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REGIO- AND STEREOSELECTIVE CONTROL IN THE ALKYLATION OF 1-ALKOXY-1,4-CYCLOHEXADIENES BY THE CHIRAL AUXILIARY APPROACH. ENANTIOSELECTIVE SYNTHESIS OF PRECURSORS FOR CIS-HYDRINDANES.

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Abstract : A method is described for the regio- and diastereoselective alkylation of optically active 1-alkoxy-1,4-cyclohexadienes. Reaction conditions were optimised for substrates **4a** with the per-O-methyl-β-D-glucopyranosyl group as chiral auxiliary. In the methylation reaction diastereoselectivities ≥ 90 % were obtained for the resulting 6-methyl-1-alkoxy-1,4-cyclohexadienes **6a**. The accompanying 6-methyl-1-alkoxy-1,3-cyclohexadienes **7a** were not found in similar systems studied before. Alkylation with functionalised electrophiles gives highly enantioselective access to precursors for cis-hydrindanes, such as (+)-**20** and (+)-**23**.

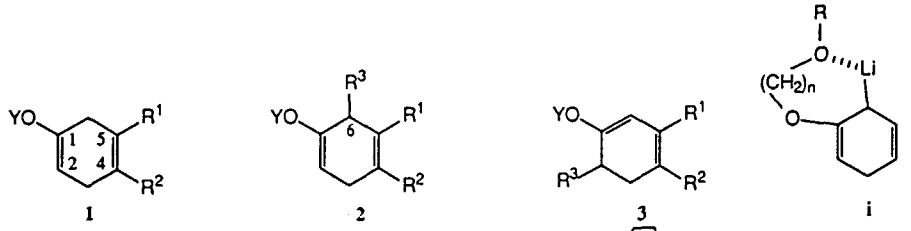
INTRODUCTION

Birch reduction and subsequent alkylation of chiral aromatic compounds offer interesting perspectives for the synthesis of optically active carbocyclic natural products. During the course of our work Schultz et al. reported efficient diastereoselective alkylations of optically active amides derived from ortho-substituted benzoic acids and L-prolinol, thereby making use of the carbonyl group as regiocontrolling element[2]. In this communication we wish to describe an enantioselective variant of Sutherland's method for alkylation of the 1-alkoxy-1,4-cyclohexadiene **1a** (figure 1). The chelating amine function controls the regioselectivity in the alkylation of lithiated anions leading to the 1,4-cyclohexadienes 2[3]. However, we observed (vide infra) that the regiocontrol is not complete, as also 1,3-cyclohexadienes **3** are found.

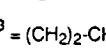
Our exploratory study involved chiral auxiliaries derived from tetrahydrofurfuryl alcohol[4] (**1b**), 2,3-isopropylideneglycerol[5] (**1c**), 3(S)-hydroxytetrahydrofuran[6] (**1d**) and 4(R)-hydroxy-3,3-dimethyltetrahydrofuran[7] (**1e**). The derived lithiated anions will form a seven-membered ring chelate (**i**; n = 2). The R- and S-enantiomers of **1b** and **1c** can, if of value, be obtained[8]. Furthermore, compounds **1b** and **1d** were compared with the respective aza-analogues **1f**[9] and **1g**[10]. A six-membered ring lithiated chelate (**i**; n = 1) prevails by using the per-O-methyl-β-D-glucopyranosyl group as chiral auxiliary. Some preliminary data, obtained with substrates **4a-c** (scheme 1), have already been reported[11]. We now describe the results obtained during the optimisation of the regio- and diastereoselectivities.

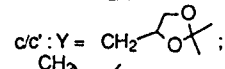
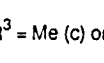
RESULTS AND DISCUSSION

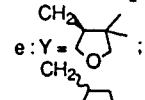
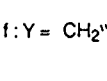
It was soon realised that one-pot Birch reduction - alkylation was unsuccessful. Therefore, substrates **1** were isolated and deprotonated again, in diethyl ether or tetrahydrofuran, under argon because of facile oxidation of the anions. At temperatures >-50°C, up to 50 % of aromatic products were obtained via lithium hydride elimination[12].

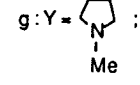


1 2 3 i

a : Y = $(CH_2)_2NEt_2$; R^1 = Me; R^2 = H; R^3 = $(CH_2)_2$-CH=CH_2. b : Y =  ; $R^1 = R^2$ = H; R^3 = Me.

c/c' : Y =  ; $R^1 = R^2$ = H; R^3 = Me (c) or Bn (c'). d/d' : Y =  ; $R^1 = R^2$ = H; R^3 = Me (d) or i-Pr (d').

e : Y =  ; $R^1 = R^2$ = H; R^3 = i-Pr. f : Y =  ; $R^1 = R^2$ = H; R^3 = i-Pr.

g : Y =  ; $R^1 = R^2$ = H; R^3 = i-Pr. h : Y = $(CH_2)_2NEt_2$; R^1 = H; $R^2 = R^3$ = Me.

i : Y = $(CH_2)_2OMe$; R^1 = H; $R^2 = R^3$ = Me. j : Y = $(CH_2)_2NEt_2$; $R^1 = R^2$ = H; R^3 = $(CH_2)_3$-CH=$C(CH_3)_2$.

Figure 1

Table 1 : Alkylation[a] of compounds 1a-j

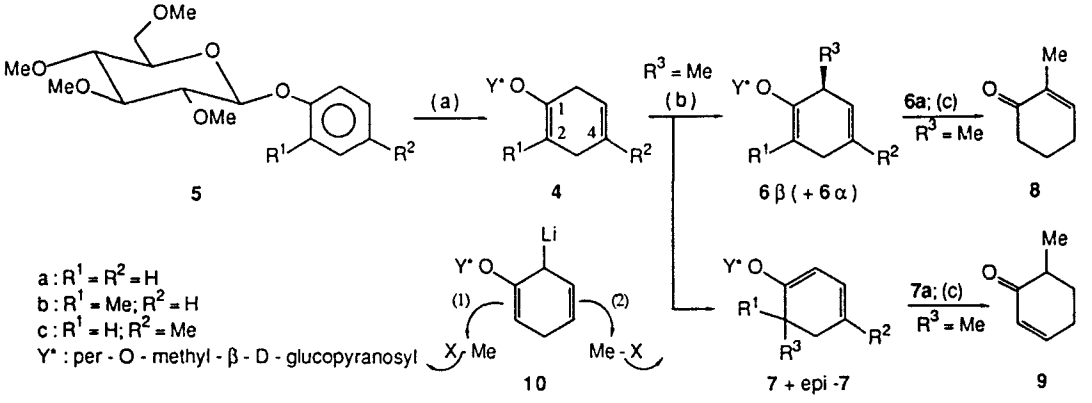
Entry	Substrate	Main product	Regioselectivity[b]	% De[c]	Total yield (%)	Solvent	Temperature (°C)	Alkylating reagent
1	**1b**	**2b**	7.3	23	92	THF	-78	MeI
2	**1b**	**2b**	8.1	35	90	Et_2O	-78	MeI
3	**1c**	**2c**	6.7	10	85	THF	-78	MeI
4	**1c**	**2c'**	5.7	15	75	THF	-78	BnBr
5	**1d**	**2d**	5.7	26	90	THF	-78	MeI
6	**1d**	**2d**	19.0	30	90	Et_2O	-78	MeI
7	**1d**	**2d'**	19.0	30	90	THF	-78	i-PrI
8	**1d**	**2d'**	>100	60	90	Et_2O	-78	i-PrI
9	**1d**	**2d'**	49.0	24	90	THF TMEDA[d]	-78	MeI
10	**1e**	**2e**	5.7	10	50	THF	-60	i-PrI
11	**1e**	**2e**	>100	20	40	Et_2O	-50	i-PrI[e]
12	**1f**	**2f**	19.0	18	88	THF	-50	i-PrI
13	**1f**	**2f**	>100	33	60	Et_2O	-50	i-PrI
14	**1g**	**2g**	19.0	24	85	THF	-50	i-PrI
15	**1g**	**2g**	>100	36	66	Et_2O	-50	i-PrI
16	**1h**	**2h**	4.6	-	90	THF	-78	MeI
17	**1i**	**2i**	4.6	-	92	THF	-78	MeI
18	**1i**	**2i**	8.1	-	90	Et_2O	-78	MeI
19	**1a**	**2a**	>100	-	84	THF HMPA[d]	-78	4-Bromobut-1-ene[f]
20	**1j**	**2j**	>100	-	100	THF HMPA[d]	-78	6-Bromo-2-methyl-2-hexene[g]

