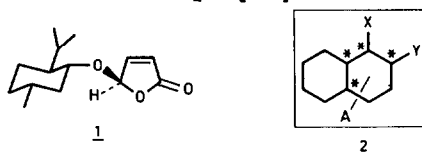


ASYMMETRIC SYNTHESIS OF DECALINES AND HEXAHYDROINDANES

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Summary: The intermolecular Diels Alder reactions of 5-menthyloxy-2[5H]-furanone with 1-vinylcyclohexenes, 1,2-dimethylenecyclohexane and 1-vinylcyclopentenes result in enantiomerically pure decalines and indanes with upto four(!) new asymmetric centers created in a single operation.

The development of efficient methodology for the preparation of optically active substituted 5,6- and 6,6- alicyclic compounds continues to be an important goal in asymmetric synthesis due to the presence of these ring systems in numerous bioactive substances. Among the many approaches the proline catalyzed asymmetric aldol cyclization (Hajos Parrish reaction)¹ and intramolecular Diels Alder reactions² have been highly successful. In this paper new routes with absolute stereocontrol, to substituted decalines and indanes are presented based on intermolecular Diels Alder reactions of enantiomerically pure 5-menthyloxy-2[5H]-furanone (1).


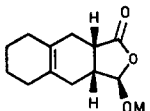

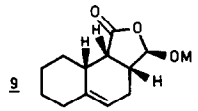

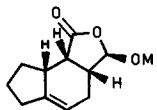

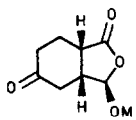
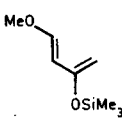
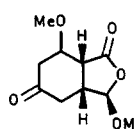


Previously³ we have shown that optically pure substituted cyclohexenes and norbornenes are readily obtained via cycloadditions of 1,3-dienes and cyclopentadiene with butenolide 1. As part of our endeavours directed towards the total synthesis of Forskolol⁴ and related compounds we considered the intriguing possibility of the formation of enantiomerically pure decalines 2 with four new asymmetric centers in a single operation.

In order to establish the regioselectivity and absolute stereocontrol in Diels Alder reactions of 1⁵ with vinyl-cyclohexenes, -cyclopentenes and siloxy-substituted dienes we investigated dienes 3-7 (table I)^{6a}. It must be emphasized that in all cases enantiomerically pure adducts are obtained.^{6b} Thus employing 1,2-dimethylenecyclohexane (3)⁷ 2,3-substituted-9,10-dehydrodecaline 8 was formed. Endo diastereofacial addition of 1 to 3 had taken place as is deduced from the singlet observed for the acetal hydrogen in the ¹H NMR spectrum of 8. Similar reactions of 1 with dienes 4 and 5⁸ lead to 9 and 10 respectively with three new asymmetric centers generated in

the addition step. The regio- and endo-selectivity was proven by extensive 2D Cosy ^1H NMR analyses of 9 and 10. Most significant are the 1,4 relationships that are established between H_9 (for 9) or H_8 (for 10) and the acetal hydrogen and the absence of a proton-proton coupling ($J < 1\text{Hz}$) for the acetal hydrogen confirming the all cis relationship of the hydrogen atoms and the menthoxy-substituent at the chiral centers.

Table Diels-Alder reactions with (1)-5-Menthoxy-2-[5H]-furanone (1)
(OM = (1)-menthoxy-)

diene ^a	product	yield % ^b	$[\alpha]_D^{20}$
<u>3</u> 	<u>8</u> 	51	-218.0 (c 0.98, $\text{C}_2\text{H}_5\text{I}_2\text{O}$)
<u>4</u> 	<u>9</u> 	70	-175.7 (c 1.0, CH_2Cl_2)
<u>5</u> 	<u>10</u> 	77	-129.0 (c 1.0, CH_2Cl_2)
<u>6</u> 	<u>11</u> 	66	—
<u>7</u> 	<u>12</u> 	77	<u>12a</u> -124.5 (c 1.08, CH_2Cl_2) <u>12b</u> -199.9 (c 1.0, CH_2Cl_2)

a. Dienes 3-7 were prepared according to literature procedures⁷⁻⁹.

