Studies Directed Towards the Total Synthesis of (+)-Himbacine

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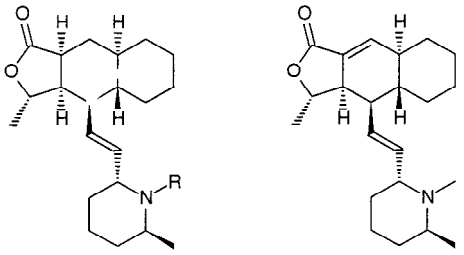
Received 29 August 1997

Abstract: A convergent strategy towards himbacine **(1)**, involving a Julia coupling between aldehyde **5** and sulfone **6** was found to be ineffective. The aldehyde **5** was synthesized via the thermal intramolecular cycloaddition of **4** with preferred formation of the *endo*-adduct. The Diels–Alder precursor **4** was obtained from butenolide **7**, the result of a single-step condensation between the enoate derived from the (*Z*)-conjugated olefin **12** and 2-acetoxypropanal. In the context of the synthesis of sulfone **6** Taber's method for the synthesis of 2,6-*trans*-disubstituted piperidine was adapted towards a large scale synthesis of **49**, a useful intermediate for the synthesis in this area.

Key words: himbacine, intramolecular Diels–Alder reaction, butenolides, Julia coupling, 2,6-*trans*-disubstituted piperidines

Himbacine **(1)** was first isolated in 1956 from the bark of *Galbulimima baccata*, a tree encountered in New Guinea and in parts of Australia.[1] A series of related alkaloids, including himbeline **(2)** and himgravine **(3)**, have also been isolated from the same source.[2] The relative and absolute configuration of **1** were determined via an X-ray diffraction study of the corresponding hydrobromic salt.[3] Interestingly, himbacine **(1)** is a potent muscarinic receptor antagonist that displays selectivity for the M_2 receptor.[4] As such it could become an important lead structure in the development of drugs for the treatment of Alzheimer's disease.[5]

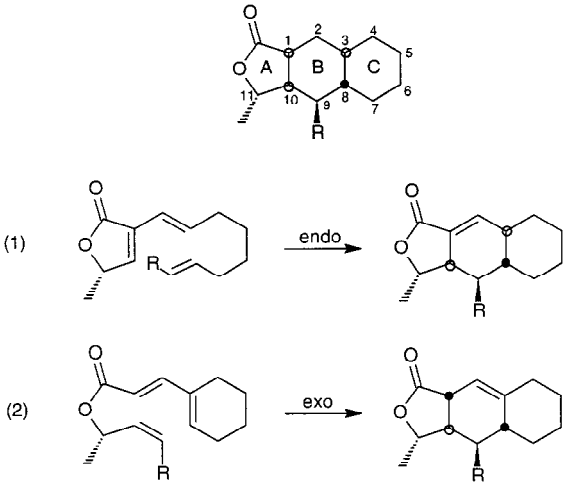


1 R = Me himbacine
2 R = H himbeline

3 himgravine

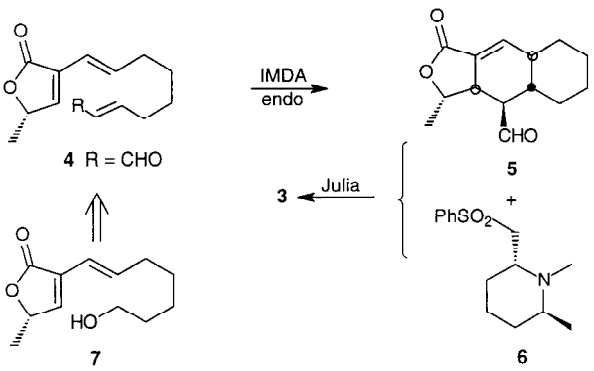
For a synthetic chemist himbacine **(1)** possesses an attractive structure. Its skeleton consists of a *trans*-fused perhydronaphthalene with a *cis*-fused γ-lactone, the ABC-ring part of the molecule, to which is connected, via a (*E*)-double bond, the *N*-methyl piperidine D-ring. A convergent strategy calls for a coupling of both parts via appropriate (*E*)-olefination methodology. The two parts further possess an interesting stereochemical pattern: in the ABC-ring part six contiguous stereocentres are present, while the D-ring consists of a 2,6-*trans*-disubstituted piperidine ring.

