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Asymmetric Synthesis of *cis*-Hydrindanediones by Diels-Alder Reaction of Cyclopentenones Bearing a 3-Sulfonyl-1,3-Oxazolidine Ring as Chiral Auxiliary[∞]

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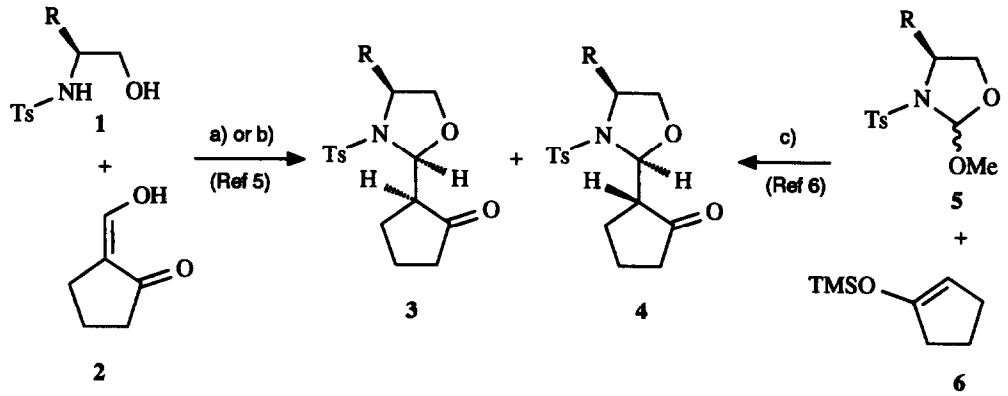
Key words: Asymmetric Diels-Alder reaction, chiral 2-cyclopentenones, chiral 1,3-oxazolidines

Abstract: The Diels-Alder reaction of enantiomerically pure 2- and 5-(1,3-oxazolidin-2-yl)-2-cyclopentenones **8** or **14** and 2-(trimethylsilyloxy)-1,3-butadiene **9** under Lewis-acid catalysis yields (after hydrolysis) protected 3,7-dioxohydrindane-carbaldehydes **11** or **16**, respectively.

Asymmetric Diels-Alder reactions[1)] of cyclopentadiene with open-chain dienophiles attached to chiral auxiliaries are numerous[2)]. The opposite combination of an achiral diene and a chirally modified cyclopentene has been used only occasionally[3,4)]. We now report on a facile method which leads to (protected) *cis*-annulated dioxohydrindane-carbaldehydes by this strategy using oxazolidine-substituted cyclopentenones as the dienophile.

The enantiomerically pure cycloalkanones **3** or **4** are accessible diastereoselectively either by condensation of the β-hydroxyalkyl-sulfonamides **1** with 2-(hydroxymethylene)cycloalkanones[5)] **2** or from 2-methoxy-1,3-oxazolidines **5** and silyl enol ethers **6**[6)] (Scheme 1)