a : Standard conditions : 1.3 equiv sec-BuLi, 0.5 h, 4 equiv alkylating reagent, 5 min, unless otherwise noted; b : ratio of **2**:**3**; c : only for 1,4-cyclohexadiene diastereoisomers **2**; d : cosolvent; e : tert-BuLi as the base; f : n-BuLi as the base; see ref. 3b; g : n-BuLi as the base; see ref. 18b.

The best results were found with the β-D-glucopyranosides **4a-c**, but we will first comment on the diastereoselectivities observed for substrates **1** (table 1, figure 1). The regio- and diastereoselectivities, mentioned in table 1, have been determined from the relevant ^{1}H NMR data and GC-MS analyses.
In all cases the expected 6-methyl-1-alkoxy-1,4-cyclohexadienes **2** were accompanied by substantial amounts (up to 18 %; entries 16 - 17) of the isomeric 6-methyl-1-alkoxy-1,3-cyclohexadienes of general formula **3**. Alkylation of **1b** under standard conditions gave **2b** in poor diastereoselectivity although the less basic diethyl ether proved to be superior to THF as solvent (entries 1-2). The presence of two oxygen functions in addition to a gem-dimethyl group (entries 3-4) or the use of a chiral auxiliary with a secondary ether linkage (entries 5-9) and of its gem-dimethyl homologue (entries 10-11) did not result in high diastereoselectivities. Also, the aza-analogues **1f** and **1g** gave low % de for the isopropylated products **2f-g**. Comparison of **1d** and **1g** suggests that substitution of oxygen for nitrogen in the chiral inductor has a negative effect on the diastereoselectivity (compare entries 8 and 15). It is of interest to note that with isopropyl iodide the formation of the 1,3-cyclohexadienes **3** was largely suppressed and that diethyl ether was in general the better solvent.

The per-O-methyl-β-D-glucopyranosyl group as chiral auxiliary

These poor results led us to concentrate our efforts solely on the per-O-methyl-β-D-glucopyranosyl group as chiral inductor (table 2, scheme 1), for which we had already observed more encouraging results[11]. The parent substrate (-)-**4a** was conveniently prepared by permethylation of the commercially available phenyl β-D-glucopyranoside, followed by Birch reduction of the mixed phenoxyacetal **5a**. The C-2 and C-4 methylated substrates were obtained from acetobromo-α-D-glucopyranose. Nucleophilic substitution at the anomeric position with the appropriate potassium cresolate[13], saponification of the acetates[14], per-O-methylation and Birch reduction of **5b-c** gave the 1-alkoxy-1,4-cyclohexadienes (-)-**4b** and (-)-**4c** (scheme 1).



(a) Li, NH_3 liq, tert - BuOH, THF; (b) see table 2; (c) HCl, THF.

Scheme 1

In order to realise sufficiently fast deprotonation at low temperatures, sec-BuLi was used (see footnotes tables 1 and 2). Although we later found (vide infra) that LDA was a far superior base, introductory experiments with this base failed.

Table 2 : Alkylation[a] of substrates 4a-c with the per-O-methyl-β-D-glucopyranosyl group as chiral auxiliary (sec-BuLi as the base).

Entry	Substrate	Main product	Regioselectivity[b]	% De[c]	Total yield (%)	Solvent	Temperature (°C)	Alkylating reagent
1	**4a**	**6a**	4.9	44	74	THF	-78	MeI
2	**4a**	**6a**	2.3	40	58	THF	-78	MeI[d]
3	**4a**	**6a**	3.8	78	34	Et_2O	-78	MeI
4	**4a**	**6a**	3.8	79	34	PhMe	-78	MeI
5	**4a**	**6a**	3.8	50	57	DME	-78	MeI
6	**4a**	**6a**	3.8	28	70	THF/HMPA[e]	-78	MeI
7	**4a**	**6a**	4.6	48	72	THF	-100	MeI
8	**4a**	**6a**	3.3	20	50	THF	-20	MeI
9	**4a**	**6a**	7.3	10	68	THF	-78	MeBr
10	**4a**	**6a**	5.7	8	68	THF	-78	MeOTs
11	**4a**	**6a**	4.9	40	60	THF	-78	BnBr
12	**4a**	**6a**	10.1	40	67	THF	-78	i-PrI
13	**4b**	**6b**	4.6	4	68	THF	-78	MeI
14	**4b**	**6b**	6.1	6	66	THF	-78	i-PrI
15	**4c**	**6c**	5.7	42	72	THF	-78	MeI
16	**4c**	**6c**	>100	44	65	THF	-78	i-PrI

a : Standard conditions : 1.3 equiv sec-BuLi, 0.5 h, 4 equiv alkylating reagent, 5 min, unless otherwise noted; b : ratio of **6**:**7**; c : only for 1,4-cyclohexadiene diastereoisomers **6**; d : deprotonation during 4 h 30 min; e : cosolvent.

Methylation of **4a** (entry 1) yielded four isomeric alkylated cyclohexadienes in a ratio of 4(**7a**) : 23(**6a**-α) : 13(**epi-7a**) : 60(**6a**-β) as determined by GC-MS. Since preparative HPLC-separation proved to be impossible, further transformations were thus always performed on the alkylated reaction mixtures.

The structure assignments follow from ^{1}H NMR, which allows distinction of the conjugated (**7**; C<u>H</u>$_3$ at δ 1.05 and δ 1.09; =C<u>H</u> at δ 5.15, δ 5.17, δ 5.40 and δ 5.81) from the unconjugated (**6**; C<u>H</u>$_3$ at δ 1.18; =C<u>H</u> at δ 4.93, δ 5.00 and δ 5.53-5.63) cyclohexadienes. Determination of the % de was based on the distinct signals of either the 2-H vinylic protons (**6a** and **6c**) or the vinylic methyl protons (**6b**) in the respective diastereoisomeric 1,4-cyclohexadienes. The regioselectivity was determined from the intensity ratios of the vinylic ^{1}H NMR signals for compounds **6a-c** and **7a-c**, respectively. The diastereoselectivity for the alkylated 1,3-cyclohexadienes has not been evaluated.