The first total syntheses of (+)-himbacine were described by the groups of Hart and Kozikowski in 1995,[6] and of Chackalamannil in 1996.[7] The two approaches involved, for the construction of the ABC-ring system, different intramolecular Diels–Alder strategies with formation of five stereogenic centres (Scheme 1). In the first strategy *endo*-cycloaddition involving approach of an (*E*)-dienophile to the least hindered side of the diene leads to an adduct with the correct stereogenicity at centres C-3, 8, 9, 10 and 11.[6] In the second strategy the *exo*-cycloaddition involving reaction of the diene to the least hindered side of the (*Z*)-dienophile gives an adduct possessing the correct stereochemistry at C-8, 9, 10 and 11 with the further possibility of facile epimerisation at C-1.[7] It is interesting to note that in the same period (1995) independent studies were also reported from this laboratory and by Baldwin and co-workers that follow the first Diels–Alder approach.[8,9] Since the reduction of himgravine **(3)** to himbacine **(1)** is a known process,[10] the choice of this particular strategy is a very logical one. In the present paper we would like to describe in detail the work we performed along this line.



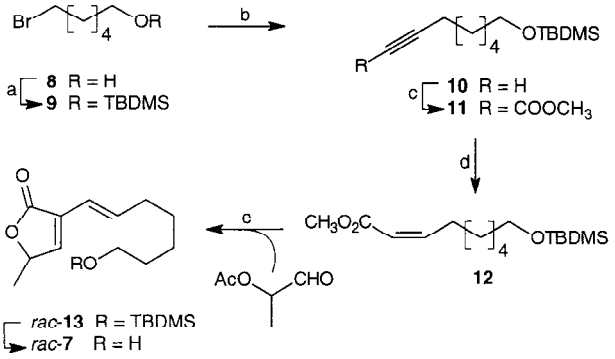
Scheme 1

The convergent route that we wanted to follow is shown in Scheme 2. Julia coupling,[11] a reliable olefination method for achieving the (*E*)-stereochemistry,[12] between aldehyde **5** and sulfone **6** would lead directly to himgravine **(3)**. As described above, the ABC-ring system in **5** would result from the cycloaddition of an adequate precursor such as **4**. In this paper we will further concentrate on the following: (1) two synthetic sequences that were elaborated in view of the synthesis of hydroxybutenolide **7**; (2) the conversion of the latter to appropriate dienophilic derivatives and their cycloaddition; and (3) our efforts towards the synthesis of piperidine **6** and the attempt at coupling it with aldehyde **5**.



Scheme 2

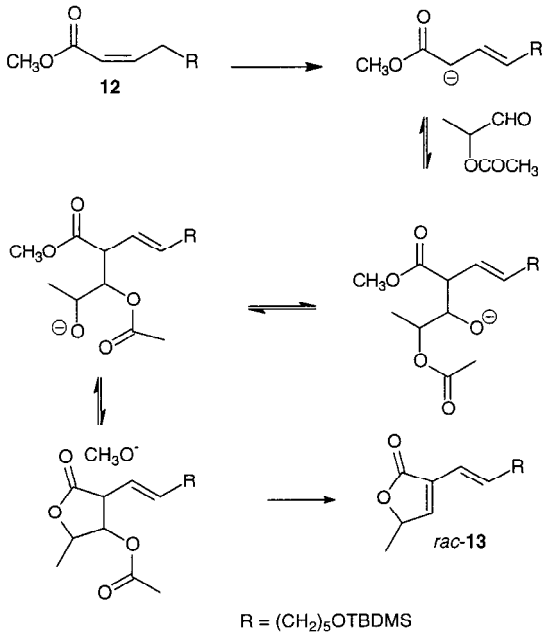
The first sequence to butenolide **7** is shown in Scheme 3 and was first developed in the racemic series. After protection of 6-bromohexan-1-ol **(8)**[13] as the *tert*-butyldimethylsilyl ether **9** (95% yield),[14] the latter is converted to the alkynyl ester **11** via a three-step sequence. Reaction with ethynyllithium/ethylenediamine complex in dimethyl sulfoxide gives **10** (92% yield). Deprotonation (butyllithium in diethyl ether), followed by addition of gaseous carbon dioxide and subsequent treatment with diazomethane leads to **11** (75% yield). The partial hydrogenation of **11** to yield (*Z*)-unsaturated ester **12** was performed using either Lindlar catalyst in toluene or palladium on barium sulfate in diethyl ether in the presence of quinoline (90% yield). In a further crucial step **12** is directly converted to butenolide **13**. This transformation involves deprotonation of **12** at –78 °C with lithium diisopropylamide in tetrahydrofuran/hexamethylphosphoramide with subsequent reaction of the resulting dienoate with 2-acetoxypropanal. Under carefully controlled conditions, whereby the mixture is kept between –78 and –53 °C for a prolonged period of time (90 h), the desired butenolide **13** is obtained in 65% yield. When the reaction mixture is allowed to reach higher reaction temperatures, a complex mixture results. On the other hand, if the reaction is terminated after shorter reaction times, substantial amounts of product **14** (unknown stereochemistry) are isolated.



