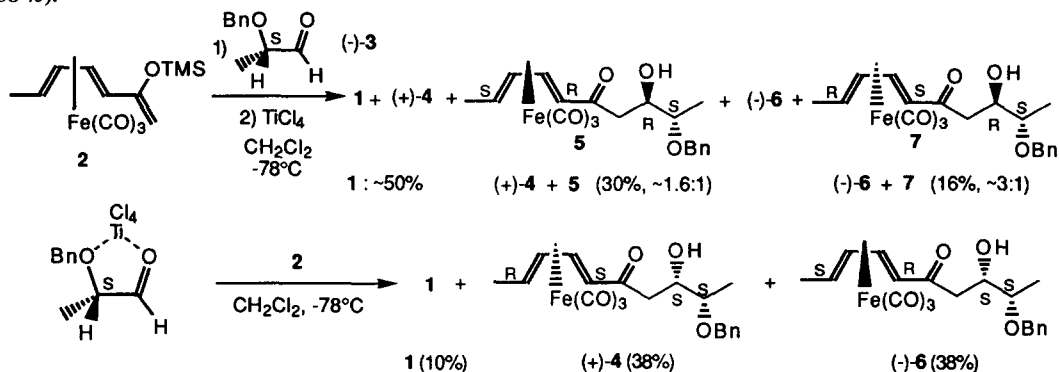
(1-Acetyl diene) tricarbonyliron complexes **1** undergo high yield crossed aldol condensation reactions with aldehydes. The reaction can be achieved with lithium enolates or preferably with silyl enol ethers **2**, where the use of TiCl₄ as a Lewis acid catalyst can dramatically enhance the diastereoselectivity¹. The obtained ketols are totally stereoselectively reduced into 1,3-diols, the selectivity depending only on the metal ($\rightarrow \Psi$ endo alcohols). After decomplexation the diene moiety can be cleaved by ozonolysis, either partially or totally, without any racemization of the alcoholic center². This makes **1** a synthetic equivalent of the chiral synthons **A** and **B** with the advantage of a stereochemical control these non metal-coordinated synthons could not offer.



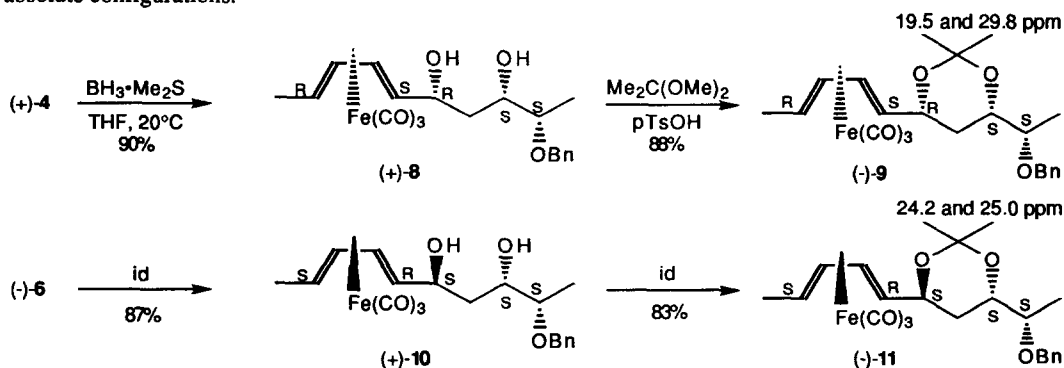
In this paper, we describe an application of this principle to the total synthesis of protected 3,6-dideoxyhexoses, a class of rare sugars which includes compounds such as coltose, isolated from the cell wall of gram negative bacteria³.

The optical activity can be introduced by starting from an enantiomerically pure dienone complex, as previously shown¹, or more interestingly in the present case, by use of an optically active α -hydroxyaldehyde for the aldol condensation reaction, allowing at the same time the resolution of the racemic complex.