Scheme 1

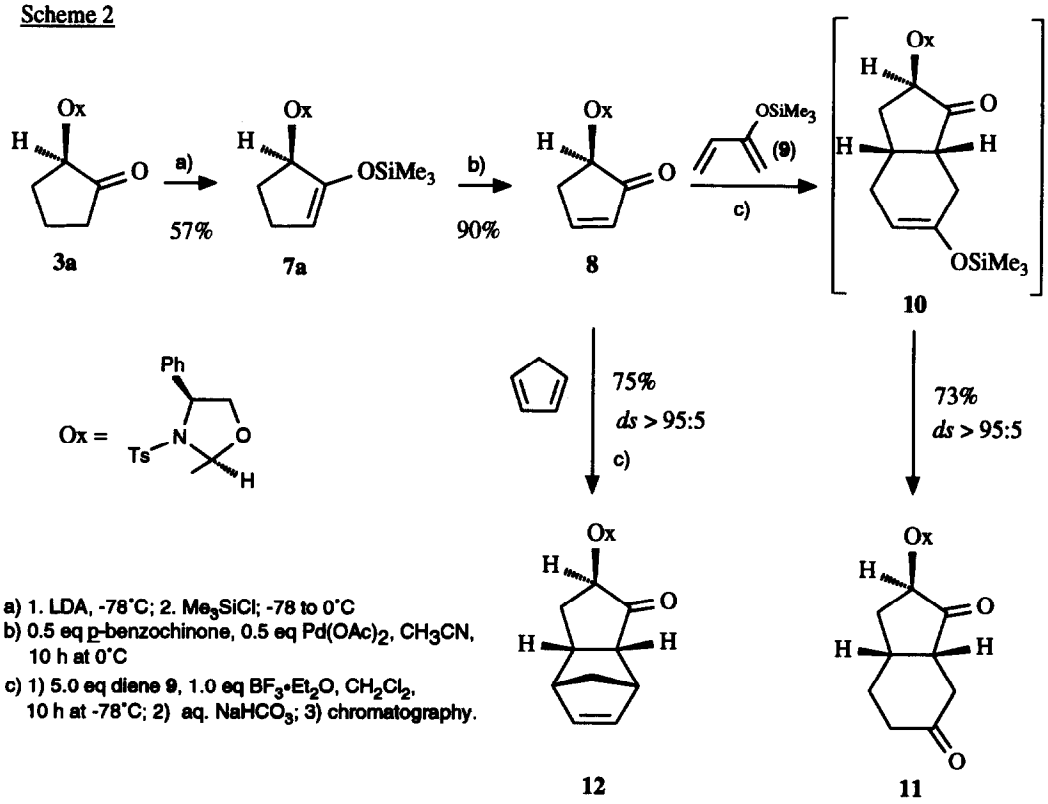


a) CH_3SO_3H, CH_2Cl_2, 0°C; b) $(CH_3)_2SiCl_2$, CH_2Cl_2, 0°C; c) $CF_3SO_3SiMe_3$, CH_2Cl_2, -78°C

The cyclopentanone **3a**[5b)], derived from (*R*)-phenylglycinol, was converted into its kinetic TMS enol ether **7**[7,8)] and oxidized to the cycloalkenone **8** by the method of Saegusa and coworkers[9)] (Scheme 2). The boron trifluoride mediated addition of **8** to 2-(trimethylsilyloxy)-1,3-butadiene[10)] proceeded smoothly at -78°C to afford **10** which yielded diketone **11**[11)] as a single diastereomer after hydrolytic workup. Similarly, with

cyclopentadiene, the norbornene **12** was obtained. Its stereostructure was elucidated NMR-spectroscopically by the combined application of NOESY and restrained MD calculations[12].