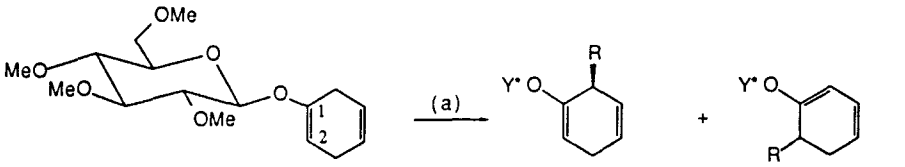
The structures were confirmed by GC-MS analysis of the α,β-enones **8** and **9** (ratio 83:17, corresponding to the ratio found in GC), obtained by acid hydrolysis of the mixture of methylated isomers. The distinct fragmentation patterns (base peak at m/z 82 for **8** and at m/z 68 for **9**; retro Diels-Alder fragmentation) allow unequivocal assignments.

Compounds **4a-c** proved to be suitable substrates for examining the influence of varying reaction conditions upon the regio- and diastereoselectivity and the total yield of alkylated products. The regioselectivity seems to be determined by steric (table 2; compare entries 1,12 and 15,16) as well as stereoelectronic (entries 12 and 16) effects. The presence of a methyl group at C-4 did not markedly influence the diastereoselectivity (entry 15), while the methylation of **4b** exhibited very poor regio- and diastereoselectivity (entry 13). In contrast, the reaction of **4c** with isopropyl iodide was totally regioselective (entry 16).

The formation of methylated 1,3-cyclohexadienes may be the result of a SE_2'-reaction on anion **10** (scheme 1), which occurs regioselectively at C-2 (pathway 1), leading to the 6-methyl-1-alkoxy-1,3-cyclohexadienes **7a**. The alternative SE_2'-reaction (pathway 2) would yield the isomeric 5-methyl-2-alkoxy-1,3-cyclohexadienes. It is known that 1-alkoxy-1,3-cyclohexadienes are thermodynamically more stable than 2-alkoxy-1,3-cyclohexadienes[15]. This may be reflected in a lower transition state for formation of 1-alkoxy-1,3-cyclohexadienes[16]. A more general explanation invokes the molecular electrostatic potential[17], showing that the highest charge density in a 1-alkoxy-1,4-cyclohexadien-6-ate anion, such as **10**, is located on C-6 and on C-2 in decreasing order. This property may well account for the regioselective formation of both 1,4- and 1,3-cyclohexadienes and for the experimentally observed ratios. However, the formation of conjugated cyclohexadienes could be partially due to the presence of the isomeric conjugated lithiated anion. Indeed, it was observed that, upon prolonged deprotonation (4 h 30 min instead of 0.5 h; table 2, entry 2), the regioselectivity decreased markedly. In related alkylation procedures the presence of conjugated isomers was not mentioned[3,18]. In order to study this discrepancy, we alkylated substrates **1h** and **1i** (figure 1), but again the regioselectivity was low (table 1; entries 16-18). In Sutherland's work the metallation of **1a** occurred with n-BuLi-HMPA, while the alkylating reagents were all primary homoallylic halides (entry 19)[3]. The same conditions were applied in the alkylation of **1j** (figure 1) by Wolf et al. (entry 20)[18]. It is very likely that the per-O-methyl-β-D-glucopyranosyl group increases the steric inhibition for the SE_2-type alkylation of the 1-alkoxy-1,4-cyclohexadienes **4**, thereby favoring the SE_2'-reaction in comparison to compounds **1a** and **1j**. A similar dual reaction pathway has been reported in the Birch reduction of sterically hindered cresol ethers[19].

The diastereoselectivities are influenced substantially by the solvent. Alkylations of **4a**, conducted in diethyl ether or toluene, produce high % de, albeit in low chemical yields (table 2; entries 3 and 4). This phenomenon could be due to insufficient solubility or to partial degradation of the monosaccharide part subsequent to proton abstraction. As expected, the addition of HMPA as cosolvent has a negative effect (entry 6). Alteration of the leaving group in the electrophile shows that iodides are to be preferred (entries 1 and 9-11). It is also obvious that upon lowering the temperature both regio- and diastereoselectivity are enhanced (entries 7 - 8).

Next, other bases were considered. Initially, we had obtained poor results with LDA because of improper reaction conditions. A more detailed study revealed that deprotonation of **4a** proceeded almost quantitatively provided the substrate was treated with 3 equiv of LDA at -50°C during 4 h, followed by alkylation at -78°C, or at -90°C during 4 h. Under these precise conditions substantial improvement was made, leading to ≥ 90 % de for **6a** and chemical yields of 90 % (compare entries 1 - 2 in table 3 with entry 3 in table 2). The regioselectivity also increased and a pronounced temperature effect on the ratio **6a**:**7a** was noted (entries 1-2). Alkylation with isopropyl iodide succeeded only in the presence of HMPA, which led to an expected lowering of the % de (entries 3-4). The contrasting results, presented in tables 2 and 3, are remarkable and suggest a different chelate of anion **10**. As the only difference is the presence of diisopropylamine when LDA is used, this amine is probably participating in the chelate thus influencing the chelate structure and hence the alkylating properties. This may explain the necessity of using HMPA (compare entry 12, table 2 and entries 3-4, table 3).



a : R = CH_2 - CH_2 - OH
b : R = CH_2 - CH(OH) - CH_3
c : R = CH_2 - CH_2 - CH_2 - OTBDMS
Y* : per - O - methyl - β - D - glucopyranosyl

(a) see table 3

Scheme 2

Table 3 : Alkylation of 4a after deprotonation with LDA.

Entry	Electrophile	Main product	Regiose-lectivity[a]	% De[b]	Total yield (%)	Reaction conditions
1	MeI	**6a**	8.1	90	90	c
2	MeI	**6a**	19.0	92	90	d
3	i-PrI	**6a**	>100	72	86	c; HMPA[e]
4	i-PrI	**6a**	>100	78	85	d; HMPA[e]
5	Ethylene oxide	**11a**	8.8	92	80	c
6	(R,S)-Propylene oxide	**11b**	8.8	94	80	c
7	(S)-Propylene oxide	**11b**	9.0	93	78	c
8	(R)-Propylene oxide	**11b**	8.8	94	78	c
9	3-tert-Butyl-dimethyl-silyloxypropyl iodide	**11c**	6.7	90	85	c

a : Ratio of **6**:**7** or **11**:**12**; b : only for 1,4-cyclohexadiene diastereoisomers **6** and **11**; c : 3 equiv LDA, Et_2O, deprotonation at -50°C, 4 h; 2 equiv alkylating reagent at -78°C, 4 h; d : deprotonation as under c; 2 equiv alkylating reagent at -90°C; e : cosolvent.