a) TBDMSCl/DMAP/Et_3N/CH_2Cl_2, 95%; b) LiC≡CH•EDA/DMSO, 8 °C, 92%; c) (i) BuLi/Et_2O, –78 °C, CO_2 (ii) CH_2N_2/Et_2O, 90%; d) H_2/10% Pd($BaSO_4$)/quinoline/Et_2O, 90%; e) LDA/HMPA/2-acetoxypropanal/THF, –5 °C, 65%; f) 48% HF/MeCN, 99%

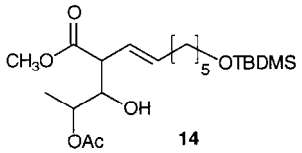
Scheme 3

Several steps are involved in the above transformation (Scheme 4). The first stage is based on the known deconjugative deprotonation/alkylation of (*Z*)-2-enoates to the corresponding (*E*)-3-enoates.[15] Reaction with 2-acetoxypropanal first leads to an acetoxy alkoxide. In the following stage, two consecutive transesterifications generate a γ-lactone with elimination of a methoxide group. The latter can further function as base for effecting the β-elimination of acetate with formation of the unsaturated butenolide with the required (*E*)-cross-conjugated diene.



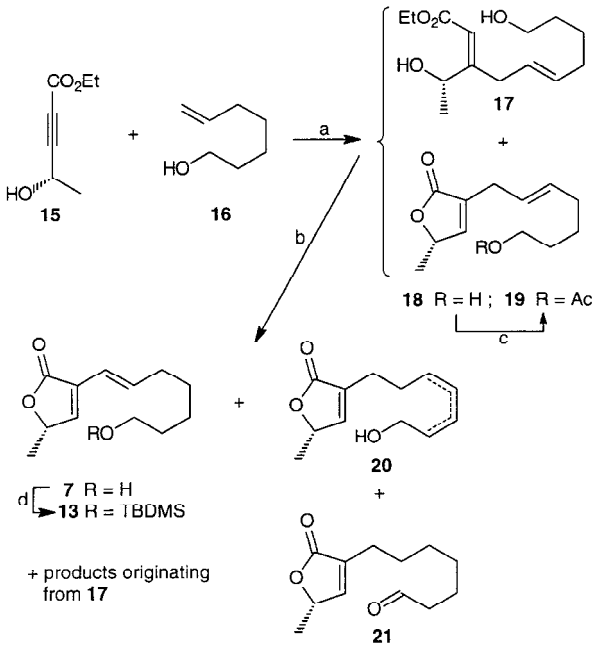
Scheme 4

Desilylation of **13** was effected using aqueous hydrogen fluoride in acetonitrile (99% yield).[16] The use of tetrabutylammonium fluoride in tetrahydrofuran led to immediate product decomposition.[14] Also the milder conditions involving a mixture of hydrogen fluoride and tetrabutylammonium fluoride led to unsatisfactory results.[17] Although the above butenolide formation is attractive and short, the protocol that is involved and the nature of the aldehyde component used in the condensation make a possible use of the method for an enantioselective application unlikely. This was indeed found to be the case. The synthesis of 2-acetoxypropanal involves esterification of but-3-en-2-ol with acetic anhydride and triethylamine in dichloromethane (80% yield), followed by the oxidative cleavage of the double bond with ozone and dimethyl sulfide in dichloromethane (65% yield).[18] Application of the sequence to enantiomerically pure (*S*)-but-3-en-2-ol[19] led to 2-acetoxypropanal with substantially reduced enantiomeric purity (80% ee determined via capillary gas chro-



matography using 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-cyclodextrine as chiral phase).[20]

