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Enantioselective Synthesis of a Bicyclic Ketal Induced by Chiral Sulfoxides : (-)-(1*R*, 3*R*, 5*S*)-*endo*-1,3-Dimethyl-2,9-Dioxabicyclo-[3,3,1]-Nonane.

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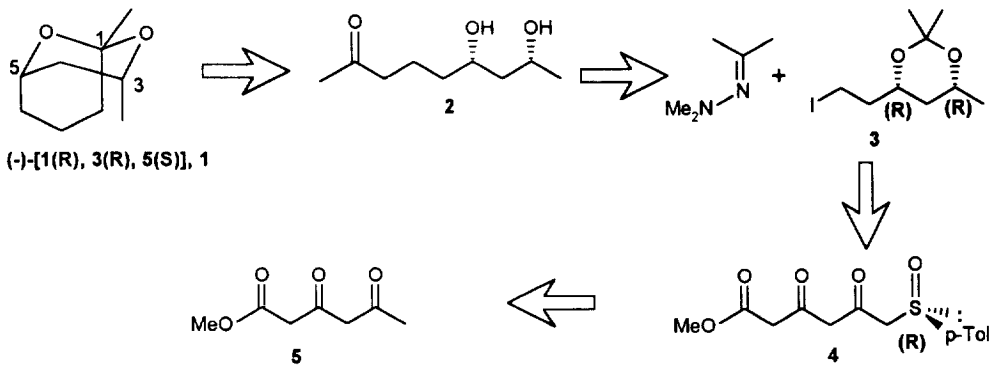
Abstract: The bicyclic ketal, (-)-(1*R*,3*R*,5*S*)-1,3-dimethyl-2,9-dioxabicyclo-[3,3,1]-nonane, was prepared by a short enantioselective reduction of an enantiomerically pure β,δ-diketosulfoxide.

Endo-1,3-dimethyl-2,9-dioxabicyclo [3,3,1]-nonane, **1**, is a host specific substance for the ambrosia beetle *Trypodendron lineatum* Oliver that infests the bark of the Norway Spruce. It was isolated and identified in 1976 by Heemann and Francke[1] from extracts of the bark of trees attacked by this beetle. However, neither the absolute configuration nor the specific rotation have not been reported. Since then, many stereoselective syntheses of the racemate[2] and both enantiomers[3] have been published. Most of the preparations of the optically active stereomers started from the chiral pool or from optically active precursors obtained via enzymatic reactions[4]. There is untill now only one report[3j] describing an asymmetric synthesis of compound **1**, using a sultam to induce the chirality.

We report in this paper an efficient enantioselective synthesis of **1** induced by a chiral sulfoxide group. The strategy of the synthesis is shown in the retrosynthetic Scheme I. The dihydroxyketone **2**, precursor of the acetal **1** can be readily prepared by coupling the anion of the N,N-dimethyl hydrazone of acetone and the dihydroxyiodide **3**. Compound **3** contains a *syn*-diol functionality which can be obtained by reduction of a diketosulfoxide as we have shown in our previous work[4]. We reported[5] also different ways to prepare enantiomerically pure diketosulfoxides. Following these results the diketoester **5** was the best precursor of **4**.

The diketoester **5** was obtained in one step from commercially available dehydroacetic acid by a known procedure[6]. Condensation of the trianion of **5**, prepared in THF with one equivalent of NaH and 2 equivalents of t-BuLi at 0°C to (-)-menthyl (S)-*p*-toluenesulfinate[7] afforded in high yield the (*R*)-diketosulfoxide **4** (Scheme II). As expected[4], only the δ-carbonyl was entirely enolized (one vinylic hydrogen giving a singlet at 5.65 ppm).

Scheme I



Following our previous results[4], reduction with DIBAL (2 eq. in THF at -78°C) gave only one diastereomer of **6**[8]. The relatively low yield of isolated product is due to some decomposition of the product during the chromatographic purification. The absolute configuration 3(*R*),S(*R*) of compound **6** was deduced from our previous results[4] and will be confirmed by correlation with the known compound **1**.

In the next step the δ-carbonyl was reduced to the syn diol **7** with $Et_2BOMe/NaBH_4$[9] in a quantitative yield and >95% d.e. (only one stereomer was detected by ^1H NMR[10]). Protection of the diol and desulfurization with Raney Nickel gave the ester **8** which was reduced to a primary alcohol and transformed into the corresponding iodide. Finally condensation with the anion of N,N-dimethyl hydrazone of acetone followed by hydrazone and acetonide hydrolysis with amberlist 15 afforded the bicyclic acetal **1** showing all the characteristics of the known product. The specific rotation of this highly volatile material, which was difficult to purify, was in the range of the literature values [3d-g, 3j] (between -35.6 and -46.5).

This enantioselective synthesis of the bicyclic ketal **1** is one of the shortest ever reported. It could be very easily applied to the preparation of all the others stereoisomers just by changing the absolute configuration of the starting sulfoxide and either forming the *syn*- or *anti*-diol by known procedure[4b].