Introduction of functionalised alkyl groups

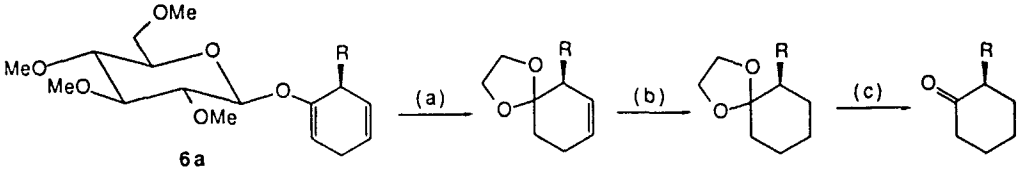
To demonstrate the versatility of the method, alkylations of **4a** (scheme 1) with ethylene oxide and racemic and optically active propylene oxides were carried out at -78°C. The propylene oxides reacted exclusively at the least substituted carbon atom. As shown in table 3 (entries 5-8) the hydroxyalkylated compounds **11a-b** (scheme 2) were obtained with excellent diastereoselectivity (> 90 % de), while good regioselectivities and yields were observed. Alkylation with the propylene oxides (entries 6-8) did not show any preference for either enantiomer thus excluding double diastereoselection. It is worthwile to note that increasing quantities of electrophile had a profound effect on the diastereoselectivity. With 10 equiv of ethylene oxide, 50 % de was obtained, while treatment with 20 equiv yielded almost racemic reaction products. Furthermore, 50 equiv of ethylene oxide caused inversion of the absolute configuration at the new chiral center in **11a** with respect to the procedure using 2 equiv. This indicates that ethylene oxide strongly competes for chelation of the lithium cation. Similar concentration-dependent inversion of the stereoselectivity of protonation by tert-butanol during

the Birch reduction of chiral amides has been reported[2f]. These excellent results with epoxides, which are normally poor electrophiles towards strong basic alkyllithium species, are remarkable. An alternative for generating a functionalised three-carbon side chain involves alkylation with 3-hydroxypropyl iodide protected as tert-butyldimethylsilyl (TBDMS) ether (entry 9).

The stereochemical analysis of compounds **11** and **12** is based on ^{1}H NMR signals of the vinylic 2-H protons (for determination of the ratios **11**:**12**) and the acetal protons (for determination of the % de). The individual signals for the respective epimers of **11b** are assigned from comparison of the ^{1}H NMR data of the reaction mixtures arising from racemic and both enantiomeric propylene oxides.

Determination of the absolute configuration

The absolute configuration has been determined by chemical conversion of **6a** (R = Me and Bn) to the known 2-alkylcyclohexanones[20] (scheme 3). Removal of the chiral auxiliary and hydrogenation led to the acetal **14** without notably affecting the chiral center[21]. Subsequent hydrolysis occurred with partial racemisation. However, the sign of the optical rotation allowed unambiguous establishment of the absolute configuration of **15**. This assignment has been confirmed by the CD data of compound (+)-**20** (scheme 4).



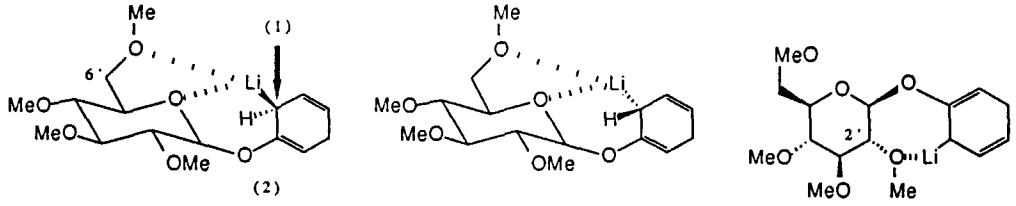
6a **13** **14** **15**

R = Me (table 3, entry 1)
R = Bn (table 2, entry 11)

(a) : glycol, $BF_3.Et_2O$; (b) : H_2 (1 atm), Pt/C, MeOH; (c) : HCl, acetone, O° C

Scheme 3

A priori two different chelates can occur, either a six-membered ring chelate involving the acetal oxygen atom, such as **16** (figure 2), or a seven-membered ring chelate incorporating the methoxy function at C-2', such as **17**. Moreover, additional weak bonds between the lithium cation and other oxygen functionalities can not be excluded. It is very likely that chelate **16** prevails in view of the six-membered ring structure and the possible additional chelation with the oxygen atom at C-6'. The lithiated species **16a** and **16b** represent opposite absolute configurations at the anionic carbon site. For each configuration several conformations can be envisaged. However, from calculations, using a combination of the program SCA[22] and Still's MacroModel, the discrete lowest energy conformers could not be found. Furthermore, these conformations may undergo configurational inversion of the chiral carbanion. It should be borne in mind that the preferred configuration cannot be determined from the absolute configuration of the alkylated reaction products. Indeed, electrophilic substitution in **16a** may involve either retention (1) or inversion (2). For example, methylation of **16a** with retention or of **16b** with inversion will yield the (S)-6-methyl-1,4-cyclohexadiene derivative **6a**-β (scheme 1). Accordingly, it is impossible to predict the steric outcome based on the available data. Depending on the particular substrates and the reaction conditions enantioselective alkylations have been reported to occur with retention[23] as well as inversion[24].

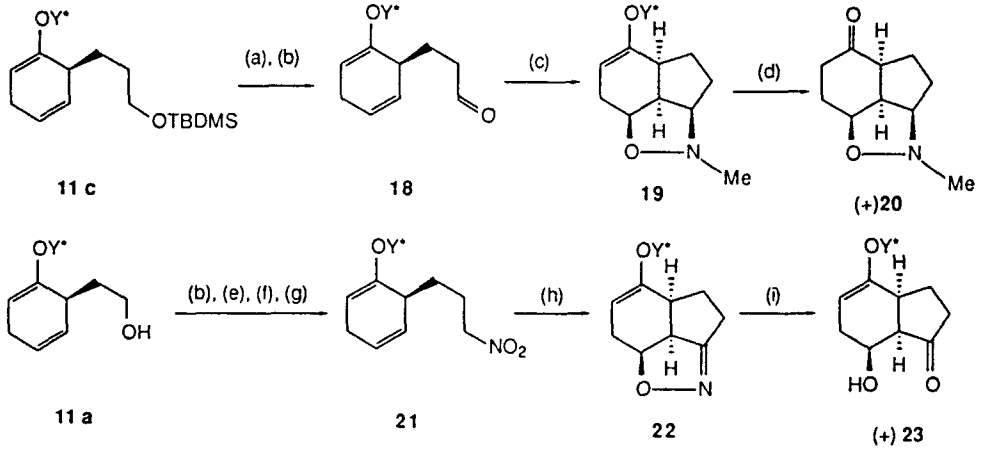


16 a 16b 17

Figure 2

Transformation of optically active alkylated 1,4-cyclohexadienes to functionalised cis-hydrindanes

We have previously reported on the regio-, stereo- and chemoselective intramolecular nitrone-alkene cycloaddition reaction of substituted 1,4-cyclohexadienes for the construction of the hydrindane skeleton[25].



Y* : per - O - methyl - β - D - glucopyranosyl

a : n-Bu_4NF, THF; b : $(COCl)_2$, DMSO, CH_2Cl_2, -60°C, then NEt_3; c : MeNH(OH).HCl, NEt_3, C_6H_6, 80°C; d : HCl, THF; e : KF, $MeNO_2$, i-PrOH; f : Ac_2O, DMAP, Et_2O; g : $NaBH_4$, EtOH; h : Ph-N=C=O, NEt_3, C_6H_6; i : H_2 (1 atm), Raney Ni (W7), $B(OH)_3$.

Scheme 4

Application to the present substrates enables enantioselective preparation of highly functionalised cis-hydrindanes. Compound **11c** (entry 9, table 3) possesses a latent terminal nitrone functionality. Swern oxidation following deprotection of the hydroxyl group furnished aldehyde **18** (scheme 4), which was converted directly to the isoxazolidine **19** via the intermediate nitrone[26]. Acid hydrolysis led to the cis-fused hydrindanone (+)-**20** (90 % ee). The absolute configuration has been proven by the CD data[27]. The R-band displays a positive Cotton effect at 292 nm with a Δε-value of +0.7 consistent with the configurational assignment deduced from chemical interconversion (vide supra).