In search of a solution for this problem we studied the possibility of using Trost's transition metal catalysed Alder-ene methodology for the synthesis of enantiomerically pure **7**. This involves reaction of the known ethyl (*S*)-4-hydroxypent-2-ynoate **(15)**[21] with hept-6-en-1-ol **(16)** using Cp(COD)RuCl as the catalyst (1–10 mol %) in methanol (60 °C, 3 h).[22] In line with the observations of Trost, two regioisomeric derivatives are formed in good yield (92%): the unsaturated (*Z*)-ester **17** and the desired butenolide **18**, in a ratio of 12:88, respectively. Unfortunately we have been unable to separate these two derivatives so far. However, the corresponding acetates, obtained from reaction with acetyl chloride, can be separated. In this manner, pure **19** was isolated in 80% yield (Scheme 5).



a) Cp(COD)RuCl/MeOH, 60 °C, 92%; b) $(Ph_3P)_3RhCl$-HCl(0.1 M) (10 mol%)/$CHCl_3$, 80 °C, 30%; c) CH_3COCl/pyridine/THF, 0 °C, 80%; d) TBDMSCl/DMAP/Et_3N/CH_2Cl_2, 95%

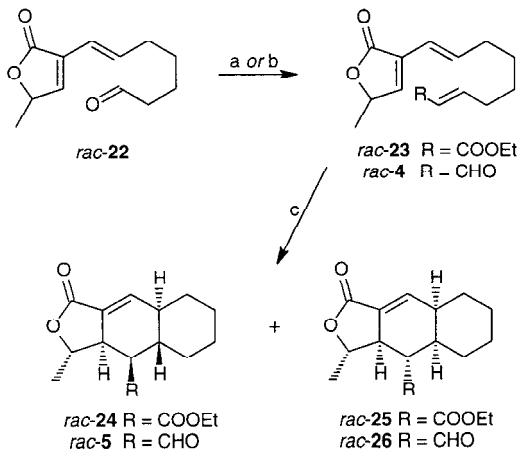
Scheme 5

The unsaturated alcohol **16** was readily obtained either from the commercial acid by lithium aluminum hydride reduction in diethyl ether (96% yield) or by copper-catalysed reaction of the Grignard derivative of 5-bromopent-1-ene with ethylene oxide [1 mol % dilithium tetrachlorocuprate(II), diethyl ether, 79%].[23]

In our hands the preparation of the required Cp(COD)RuCl catalyst following the reported procedure of Singleton[24] was tedious and difficult to reproduce. The preparation involves two stages: (1) reaction of dichloro(1,5-cyclooctadiene)ruthenium(II) polymer ($[RuCl_2(COD)]_n$) with unsymmetrical dimethylhydrazine followed by counter ion exchange leading to an intermediate hydridoruthenium complex ($[(COD)HRu(NMe_2NH_2)_3]PF_6$); and (2) displacement of the hydrazine ligands by cyclopentadienylthallium, followed by chlorination with tetrachloromethane. In particular we found the correct preparation of the hydrazine ligated complex to be crucial. The following steps should be performed carefully: (1) precipitation of the complex; (2) washing the latter with an aqueous solution of dimethylhydrazine; and (3) careful drying of the complex (35 °C/0.5 Torr, 17 h).

The synthesis of butenolide **7** further requires isomerization of the unconjugated double bond in **18** to a cross-conjugated diene. Trost has reported already on the reluctance of this migration to occur using palladium, rhodium and ruthenium catalysts.[25] After considerable experimentation we found that the use of Wilkinson's catalyst, in the presence of a 0.1 M aqueous solution of hydrochloric acid in chloroform at 80 °C, led after 17 hours to a mixture of the desired **7**, next to a series of unsaturated alcohols **20** and aldehyde **21**.[26] Tedious separation on silver nitrate impregnated silica gel afforded alcohol **7** in 30% isolated yield. The enantiomeric purity of the latter was evaluated to be more than 95% by ^{1}H NMR (500 MHz) spectroscopy using the chiral shift reagent Eu(hfc). Whereas in the presence of one molar equivalent of shift reagent *rac*-**13** led to two methyl doublets at δ = 1.606 and 1.594, and to two olefinic hydrogen doublets at δ = 6.568 and 6.537 (500 MHz), no peak separation was observed in the case of **13** that was obtained by silylation of the alcohol **7** (Scheme 5). Again this is in line with Trost's observation of maintenance of the stereochemical integrity in the Alder-ene process.[21]