Scheme 2

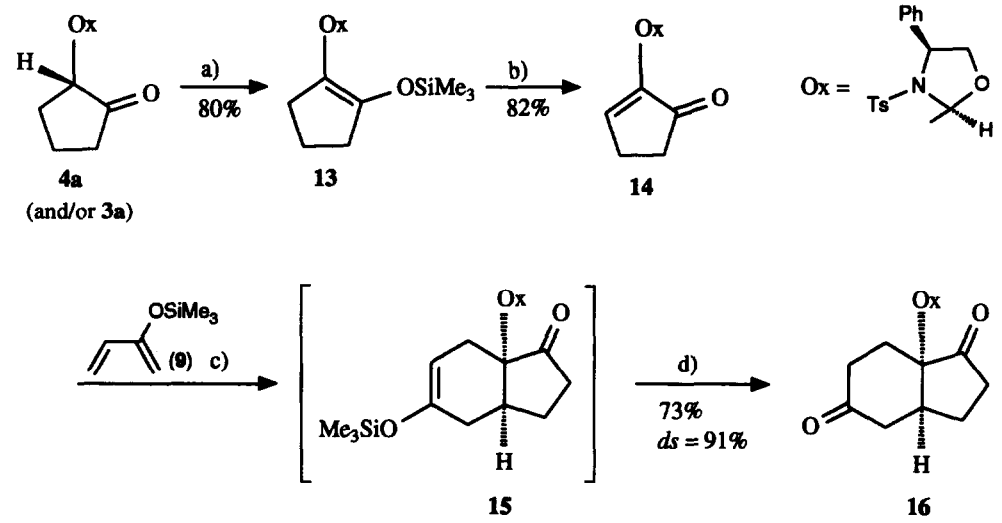


a) 1. LDA, -78°C; 2. Me_3SiCl; -78 to 0°C
b) 0.5 eq p-benzochinone, 0.5 eq $Pd(OAc)_2$, CH_3CN, 10 h at 0°C
c) 1) 5.0 eq diene **9**, 1.0 eq $BF_3 \cdot Et_2O$, CH_2Cl_2, 10 h at -78°C; 2) aq. $NaHCO_3$; 3) chromatography.

In the cycloaddition of **8**, the stereochemical course is directed by the stereogenic center in the cyclopentenone ring, where the front face is shielded by the bulky oxazolidine residue. Now the extent to which the oxazolidine ring, attached to a non-stereogenic cyclopentenone ring, is capable of inducing a diastereofacial differentiation was investigated. Enone **14**[8] could be prepared either from the thermodynamic silyl enol ether **13**[8] - formed from **4a** or **3a** (or mixtures thereof) - by the Saegusa method[9] or via the bromination/dehydrobromination procedure[13]. The reaction of **14** with diene **9** gave rise to a 91 : 9 mixture, from which the major diastereomer **15**[11] afforded pure diketone **16**[11] after desilylation with tetrabutylammonium fluoride and recrystallization (Scheme 3).

16 was subjected to a single-crystal X-ray structure analysis[14] (Figure 1). Figure 2 suggests a rationalisation for the observed stereochemistry. The diene **9** approaches the complex **14**•BF_3 from the less shielded rear half-sphere in an *endo*-mode. The chosen combination offers a good compromise between minimized steric interaction and electrostatic attractions of the sulfonyl oxygen atoms and the complexed positively charged enone moiety. Bonding interactions of the σ C-N or C-O bonds with the π* orbital in the transition state are considered to be relatively unimportant in this situation.

Scheme 3



a) Me_3SiCl, LiI, NEt_3, 5 h, THF, reflux; b) 0.5 eq p-benzoquinone, 0.5 eq $Pd(OAc)_2$, 10 h at 0°C, CH_3CN; c) 5.0 eq **9**, 1.0 eq $BF_3 \cdot Et_2O$, CH_2Cl_2, 24 h at -78°C; d) 1) 1 eq n-Bu_4NF, 1 h at -10°C, THF, 2) LC; crystallization from EtOAc-pentane; 64% pure **16**.

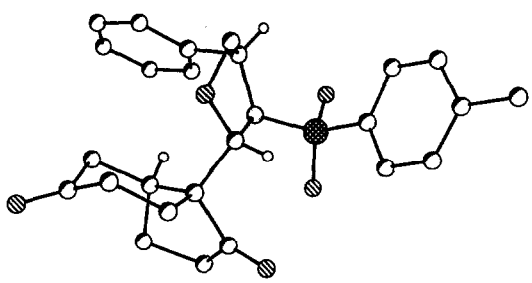


Figure 1:
Structure of the major conformer **16** in crystal[14)]

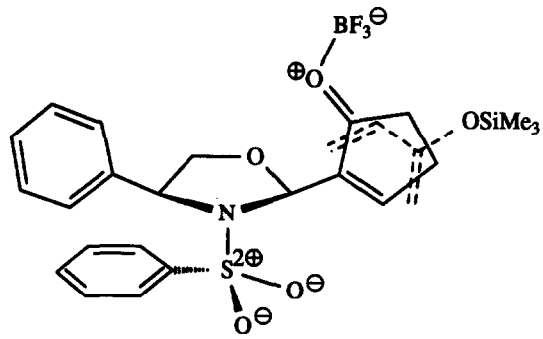


Figure 2:
Proposed transition state in the reaction of **14** and **9**

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∞ Dedicated to Professor Wolfgang Steglich on the occasion of his 60th birthday.