A variant for the construction of optically active cis-hydrindanes involves an intramolecular nitrile oxide - alkene cycloaddition reaction[26], starting from compound **11a** (entry 5, table 3). Consecutive Swern oxidation and Wollenberg homologation[28] afforded the nitro derivative **21**. Cycloaddition of the unstable nitrile oxide occurred regioselectively at the least substituted double bond affording the isoxazoline **22**[25]. Reductive cleavage of the N-alkoxyimine group[29] led to the cis-hydrindanone (+)-**23** (92 % ee). Compounds (+)-**20** and (+)-**23** are versatile precursors in the asymmetric synthesis of naturally occurring cis-hydrindanes.

EXPERIMENTAL SECTION

The IR spectra were recorded on a Beckman IR-4230 spectrometer, the mass spectra on an AEI MS-50 or a Finnigan 4000 spectrometer and the UV spectra on a Perkin Elmer lambda 3 spectrophotometer. The ^{1}H NMR spectra were obtained on a Bruker AN-500 (500 MHz) or a Bruker WH-360 (360 MHz) machine in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are expressed in ppm, coupling constants (J) in Hz. GC/MS analyses were carried out with an OV-1 column (25 m, 0.32 mm, film thickness 0.17 µm) coupled to a Finnigan 4000 spectrometer equipped with Superincos Data System.
All alkylations were performed under oxygen-free argon with magnetic stirring. "Work-up" denotes addition of H_2O, extraction with Et_2O (unless otherwise noted), washing of the organic phase with saturated NaCl solution, drying over anhydrous $MgSO_4$ and removal of the solvent from the filtered solution by distillation in vacuo using a rotatory evaporator. The R_f values refer to TLC plates type Merck SiO_2 60 GF_{254} (thickness 0.25 mm). The instruments, used for isocratic HPLC analyses and preparative separations with RI detection, were Knauer Model 64 (RSiL or RSiLC_{18}HL 10 µm, 25 x 2.2 cm, 10 ml.min^{-1}), Waters M6000A pump (RSiL 10 µm, 25 x 1 cm, 5 ml.min^{-1}) and Kontron HPLC pump 420 (RSiL 10 µm, 25 x 1 cm, 5 ml.min^{-1}). The isolated and purified compounds were dried at high vacuum (< 0.1 mm Hg) and stored at -18°C. Melting points are uncorrected.

Preparation of 1-alkoxy-1,4-cyclohexadienes by Birch reduction of the corresponding phenol ethers. General procedure.

To a solution of phenol ether (16 mmol) in ammonia (100 mL, distilled from sodium) was added tert-butanol (20 mL) and dry THF (20 mL) under argon. While stirring vigorously, lithium (1 g, 143 mmol) was added portionwise until the blue color persisted during 10 min. The reaction was quenched by addition of saturated NH_4Cl solution. Ammonia was allowed to evaporate at rt under a nitrogen flow. The residue was taken up in H_2O (100 mL) and extracted with Et_2O (3 x 50 mL). Work-up and purification by chromatography led to the 1-alkoxy-1,4-cyclohexadienes.

Alkylation of 1-alkoxy-1,4-cyclohexadienes. General procedure.

a. Sec-BuLi as the base.
Sec-BuLi (1.3 M in hexane, 1.3 equiv) was added dropwise to a solution of 1-alkoxy-1,4-cyclohexadiene in THF or Et_2O (see tables 1 and 2; 10 mL). After stirring during 0.5 h at -78°C, alkylating reagent (4 equiv) was added via syringe and stirring was continued during 5 min at -78°C. Work-up and chromatographic separation furnished C-6 alkylated 1-alkoxy-1,4-cyclohexadiene.

b. LDA as the base.
To a solution of $(i\text{-}Pr)_2NH$ (662 µL, 4.78 mmol) in Et_2O (10 mL) was added dropwise n-BuLi (2.45 M in hexane; 1.82 mL; 4.46 mmol) at -78°C under argon. The solution was stirred during 15 min at -78°C. The LDA-solution (3 equiv) was transferred to a suspension of 1-alkoxy-1,4-cyclohexadiene at -78°C under argon. The mixture was allowed to warm up to -50°C and stirred during 4 h. After dissolution of the precipitate the solution was cooled to -78°C or -90°C (see table 3) and alkylating reagent (2 equiv) was added via syringe. Work-up after stirring during 4 h and chromatographic separation afforded C-6 alkylated 1-alkoxy-1,4-cyclohexadiene.

Phenyl per-O-methyl-β-D-glucopyranoside.

To a solution of phenyl β-D-glucopyranoside (10 g, 39 mmol) in acetone (250 mL) was added under stirring NaOH (40 %, 20 mL), followed by simultaneous addition of NaOH (40 %, 70 mL) and Me_2SO_4 (41.7 mL,

44 mmol) during 1.5 h at 50°C. After stirring during 1 h at 50°C the excess acetone was evaporated and the residue was poured in ice (100 mL). The crystalline product was filtered off and washed with ice-cold water until neutral. The collected aqueous layers were extracted with $CHCl_3$ (2 x 250 mL). After work-up and removal of the solvent, the solid material, combined with the crystals, was purified by column chromatography (hexane/EtOAc 7:3) to give pure **5a** (10.5 g, 86 %). Mp : 71°C. Rf (hexane/EtOAc 1:1) : 0.54. IR (KBr) : 3160-2820, 1635, 1525, 1480, 1200-1050, 1015 cm^{-1}. MS : m/z : 312 ($M^{+\cdot}$, 1), 187 (50), 167 (32), 166 (21), 111 (45), 101 (83), 89 (34), 88 (28), 75 (33), 71 (57), 45 (100). ^1H NMR (360 MHz, C_3D_6O) : 3.20-3.31 (m, 2H), 3.44 (s, 3H), 3.52-3.70 (m, 13H), 4.83 (d, J = 7.5 Hz, 1H), 6.96-7.35 (m, 5H) ppm.

1-(Per-O-methyl-β-D-glucopyranosyloxy)-1,4-cyclohexadiene.

Compound **5a** (5 g, 16 mmol) was subjected to Birch reduction as described above. Isolation of **4a** (4.93 g, 98 %) was achieved by column chromatography (Et_2O/hexane 2:3). Analysis found : C, 61.13; H, 8.34; $C_{12}H_{26}O_6$ requires : C, 61.24; H, 8.47. Mp : 101°C. $[\alpha]_D^{20}$: -39.62 (c = 1.05; $CHCl_3$). IR (KBr) : 3050-2785, 1590, 1445, 1170-1000 cm^{-1}. MS : m/z : 314 ($M^{+\cdot}$, 1), 187 (45), 127 (22), 111 (46), 101 (83), 89 (32), 127 (22), 111 (46), 101 (83), 89 (32), 75 (32), 73 (26), 71 (49), 45 (100). ^1H NMR (360 MHz, C_3D_6O) : 2.77 (m, 4H), 3.02 (dd, J = 9.0, 7.5 Hz, 1H), 3.10 (t, J = 9.0 Hz, 1H), 3.19 (t, J = 9.0 Hz, 1H), 3.35 (s, 3H), 3.44 (ddd, J = 9.0, 5.0, 2.0 Hz, 1H), 3.51 (s, 3H), 3.54 (d, J = 5.0 Hz, 1H), 3.55 (s, 3H), 3.58 (d, J = 2.0 Hz, 1H), 3.59 (s, 3H), 4.77 (d, J = 7.5 Hz, 1H), 5.03 (bs, 1H), 5.69 (bs, 2H) ppm.