Aldehyde **22**, which is also an intermediate in the synthesis of Hart and Kozikowski,[6] is obtained from **7** via Swern oxidation (84% yield).[27] We started the Diels–Alder study with the unsaturated ethyl ester **23** as the activated dienophile. The latter was obtained by reaction of **22** with the lithium salt of triethylphosphonoacetate (obtained via treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene and lithium chloride) in acetonitrile, a reliable method when base-sensitive substrates are involved.[28] Since the substrate was found to be rather unreactive in the thermal cycloaddition (vide infra), we also investigated the reactivity of unsaturated aldehyde **4**.[29] Our first attempts at synthesising the latter from **22** proceeded via Corey's aldimine methodology which involves reaction with the lithium salt of *N*-*tert*-butyl-2-(trimethylsilyl)acetaldimine in tetrahydrofuran.[30] Instead of the expected **4**, a bisaldehyde was obtained in which concomitant 1,4-addition on the butenolide was observed (^{1}H NMR of the crude product). We therefore took recourse to a modification introduced by Gaudemar in which *N*-*tert*-butyl-2,2-bis(trimethylsilyl)acetaldimine is used in the presence of zinc bromide as a catalyst.[31] Application of this strategy to **22** led to the desired aldehyde **4**, with the introduced double bond possessing the (*E*)-stereochemistry exclusively (66% yield) (Scheme 6). The same aldehyde **4** has been described by Hart and Kozikowski[6] and by Baldwin and co-workers.[9]



a) $(EtO)_2P(O)CH_2CO_2Et$/DBU/LiCl/MeCN, 75%;
b) $(Me_3Si)_2CH_2CH{=}NBu\text{-}t/ZnBr_2$/THF, 66%; c) toluene, 170 °C

Scheme 6

When the Diels–Alder precursor **23** was heated in toluene at 170 °C in the presence of di-*tert*-butylcresol (24 h, steel vessel), a 1:1 mixture of the *endo*- and *exo*-adducts **24** and **25** is obtained (85% yield) (Scheme 6). Quite to our surprise Lewis acid catalysis (diethylaluminum chloride, ethylaluminum dichloride or titanium tetrachloride) at lower temperature failed to yield any adduct. Although we have been unable to separate the two stereoisomers, their relative structural assignment was possible via 2D-NMR spectroscopy. The most significant difference in the COSY spectrum was observed for the H-3 signal which appears at δ = 1.80 and 2.46 (ΣJ_{vic} = 23.0 Hz) in **24** and **25**, respectively. The structural assignment was based on the corresponding calculated sum of vicinal *J* values: 31.6 and 25.2 Hz, respectively.[32] Hart and Kozikowski used the chemical shift of the olefinic proton in the ^{1}H NMR spectrum as diagnostic signal for identification: δ = 6.64 and 6.69 for **24** and **25**, respectively.[6] This is also in accord with our assignment.

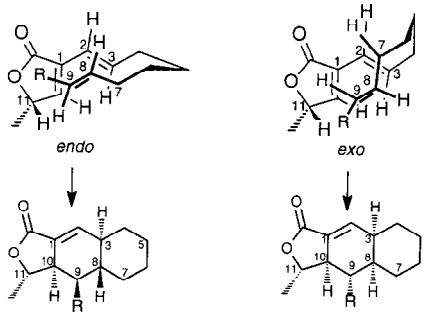
Reaction of the unsaturated aldehyde **4** at 170 °C (toluene, 24 h) led to a 10:8:6:1 mixture of adducts (85% isolated yield). We were fortunate here to be able to separate the two adducts, that were identified as the *anti*-adducts **5** and **26** (40% and 25% isolated yield, respectively) on the basis of their ^{1}H NMR COSY spectra. In particular the assignment rests on the nice correspondence between experimental and calculated data (Table). The determining factor in the relative assignment is the large coupling between H-10 and H-11 (9.2 Hz), whereas the same coupling in *syn*-adducts is calculated to be smaller (6 to 7 Hz). The differentiation between the *endo*- and *exo*-adducts is again based on the sum of the vicinal *J* values for H-3. The two remaining adducts (ratio 8:1, 35% isolated) could not be separated and were not further identified.