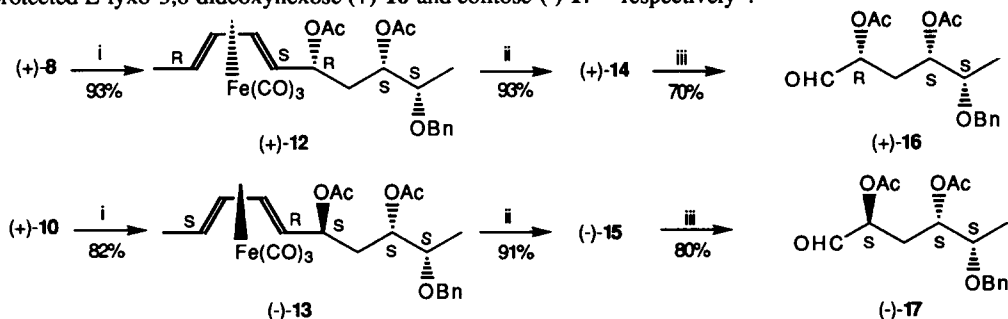
(S)-(-)-Benzyloxylactaldehyde (-)-3⁴ is known to give a highly stereoselective aldol condensation reaction (~96 : 4) with the silyl enol ether of methylketones such as acetophenone when promoted by the chelating Lewis acid TiCl₄⁵. The diastereomer resulting from the attack of the nucleophile from the less hindered side (S,S) is then nearly exclusively formed. We have shown that the reaction of the silyl enol ether of the organometallic ketone (2-acetyl butadiene) tricarbonyliron is in fact totally stereoselective, since only two diastereomers are formed, differing only in the configuration of the metal-ligand attachment⁶. In the present case, the addition of aldehyde (-)-3 to enoxysilane **2**, prepared in situ from dienone complex **1**, followed by addition of TiCl₄ at -78° C led in an incomplete reaction to the formation of four diastereomers [(+)-**4** + **5** (not separated) and (-)-**6** + **7** (not separated)] but the addition of the isolated silyl enol ether **2** to the preformed aldehyde-Lewis acid complex (1.1 equivalents) gave only the diastereomers (+)-**4** (less polar) and (-)-**6** (more polar)⁷ which could easily be separated by silica gel column chromatography (isolated 38 % and 38 %).



The ketols (+)-**4** and (-)-**6** were reduced completely stereoselectively (ca 90 %) and the ψ -endo alcohols (+)-**8** and (+)-**10**⁷ were converted into the acetonides (-)-**9** and (-)-**11**. The relative configurations of the 1,3-diols (+)-**8** (syn) and (+)-**10** (anti) were assigned by means of the ¹³C NMR spectra⁸ of their acetonides⁷ [$\Delta \delta$ of the acetal methyl groups : 10.3 ppm for (-)-**9**, 0.8 ppm for (-)-**11**], thus allowing the assignment of all absolute configurations.

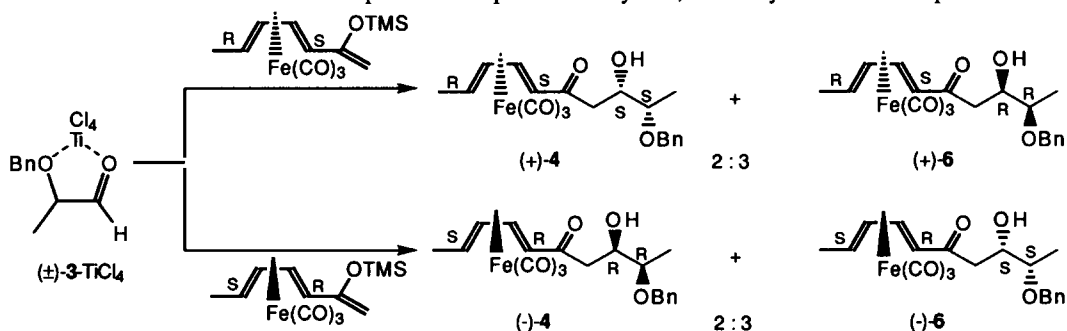


Decomplexation of the acetonides gave the free dienes but the following ozonolysis to aldehydes proceeded with only moderate yields. We therefore transformed the alcohols (+)-8 and (+)-10 into the diacetates (+)-12 and (-)-13 before decomplexation [(+)-14, (-)-15, CAN ~ 90 %]. With this protecting group, ozonolysis in dilute or slightly acidic⁹ methanolic solution, followed by in situ reduction (Me₂S) yielded the protected L-lyxo-3,6-dideoxyhexose (+)-16 and colitose (-)-17¹⁰ respectively⁷.