Methylation of 4a.

Methylation of **4a** using sec-BuLi as the base was performed as described above. Compounds **6a + 7a** (74 %) were isolated by reversed phase chromatography (MeOH/H_2O 77:23). Rf (hexane/EtOAc 4:1) : 0.24. UV (MeOH) : 269 nm. GC-MS : m/z: for **7a** : 328 ($M^{+\cdot}$, 1), 187 (100), 155 (23), 127 (20), 111 (53), 101 (63), 89 (23), 75 (23), 71 (32), 45 (68); for **6a**-α : 328 ($M^{+\cdot}$, 0.5), 187 (100), 155 (20), 111 (52), 101 (62), 89 (21), 75 (23), 71 (31), 45 (70); for epi-**7a** : 328 ($M^{+\cdot}$, 1), 187 (100), 155 (26), 127 (21), 111 (63), 101 (80), 89 (28), 75 (29), 71 (40), 45 (90); for **6a**-β : 328 ($M^{+\cdot}$, 0.5), 187 (100), 155 (22), 127 (20), 111 (68), 101 (82), 75 (29), 71 (42), 45 (94). ^1H NMR (360 MHz) : 1.05 (d, J = 7.0 Hz, 0.79x3H'), 1.09 (d, J = 6.7 Hz, 0.21x3H'), 1.18 (d, J = 6.8 Hz, 3H), 2.02 (m, 1H'), 2.40 (m, 1H'), 2.57 (m, 1H'), 2.77 (m, 2H), 2.91 (m, 1H), 3.10-3.72 (m, 18H+18H'), 4.61 (d, J = 7.5 Hz), 4.63 (d, J = 7.5 Hz), 4.67 (d, J = 7.5 Hz), 4.93 (t, J = 3.2 Hz, 0.72 H), 5.00 (t, J = 3.2 Hz, 0.28 H), 5.15 (d, J = 6.0 Hz), 5.17 (d, J = 6.0 Hz), 5.40 (m, 1H'), 5.53-5.63 (m, 2H), 5.81 (m, 1H') ppm. H/H' = 83/17.

Alkylation of 4a with ethylene oxide.

Alkylation of **4a** with ethylene oxide using LDA as the base and THF as solvent was achieved as described before. The β-hydroxyethylated cyclohexadienes **11a** and **12a** (80 %, see table 3) were isolated by column chromatograhy (hexane/EtOAc : 9:11). Rf (hexane/EtOAc 9:11) : 0.19. MS : m/z : 219 ($M^{+\cdot}$, 2), 123 (48), 111 (49), 101 (100), 89 (22), 88 (20), 75 (25), 71 (27), 45 (31). ^1H NMR (360 MHz) : 1.78 (m, 1H+1H'), 1.98 (m, 1H+1H'), 2.15-2.55 (m, 3H'), 2.71-2.80 (m, 2H), 3.08 (m, 1H), 3.10-3.62 (m, 18 (H+H')), 3.65 (m, 2 (H+H')), 4.60 (d, J = 7.5 Hz, 0.96 (H+H')), 4.65 (d, J = 7.5 Hz, 0.04 (H+H')), 5.04 (t, J = 3.5 Hz, 0.96 (H+H')), 5.09 (t, J = 3.5 Hz, 0.04 H), 5.22 (d, J = 5.8 Hz, 1H'), 5.41 (ddd, J = 9.5, 5.8, 2.8 Hz), 1H'), 5.51 (ddd, J = 10.1, 3.5, 1.8 Hz, 1H), 5.69 (dm, J = 10.1 Hz, 1H), 5.78 (ddd, J=9.5, 6.0, 3.0 Hz, 1H') ppm. H/H' = 89/11.

For **11b** (alkylation with (S)-propylene oxide) : ^1H NMR (360 MHz) : 1.14 (d, J = 6.2 Hz, 3 (H+H')), 1.50-1.95 (m, 2 (H+H')), 2.25-2.65 (m, 3H'), 2.78 (m, 2H), 3.03-3.65 (m, 19H+18H'), 3.93 (m, 1H+1H'), 4.61 (d, J = 7.5 Hz, 0.97H+1H'), 4.67 (d, J = 3.5 Hz, 0.03H), 5.06 (t, J = 3.5 Hz, 0.97H), 5.09 (t, J = 3.5 Hz, 0.03H), 5.22 (d, J = 5.8 Hz, 1H'), 5.41 (ddd, J = 9.5, 5.8, 2.8 Hz, 1H'), 5.78 (ddd, J = 9.4, 6.0, 3.0 Hz, 1H') ppm. H/H' = 90/10.

For **11b** (alkylation with (R)-propylene oxide) : ^1H NMR (360 MHz) : 1.13 (d, J = 6.2 Hz, 3 (H+H')), 1.58 (m, 1H+1H'), 1.88 (m, 1H+1H'), 2.25-2.65 (m, 3H'), 2.77 (m, 2H), 3.05 (bs, 1H), 3.08-3.65 (m, 18 (H+H')), 3.93 (m, 1H+1H'), 4.61 (d, J = 7.5 Hz, 0.97H+1H'), 4.63 (d, J = 7.5 Hz, 0.03H), 5.05 (t, J = 3.5 Hz, 0.97H), 5.08 (t, J = 3.5 Hz, 0.03H), 5.22 (d, J = 5.8 Hz, 1H'), 5.41 (ddd, J = 9.4, 5.8, 2.8 Hz, 1H'), 5.51 (ddd, J = 10.1, 3.5, 1.8 Hz, 1H), 5.69 (dm, J = 10.1 Hz, 1H), 5.78 (ddd, J = 9.5, 6.0, 3.0 Hz, 1H') ppm. H/H' = 89/11.

For **11c** : Rf (hexane/EtOAc 4:1) : 0.27. MS : m/z : 486 ($M^{+\cdot}$, 2), 187 (78), 155 (25), 127 (21), 111 (100), 101 (76), 100 (20), 89 (36), 75 (49), 73 (21), 71 (29), 45 (24). ^{1}H NMR (360 MHz) : 0.02 (s, 6 (H+H')), 0.88 (s, 9 (H+H')), 1.40-1.70 (m, 4 (H+H')), 2.05-2.55 (m, 3H'), 2.74 (m, 2H), 2.94 (bs, 1H), 3.10-3.23 (m, 3 (H+H')), 3.32 (m, 1H+1H'), 3.38 (s, 3 (H+H')), 3.51-3.65 (m, 13 (H+H')), 4.64 (d, J = 7.5 Hz, 0.95 (H+H')), 4.65 (d, J = 7.5 Hz, 0.05 (H+H')), 4.96 (t, J = 3.6 Hz, 0.05 H), 4.99 (t, J = 3.6 Hz, 0.95 H), 5.16 (d, J = 5.9 Hz, 1H'), 5.38 (m, 1H'), 5.54 (dm, J = 10.0 Hz, 1H), 5.69 (d, J = 10.0 Hz, 1H), 5.79 (m, 1H') ppm. H/H' = 87/13.