In many cases the cycloaddition of (*E*,*E*,*E*)-1,3,9-decatrienes occurs with low stereoselectivity, and quite often the substitution pattern of the precursor determines the stereochemical outcome.[29e] In general the use of Lewis acid catalysis is known to enhance the *endo*-selectivity. This has also been observed with the use of unsaturated aldehydes as dienophiles.[33] Our observations are further consistent with those reported by Hart and Kozikowski (Scheme 7).[6] They also observed a lack of selectivity in the thermal cyclization of **23**. The use of homogeneous Lewis catalysis (diethylaluminum chloride) was also ineffective. Interestingly the use of a heterogeneous catalyst (diethylaluminum chloride on silica gel) proved successful.

Table. ^{1}H NMR (500 MHz) Spectral Data of *exo*- and *endo*-Adducts **5** and **26**

Product	^{1}H NMR ($CDCl_3$/TMS)			
	δ	*J* (Hz)	found	calc.[a]
endo-**5**	9.74 (CHO)	H-9, CHO	4.4	–
	6.72 (H-2)	H-2, H-3	3.8	3.8
		H-2, H-10	3.2	2.6
	2.46 (H-3)	Σ (H-3)	29.1	31.6
	2.31 (H-8)	H-9, H-8	10.9	12.3
	2.55 (H-9)	H-9, H-10	9.3	11.4
	2.93 (H-10)	H-10, H-11	9.2	10.1
	4.15 (H-11)	H-11, CH_3	6.1	6.1
exo-**26**	9.69 (CHO)	H-9, CHO	4.3	–
	6.74 (H-2)	H-2, H-3	3.4	4.0
		H-2, H-10	3.0	2.6
	1.80 (H-3)	Σ (H-3)	25.0	25.2
	2.12 (H-8)	H-9, H-8	10.6	12.5
	2.73 (H-9)	H-9, H-10	10.4	13.2
	2.88 (H-10)	H-10, H-11	9.2	9.9
	4.42 (H-11)	H-11, CH_3	6.1	6.1

[a] Calculated using Macromodel.[32]

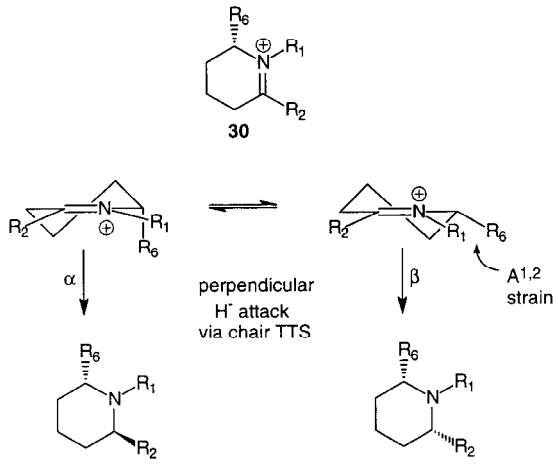


Scheme 7

Substrate	Reaction Conditions	*endo*/*exo* Ratio of the Product[a]	Yield (%)	Ref.
23, R = CO_2Et	110 °C, 24 h	1:1	58	6
	40 °C, 96 h	3:1	31	6
27, R = $CH_2OTBDMS$	210 °C, 18 h	1:4	82	6
28, R = COSPh	110 °C, 16 h	1:1	30	6
	40 °C, 96 h	20:1	75	6
29, R = $CH(OCH_2)_2$	TMSOTf/CH_2Cl_2	40:1	53	9
4, R = CHO	TMSOTf/CH_2Cl_2	3 isomers	20	9

[a] For the formula numbers of the cyclized products, see Scheme 6.