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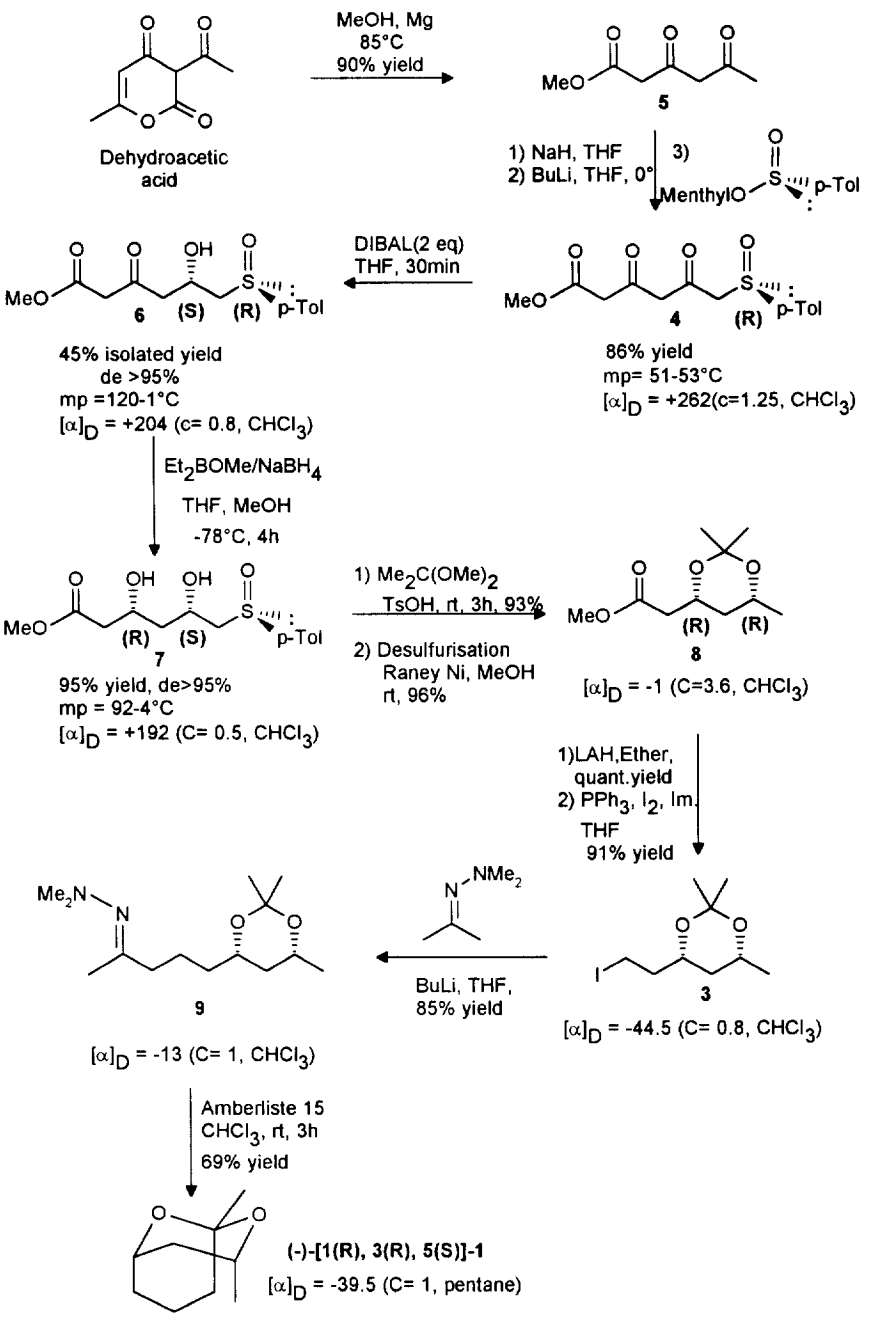
Scheme II


MeOH, Mg
85°C
90% yield
Dehydroacetic acid
5
1) NaH, THF
2) BuLi, THF, 0°
3)
MenthylO
p-Tol
DIBAL(2 eq)
THF, 30min
6 (S) (R) p-Tol
4 (R) p-Tol
45% isolated yield
de >95%
mp =120-1°C
[α]D = +204 (c= 0.8, CHCl3)
86% yield
mp= 51-53°C
[α]D = +262(c=1.25, CHCl3)
Et2BOMe/NaBH4
THF, MeOH
-78°C, 4h
7
95% yield, de>95%
mp = 92-4°C
[α]D = +192 (C= 0.5, CHCl3)
1) Me2C(OMe)2
TsOH, rt, 3h, 93%
2) Desulfurisation
Raney Ni, MeOH
rt, 96%
8
[α]D = -1 (C=3.6, CHCl3)
1)LAH,Ether,
quant.yield
2) PPh3, I2, Im.
THF
91% yield
3
[α]D = -44.5 (C= 0.8, CHCl3)
BuLi, THF,
85% yield
9
[α]D = -13 (C= 1, CHCl3)
Amberliste 15
CHCl3, rt, 3h
69% yield
(-)-[1(R), 3(R), 5(S)]-1
[α]D = -39.5 (C= 1, pentane)

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8) ^{1}NMR of **6** ($CDCl_3$, 200 MHz): δ : 2.42 (s, 3H), 2.79 (d, 2H, J=6.5 Hz), 2.90 (AB part of ABX, 2H, J_{AB}= 13.5 Hz, J_{AX}=2.5 Hz, J_{BX}= 9.5 Hz, Δν=59 Hz), 3.48 (s, 2H), 3.71 (s, 3H), 4.22 (d, 1H, J=3.5 Hz), 4.62 (m, 1H), 7.41[(AB)2, 4H, J_{AB}=8.O Hz, Δν=35 Hz].

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10) ^{1}NMR of **7** ($CDCl_3$, 200 MHz): δ : 1.53–1.76 (m, 2H), 2.42 (s, 3H), 2.45 (m, 2H), 2.85 (AB part of ABX, 2H, J_{AB}=13.5 Hz, J_{AX}= 2.5 Hz, J_{BX}=9.5 Hz, Δν= 80 Hz), 3.69 (s, 3H), 3.88 (d, 1H, J=2.5 Hz), 4.30 (m, 1H), 4.47 (m, 1H), 4.67 (d, 1H, J=1.5 Hz), 7.43 [(AB)2, 4H, J_{AB}= 8.0 Hz, Δν= 34 Hz].

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