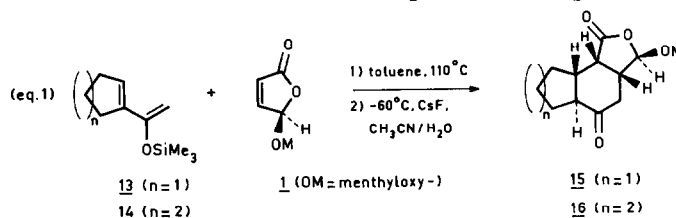
b. Isolated yield.

c. After treatment of DA adduct with $(\text{nBu})_4\text{NF}$ in ether.

d. After treatment of DA adduct with $(\text{nBu})_4\text{NF}$ in ether followed by chromatography; 12a, α -OMe isomer, 12b, β -OMe isomer.

The high regioselectivity with 4 and 5 is mainly attributed to steric effects. Cycloadditions of trimethylsilyloxybutadiene 6 and Danishefski's diene 7⁹ also proceed regioselective; not unexpected considering the diene HOMO's. Although 6 gives a single diastereoisomer (66% yield), two diastereoisomeric adducts (2:1 ratio, epimeric at the carbon atom bearing the MeO-substituent)¹⁰ were obtained with diene 7. Treatment of these

adducts with $(n\text{Bu})_4\text{NF}$, followed by flash chromatography (Silica, CH_2Cl_2) in the case of 7, provided 3,4-substituted cyclohexanone 11 and 3,4,5-substituted cyclohexanones 12a, 12b.⁶ As further functionalization of 11 and 12 is easily conceivable this route gives access to various chiral cyclohexanone synthons. Next we extended the cycloaddition to 1-(1-trimethylsilyloxyvinyl)-cycloalkenes 13 and 14 readily obtained from the corresponding enones using LDA, THF/ Me_3SiCl . Treating these dienes with equimolar amounts of 1 and hydrolysis of the resulting silylenoethers in situ at -60°C with CsF in wet acetonitrile afforded enantiomerically pure 15 and 16 (80% and 70% yield respectively)⁶. ^1H NMR indicated the stereochemistry at the chiral centers as depicted in eq. 1. It must be



emphasized that only the trans fused ring systems are formed in the hydrolysis step and furthermore that the trans relationship between H_a and the acetal hydrogen ($J = 4.5$ Hz (15); $J = 0.9$ Hz (16)) is in accordance with an endo-selective cycloaddition.¹¹ The absolute stereochemistry of 15 and 16 was confirmed by single crystal X-ray analysis.¹² The structure of 1⁶ is shown in figure 1. These results show that in a "one pot" procedure enantiomerically pure 1,2,4-trisubstituted-decalines and hexahydroindanes with four consecutive new chiral centers can be generated in high yields. The application in natural product synthesis of this highly efficient methodology for optically active carbocyclic systems is currently in progress.

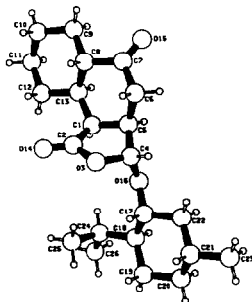


Figure 1. ORTEP plot of 16

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6. a. All products showed correct elemental analyses and IR, ^1H - and ^{13}C NMR and HRMS data in accordance with the structures shown; 1 $[\alpha]_{\text{D}}^{20}$ -136.8° (c 1.00, CHCl_3); b. The enantiomeric purity was based on 300 MHz ^1H NMR analyses of the (1)-5-menthyloxy-2[5H]-furanone adducts, in case a epimeric mixture of 1 was used clearly distinctable diastereomeric adducts are observed.
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11. Chiroptical data of 15: $[\alpha]_{\text{D}}^{20}$ -159.6° (c 0.228, CH_2Cl_2); 16: $[\alpha]_{\text{D}}^{20}$ -155.8° (c 1.520, CH_2Cl_2).
12. Details of the crystal and molecular structure determination will be published elsewhere. We thank Mr. F. van Bolhuis for his contributions to this work.
13. These investigations were supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

(Received in UK 5 April 1990)