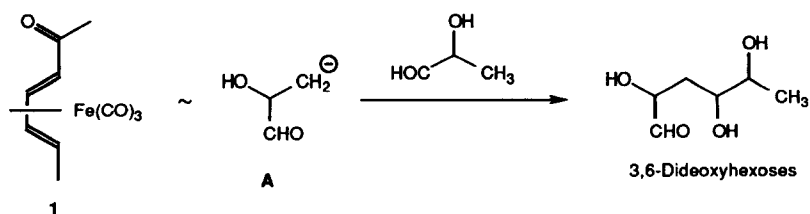


i : Ac₂O, Et₃N, DMAP, CH₂Cl₂, 20°C ii : CAN, MeCN-H₂O, 0°C iii : 1) O₃, MeOH, -78°C 2) Me₂S

The other way to introduce the optical activity, which is more general although less interesting in the present case (availability of optically active lactaldehydes) was also investigated. We studied therefore the reaction of the TiCl₄-coordinated racemic aldehyde (±)-3 with the silyl enol ethers of the enantiomerically pure dienone complexes (+)-1 (3*S*,6*R*) and (-)-1 (3*R*,6*S*)¹. We obtained from the former the separable ketols (+)-4 and (+)-6 [19 % and 29 %, isolated along with 24 % recovered (+)-1] and from the latter the ketols (-)-4 and (-)-6 [21 % and 31 %, isolated along with 20 % recovered (-)-1]. The two new ketols (+)-6 and (-)-4 would lead with a similar reaction sequence to the protected D-lyxo-3,6-dideoxyhexose and abequose¹¹.



The crossed aldol condensation reaction of (hepta-3,5-diene-2-one) tricarbonyliron with lactaldehydes therefore opens up a convenient access to 3,6-dideoxyhexoses. Interestingly these sugars can be considered as unusual dimers of lactaldehyde and in the present synthesis were formally obtained this way :



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References and Notes :