References and Footnotes

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8) All compounds were obtained analytically pure and characterized by ^{1}H NMR, ^{13}C NMR, IR. **7**: colourless oil, $[\alpha]_D^{20}$ = +67.6 (*c* = 1.0, $CHCl_3$]; **13**: colourless oil, $[\alpha]_D^{20}$ = +38.8 (*c* = 1.0, $CHCl_3$]; **8**: mp 182°C, $[\alpha]_D^{20}$ = +45.9 (*c* = 1.0, $CHCl_3$]; **14**: colourless oil, $[\alpha]_D^{20}$ = +87.3 (*c* = 1.0, $CHCl_3$].

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11) All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR. **11**: mp 62°C, $[\alpha]_D^{20}$ = +86.3 (*c* = 1.0, $CHCl_3$]; 300 MHz ^{1}H-NMR ($CDCl_3$, δ): 1.837 (ddd, J_{gem} = 13.5 Hz, $J_{4a,5a}$ = 8.7, $J_{4a,5a}$1H, 4-H_a), 1.866 - 2.155 (m, 2H), 2.20 (m, 2H), 2.33 - 2.40 (m, 2H), 2.46 (s, 3-H, Tos-CH_3), 2.42 - 2.51 (m, 2H), 2.71 (m, 1H), 3.30 (ddd, $J_{1,5}$ = 10.2, $J_{1,9a}$ = 2.0, $J_{1,9b}$ = 1.8 Hz, 1H, 1-H), 3.58 (dd, $J_{34,35Si}$ = 6.6, $J_{35Si,35Re}$ = 9.1 Hz, 35-H_{Si}), 4.10 (dd, $J_{34,35Re}$ = 2.4 Hz, 35-H_{Re}), 4.74 (dd, 34-H), 5.33 (d, $J_{3,32}$ = 2.9 Hz, 32-H), 7.26 - 7.45 (m, 7H, 34-Ph, 31-Tos-3- and 5-H), 7.70 (d, *J* = 8.4 Hz, 31-Tos-2- and 6-H); **12**: mp 152°C, $[\alpha]_D^{20}$ = -57.9 (c = 1.0, $CHCl_3$]; **15**: mp 175°C, $[\alpha]_D^{20}$ = +25.6 (*c* = 1.0, $CHCl_3$].

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14) X-ray crystallographic analysis of **16**: $C_{25}H_{27}NO_5S$ (MW = 453.5), monoclinic, space group $P2_1$, a= 895.7(2)pm, b= 1321.1(1)pm, c= 974.6(2)pm, β= 107.09(1)°, V= 1.102nm^3, Z= 2, ρ_{calc}= 1.366gcm^{-3}, $\mu(CuK_\alpha)$= 1.575mm^{-1}.
A crystal measuring 0.1x0.2x0.5mm grown from an ethyl acetate/hexane solution was used. Intensities were collected with $2° \le 2\theta \le 120°$ at 293K on an Enraf Nonius CAD4 diffractometer with graphite monochromated CuK_α radiation (λ= 154.18pm). A total of 1843 intensities were measured which were merged to 1688 independent reflections, of which 1673 were considered to be observed ($|F_O| > 3\sigma(F_O)$).
The structure was solved by extracting the position of the sulfur atom from a sharpened Patterson list and extending the structure with a tangent expansion. The SHELXTL PLUS program system was used for structure solution, refinement and graphical representation. Refinement of 308 parameters converged at R= 0.039, R_w=0.053 and goodness-of-fit=3.09: (data to parameter ratio=5.4). The correct absolute configuration was confirmed by η-refinement (η=1.2(2)). The structure contains two conformations differing in the bicyclic residue (static disorder, ratio 2:1).
Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Karlsruhe GmbH, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the deposition number CSD-56 183, the names of the authors and journal citation.

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