Acetal 13 (R=Me).

To a solution of **6a + 7a** (500 mg, 1.57 mmol) in THF were added glycol (700 µL, 12.6 mmol) and $BF_3.Et_2O$ (75 µL, 0.61 mmol). After stirring during 20 h and work-up acetal **13** (180 mg, 77 %) was separated by column chromatography (Et_2O/pentane 1:19). Rf (Et_2O/pentane 1:19) : 0.24. ^{1}H NMR (500 MHz) : 1.01 (d, J = 7.2 Hz, 3H), 1.62 (m, 1H), 1.81 (dt, J = 13.0, 5.9 Hz, 1H), 2.22 (m, 2H), 2.43 (m, 1H), 3.92-4.01 (m, 4H), 5.49 (m, 1H), 5.63 (m, 1H) ppm.

Conversion of 13 (R=Me) to (+)-2(S)-methylcyclohexanone.

Pt/C (5 %, 5 mg) was added to a solution of **13** (R=Me) (150 mg, 0.974 mmol) in MeOH (5 mL). After stirring during 3 h under hydrogen (1 atm) the catalyst was filtered off. Evaporation of the solvent and column chromatography (pentane/Et_2O 19:1) gave the reduced acetal **14** (R=Me) (110 mg, 72 %). Rf (hexane/Et_2O 23:2) : 0.35. ^{1}H NMR (500 MHz) : 0.88 (d, J = 6.7 Hz, 3H), 1.19-1.78 (m, 9H), 3.88-3.99 (m, 4H) ppm.

To a solution of **14** (R=Me) (30 mg, 0.192 mmol) was added at 0°C HCl in acetone (0.1 N, 0.5 mL). After stirring during 5 h at 0°C CH_2Cl_2 (4 mL) was added. Work-up and column chromatography (pentane/Et_2O 19:1) afforded 2(S)-methylcyclohexanone (15 mg, 71 %). Rf (hexane/Et_2O 23:2) : 0.25. $[\alpha]_D^{20}$: +2.1 (c = 1.5, $CHCl_3$).

Aldehyde 18.

To compound **11c** (300 mg, 0.617 mmol) was added n-Bu_4NF (1 M) in THF (5 mL). Stirring during 30 min, prior to addition of Et_2O (10 mL), work-up and chromatographic separation (hexane/EtOAc 2:3) led to the corresponding alcohol (211 mg, 92 %). Rf (hexane/EtOAc 2:3) : 0.19. MS : m/z : 372 ($M^{+\cdot}$, 1.5), 187 (43), 155 (22), 111 (43), 101 (49), 89 (23), 71 (50), 45 (100). ^{1}H NMR (360 MHz) : 1.15-1.93 (m, 4H+4H'), 2.06-2.55 (m, 3H'), 2.76 (m, 2H), 3.01 (bs, 1H), 3.11-3.24 (m, 3H+3H'), 3.33 (m, 1H+1H'), 3.38 (s, 3H+3H'), 3.52-3.66 (m, 13H+13H'), 4.61 (d, J = 7.5 Hz, 0.95 (1H+1H')), 4.67 (d, J = 7.5 Hz, 0.05 (1H+1H')), 5.04 (t, J = 3.5 Hz, 0.95 (1H+1H')), 5.07 (t, J = 3.5 Hz, 0.05 (1H+1H')), 5.19 (d, J = 5.9 Hz, 1H'), 5.38 (m, 1H'), 5.53 (d, J = 10.0 Hz, 1H), 5.71 (d, J = 10.0 Hz, 1H), 5.79 (m, 1H') ppm. H/H' 87/13.

To a solution of oxalyl chloride (26.2 µL, 0.30 mmol) in CH_2Cl_2 (1 mL) was added at -60°C a solution of DMSO (43 µL, 0.60 mmol) in CH_2Cl_2 (200 µL). After stirring during 2 min at -60°C a solution of the alcohol (75 mg, 0.20 mmol) in CH_2Cl_2 (250 µL) was added during 5 min. Stirring was continued during 15 min at -60°C and Et_3N (180 µL, 1.20 mmol) was added. The reaction mixture was allowed to warm up to rt. Work-up and column chromatography (hexane/EtOAc 13:7) furnished aldehyde **18** (63 mg, 83 %). Rf (hexane/EtOAc 13:7) : 0.21. IR (neat) : 3000-2800, 1720, 1680, 1085, 1060 cm^{-1}. MS : m/z : 370 ($M^{+\cdot}$, 0.1), 187 (39), 111 (31), 101 (42), 75 (20), 71 (30), 45 (100). ^{1}H NMR (360 MHz) : 1.78 (m, 1H), 2.19 (m, 1H), 2.35 (dt, J = 7.6, 1.8 Hz, 2H), 2.64-2.87 (m, 2H), 3.07-3.23 (m, 4H), 3.33 (m, 1H), 3.38 (s, 3H), 3.52-3.68 (m, 11H), 4.61 (d, J = 7.6 Hz, 0.95H), 4.63 (d, J = 7.6 Hz, 0.05H), 5.03 (t, J = 3.3 Hz, 1H), 5.45 (ddt, J = 9.9, 3.6, 1.9 Hz, 1H), 5.75 (dm, J = 9.9 Hz, 1H) ppm.

Isoxazolidine 19.

To a solution of aldehyde **18** (45 mg, 0.122 mmol) in benzene (8 mL) were added N-methylhydroxylamine hydrochloride (15 mg, 0.183 mmol) and Et_3N (25 µL, 0.183 mmol). The reaction mixture was stirred during 3 h at 80°C and cooled to rt. Work-up and column chromatography (EtOAc) gave **19** (39 mg, 80 %). Rf (EtOAc) : 0.18. IR (neat) : 3000-2800, 1680, 1460, 1200-1050 cm^{-1}. MS : m/z : 399 ($M^{+\cdot}$, 2), 187 (23),

111 (40), 101 (36), 89 (20), 75 (25), 73 (20), 71 (41), 70 (26), 57 (21), 55 (20), 45 (100). ^{1}H NMR (360 MHz) : 1.47-1.70 (m, 2H), 2.35 (dt, J = 17.3, 3.8 Hz, 1H), 2.44 (m, 1H), 2.51 (ddt, J = 17.3, 5.7, 1.4 Hz, 1H), 2.71 (s, 3H), 3.01 (dt, J = 9.8, 6.7 Hz, 1H), 3.08-3.22 (m, 3H), 3.32 (ddd, J = 9.5, 5.0, 1.9 Hz, 1H), 3.37 (s, 3H), 3.49-3.65 (m, 11H), 4.37 (dt, J = 6.0, 3.5 Hz, 1H), 4.58 (d, J = 7.4 Hz, 0.05H), 4.66 (d, J = 7.4 Hz, 0.95H), 4.78 (t, J = 4.3 Hz, 1H) ppm.

Cis-hydrindanone (+)-20.