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7. Selected data : (+)-**4** : C₂₀H₂₂FeO₆ (C,H), orange oil ; (-)-**6** : C₂₀H₂₂FeO₆ (C,H), orange oil ; (+)-**8** : C₂₀H₂₄FeO₆ (C,H), yellow oil ; (-)-**9** : C₂₃H₂₈FeO₆ (C,H), orange oil ; (+)-**10** : C₂₀H₂₄FeO₆ (C,H), yellow oil ; (-)-**11** : C₂₃H₂₈FeO₆ (C,H), orange oil ; (+)-**16** : C₁₇H₂₂FeO₆ (C,H), colorless oil ; (-)-**17** : C₁₇H₂₂O₆ (C,H), colorless oil ; [α]_D (c=1, CHCl₃) : (+)-**4** +184, (-)-**4** -189, (-)-**6** -192, (+)-**6** +194, (+)-**8** +7.5, (-)-**9** -23, (+)-**10** +21.5, (-)-**11** -47, (+)-**16** +5, (-)-**17** -20 ; IR (CCl₄, cm⁻¹) ν (C≡O) : (+)-**4** : 2059, 1998, 1982 ; (-)-**6** : 2059, 1994, 1982 ; (+)-**8** : 2043, 1962 ; (-)-**9** : 2047, 1982, 1968 ; (+)-**10** : 2046, 1969 ; (-)-**11** : 2047, 1982, 1968 ; ν (C=O) : (+)-**4** : 1670 ; (-)-**6** : 1671 ; (+)-**16** : 1746 ; (-)-**17** : 1746 ; ν (OH) : (+)-**4** : 3582 ; (-)-**6** : 3584 ; (+)-**8** : 3527 ; (+)-**10** : 3461 ; ¹H-NMR (CDCl₃, 200 MHz, ppm/TMS, Hz) : (+)-**4** : δ = 1.22 (d, 3H, J = 6.3), 1.24 (dd, 1H, J = 1.0 and 8.1), 1.47 (m, 1H), 1.48 (d, 3H, J = 5.8), 2.55 (d, 2H, J = 6.1), 2.89 (d, 1H, J = 4.3), 3.52 (dq, 1H, J = 4.9 and 6.3), 4.01 (m, 1H), 4.45 (d, 1H, J = 11.7), 4.64 (d, 1H, J = 11.7), 5.24 (dd, 1H, J = 5.0 and 7.7), 5.78 (ddd, 1H, J = 0.9, 5.7 and 8.0), 7.26-7.34 (m, 5H, arom) ; (-)-**6** : δ = 1.21 (d, 3H, J = 6.3), 1.25 (dd, 1H, J = 0.9 and 8.0), 1.48 (m, 1H), 1.48 (d, 3H, J = 5.9), 2.56 (d, 2H, J = 6.2), 3.02 (d, 1H, J = 4.1), 3.51 (dq, 1H, J = 4.9 and 6.3), 4.00 (m, 1H), 4.47 (d, 1H, J = 11.7), 4.66 (d, 1H, J = 11.7), 5.24 (dd, 1H, J = 5.1 and 8.0), 5.79 (ddd, 1H, J = 1.0, 5.0 and 8.0), 7.26-7.36 (m, 5H, arom) ; (+)-**8** : δ = 0.99 (dd, 1H, J = 6.0 and 8.2), 1.12 (m, 1H), 1.20 (d, 3H, J = 6.2), 1.41 (d, 3H, J = 6.3), 1.64-1.73 (m, 2H), 3.05 (d, 1H, J = 2.7), 3.33 (s, 1H), 3.41 (quint., 1H, J = 6.3), 3.69 (m, 1H), 3.91 (m, 1H), 4.44 (d, 1H, J = 11.4), 4.68 (d, 1H, J = 11.4), 5.04 (dd, 1H, J = 5.0 and 8.6), 5.24 (dd, 1H, J = 5.0 and 8.6), 7.26-7.40 (m, 5H, arom) ; (+)-**10** : δ = 1.01-1.14 (m, 2H), 1.20 (d, 3H, J = 6.2), 1.41 (d, 3H, J = 6.3), 1.66-1.76 (m, 2H), 2.61 (d, 1H, J = 3.8), 2.86 (d, 1H, J = 3.3), 3.45 (quint., 1H, J = 6.3), 3.64 (m, 1H), 3.86 (m, 1H), 4.44 (d, 1H, J = 11.5), 4.68 (d, 1H, J = 11.5), 5.03 (dd, 1H, J = 5.0 and 8.7), 5.16 (dd, 1H, J = 5.0 and 8.6), 7.26-7.40 (m, 5H, arom) ; (+)-**16** : δ = 1.17 (d, 3H, J = 6.4), 2.02 (s, 3H), 2.14 (s, 3H), 2.22 (t, 2H, J = 6.2), 3.65 (dq, 1H, J = 4.0 and 6.4), 4.48 (d, 1H, J = 12.0), 4.65 (d, 1H, J = 12.0), 5.06 (t, 1H, J = 5.8), 5.16 (dt, 1H, J = 4.0 and 6.8), 7.24-7.39 (m, 5H, arom), 9.50 (s, 1H) ; (-)-**17** : δ = 1.17 (d, 3H, J = 6.4), 1.89 (ddd, 1H, J = 2.8, 11.0 and 14.7), 2.06 (s, 3H), 2.16 (s, 3H), 2.24 (ddd, 1H, J = 3.3, 10.8 and 14.7), 3.64 (dq, 1H, J = 4.1 and 6.4), 4.47 (d, 1H, J = 11.9), 4.65 (d, 1H, J = 11.9), 5.01 (dd, 1H, J = 3.3 and 11.0), 5.13 (ddd, 1H, J = 2.7, 4.1 and 10.7), 7.23-7.40 (m, 5H, arom), 9.50 (s, 1H) ; ¹³C-NMR (CDCl₃, 100 MHz, ppm/TMS) : (-)-**9** : δ = 14.9, 19.1, 19.5, 29.8, 34.5, 57.0, 65.1, 70.7, 71.7, 71.8, 76.7, 80.1, 85.4, 98.8, 127.4, 127.7, 128.3, 139.1 ; (-)-**11** : δ = 15.3, 19.1, 24.2, 25.0, 37.0, 57.0, 65.7, 65.8, 68.2, 69.9, 71.7, 79.9, 85.0, 100.6, 127.4, 127.7, 128.3, 139.0.
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10. No contamination of (+)-**16** by (-)-**17** or vice versa was observed : the decomplexation and ozonolysis steps proceeded therefore without any epimerization.
11. Starting from the other protected lactaldehyde enantiomer (R)-(+)-**3**¹² and the racemic complex **1** one would also obtain the ketols (-)-**4** and (+)-**6**.
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