To a vigorously stirred solution of isoxazolidine **19** (20 mg, 0.05 mmol) in THF (300 µL) was added via syringe conc. HCl (12 µL). After stirring during 1.5 h solid Na_2CO_3 was added until the reaction medium was basic. After filtration and work-up cis-hydrindanone **20** (7 mg, 78 %) was isolated by column chromatography (CH_2Cl_2/MeOH 49:1). Rf (EtOAc) : 0.19. $[\alpha]_D^{20}$: +50.2 (c = 1.4, $CHCl_3$). CD : ε : +0.7 (R-band at 292 nm) (c = 1.015 mmol.L^{-1}, MeCN). IR (neat) : 3000-2840, 2790, 1700, 1155, 1120, 1070, 1055, 1035 cm^{-1}. MS : m/z : 281 ($M^{+\cdot}$, 1), 281 (60), 86 (100), 79 (20), 73 (41), 70 (20). ^{1}H NMR (360 MHz) : 1.68 (m, 1H), 1.80-1.90 (m, 2H), 2.02-2.20 (m, 3H), 2.27 (m, 1H), 2.54 (dd, J = 16.5, 9.3 Hz, 1H), 2.64-2.76 (m, 4H), 3.27 (dt, J = 9.3, 7.1 Hz, 1H), 3.43 (bs, 1H), 4.44 (bs, 1H) ppm.

Nitro derivative 21.

Alcohol **11a** (270 mg, 0.754 mmol) was subjected to Swern oxidation as described after the deprotection of **11c**. The corresponding aldehyde (220 mg, 82 %) was separated by column chromatography (hexane/EtOAc 13:7). Rf (hexane/EtOAc 1:1) : 0.41. IR (neat) : 3000-2800, 1720, 1650, 1150, 1080, 1060 cm^{-1}. MS : m/z : 356 ($M^{+\cdot}$, 0.5), 187 (54), 111 (41), 101 (59), 89 (23), 75 (25), 71 (38), 45 (100). ^{1}H NMR (360 MHz) : 2.70 (ddd, J = 16.7, 7.3, 2.0 Hz, 1H), 2.75 (ddd, J = 16.7, 4.5, 2.3 Hz, 1H), 2.78 (m, 2H), 3.09-3.23 (m, 4H), 3.34 (m, 1H), 3.38 (s, 3H), 3.51-3.69 (m, 11H), 4.64 (d, J = 7.7 Hz, 0.96 H), 4.67 (d, J = 7.7 Hz, 0.04 H), 5.05 (t, J = 3.5 Hz, 0.04 H), 5.09 (t, J = 3.5 Hz, 0.96 H), 5.61 (dm, J = 10.0 Hz, 1H), 5.72 (d, J = 10.0 Hz, 1H) ppm.

To a solution of the aldehyde (180 mg, 0.506 mmol) in i-PrOH (400 µL) were added KF (1 mg, 0.017 mmol) and nitromethane (38 µL, 0.705 mmol). After stirring during 24 h the solvent was evaporated in vacuo and to the residue were added dry Et_2O (1 mL), acetic anhydride (60 µL, 0.632 mmol) and an aliquot of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred during 20 h and concentrated in vacuo. To the residue was added dropwise sodium borohydride (1 M) in ethanol (1 mL). After stirring during 2 h and work-up the nitro derivative **21** (130 mg, 64 %) was isolated by column chromatography (hexane/EtOAc 3:1). Rf ($CHCl_3$/MeOH 99:1) : 0.35. IR (neat) : 3040-2800, 1685, 1645, 1550, 1220-1040 cm^{-1}. MS : m/z : 401 ($M^{+\cdot}$, 0.1), 187 (51), 111 (38), 101 (48), 89 (21), 75 (27), 71 (34), 45 (100). ^{1}H NMR (360 MHz) : 1.48-1.62 (m, 2H), 1.80-2.23 (m, 4H), 2.67-2.85 (m, 2H), 3.05 (bs, 1H), 3.09-3.22 (m, 4H), 3.30 (m, 1H), 3.43-3.69 (m, 11H), 4.34 (t, J = 6.9 Hz, 1H), 4.35 (t, J = 6.9 Hz, 1H), 4.61 (d, J = 7.7 Hz, 0.96 H), 4.65 (d, J = 7.7 Hz, 0.04 H), 5.05 (t, J = 3.4 Hz, 0.96 H), 5.10 (t, J = 3.4 Hz, 0.04 H), 5.50 (ddt, J = 10.0, 3.6, 1.9 Hz, 1H), 5.77 (d, J = 10.0 Hz, 1H) ppm.

Isoxazoline 22.

To a solution of **21** (95 mg, 0.237 mmol) in benzene (1.5 mL) were added phenyl isocyanate (77 µL, 0.711 mmol) and Et_3N (108 µL, 0.782 mmol). After stirring during 20 h, addition of Et_2O and work-up isoxazoline **22** (70 mg, 77 %) was separated by column chromatography (hexane/EtOAc 7:13). Rf (EtOAc) : 0.48. $[\alpha]_D^{20}$: +9.8 (c = 1.6, $CHCl_3$). IR (neat) : 3020-2800, 1670, 1600, 1550, 1220-1050 cm^{-1}. MS : m/z : 383 ($M^{+\cdot}$, 1), 187 (23), 111 (23), 101 (47), 71 (29), 45 (100). ^{1}H NMR (500 MHz, C_6D_6) : 1.78-1.90 (m, 2H), 2.03 (m, 1H), 2.11-2.19 (m, 2H), 2.21 (m, 1H), 2.29 (m, 1H), 3.08-3.60 (m, 19H), 4.34 (ddd, J = 9.9, 6.6, 5.3 Hz, 0.96 H), 4.37 (ddd, J = 9.8, 6.8, 4.9 Hz, 0.04 H), 4.50 (d, J = 7.4 Hz, 0.96 H), 4.58 (d, J = 7.4 Hz, 0.04 H), 4.84 (t, J = 4.8 Hz, 0.96 H), 4.92 (t, J = 4.5 Hz, 0.04 H) ppm.

Cis-hydrindanone (+)-23.

To a solution of isoxazoline **22** (16 mg, 0.0417 mmol) in MeOH/H_2O 5:1 (300 µL) were added boric acid (5.1 mg, 0.0835 mmol) and Raney Ni (W7). This suspension was stirred during 2 h under hydrogen (1 atm). After filtration of the catalyst, work-up and separation by column chromatography (hexane/EtOAc 3:7) cis-hydrindanone **23** (15 mg, 93 %) was obtained. Rf (hexane/EtOAc 3:7) : 0.21. $[\alpha]_D^{20}$: +60.5 (c = 0.4,

$CHCl_3$). IR (neat) : 3580-3220, 3000-2880, 1740, 1675, 1130-1040 cm^{-1}. MS : m/z : 218 ($M^{+\cdot}$, 2), 187 (43), 111 (33), 110 (42), 75 (20), 71 (38), 45 (100). ^1H NMR (360 MHz) : 1.96-2.11 (m, 3H), 2.23-2.29 (m, 2H), 2.32-2.49 (m, 2H), 2.67 (dd, J = 8.0, 5.2 Hz, 1H), 3.10-3.65 (m, 18H), 4.06 (dt, J = 9.2, 5.2 Hz, 1H), 4.59 (d, J = 7.4 Hz, 1H), 4.96 (dd, J = 5.4, 2.1 Hz, 1H) ppm.

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10. Substrate **1g** was prepared from 3-pyrrolidinol by N-methylation (CH_2O, HCO_2H; 92 %), Mitsunobu reaction with phenol (ref. 6; 82 %) and Birch reduction (ref. 4; 90 %). For a preparation of (S)-**1g**, see : Bowers Nemia, M.M.; Lee, J.; Joullié, M.M. Synthetic Commun. **1983**, *13*, 111.
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