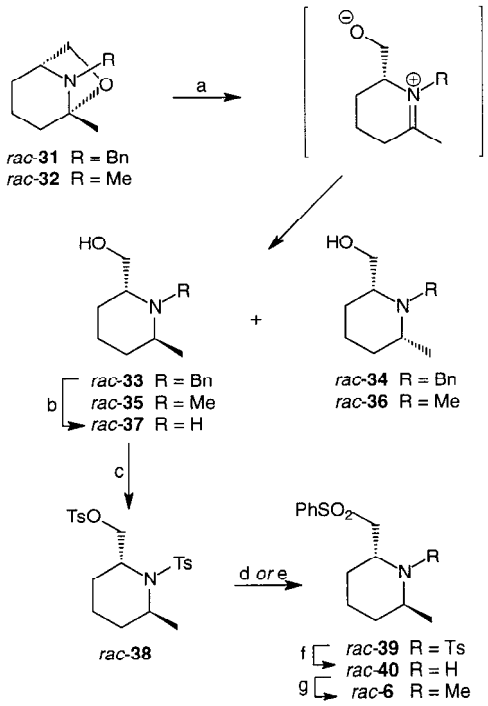
The application of an olefination protocol involving aldehyde **5** requires as coupling partner a 2,6-*trans*-disubstituted piperidine possessing a functionalised one-carbon moiety as one of the substituents. One of the several methods available for realising the thermodynamically less favoured *trans*-configuration is based on the hydride reduction of 1,2,6-trisubstituted iminium derivatives like **30**.[34] As illustrated in Scheme 8, derivatives in which substantial $A^{1,2}$ strain between R_1 and R_6 is involved will preferentially react via a transition state in which this strain is minimized. The stereoelectronically preferred perpendicular hydride attack involving a chair geometry then leads to the *trans*-derivative (α-pathway). In cases where this strain is absent or not determining, reaction will involve a transition state in which R_6 adopts the equatorial orientation and the preferred attack leads now to a *cis*-derivative (β-pathway).



Scheme 8

In the context of himbacine synthesis we were interested in the approach of Wasserman who reported on the synthesis of the hydroxymethyl-substituted piperidine **33** via the reduction of oxatropane **31** with sodium borohydride in methanol (Scheme 9). In accord with the expected stereochemical outcome (cf. Scheme 8), a mixture of *trans*- and *cis*-derivatives **33** and **34** was obtained (93% yield) in a ratio of 92:8, respectively.[35] The synthesis of **31** involves treatment of 5-(oxiran-2-yl)pentan-2-one with benzylamine, a reaction that in principle should allow for an enantioselective application. In view of the *N*-methyl substitution in himbacine we first repeated Wasserman's sequence using methylamine for the preparation of **32**. Unfortunately, reduction of the latter led to a mixture of the *trans*- and *cis*-derivatives **35** and **36**, in a ratio of 2:3, respectively, the loss of stereoselectivity being due to the diminished $A^{1,2}$ strain.

In the context of a synthesis of **6** we decided first to proceed via alcohol **33**. Debenzylation to amino alcohol **37** involved a catalytic hydrogenolysis procedure with ammonium formate (92% yield when using one equivalent of palladium on carbon and five equivalents of ammonium formate).[36] Further treatment with tosyl chloride and tri-



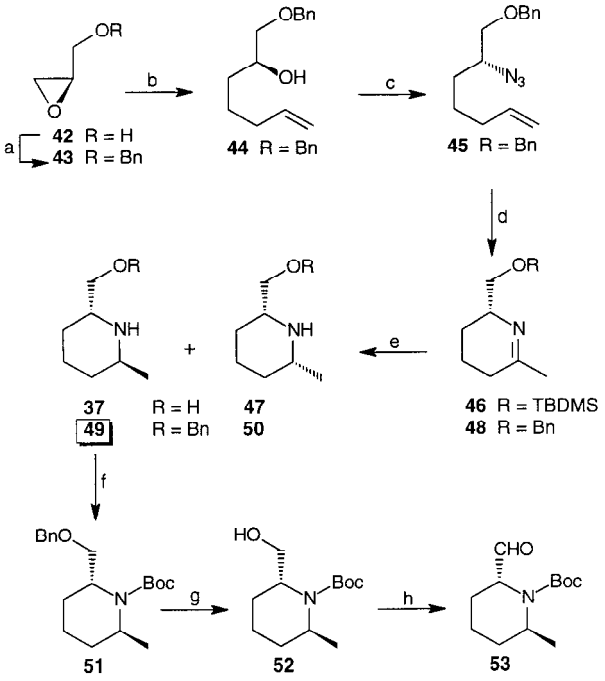
a) $NaBH_4$/MeOH, 93%; b)Pd-C/NH_4HCO_2/MeOH, 92%; c) TsCl/Et_3N/CH_2Cl_2, 40%; d) (i) NaBr in acetone, 85%, (ii) $NaSO_2Ph$/HMPA, 57%; e) (i)PhSH/KOBu-*t*, (ii) MCPBA/Na_2HPO_4, 58% (2 steps); f) HBr in AcOH/phenol/EtOAc, 81%; g) H_2CO in H_2O/$NaCNBH_3$/MeCN/AcOH, 88%

Scheme 9

ethylamine in the presence of dimethylaminopyridine gave the bis-tosylated **38** in low yield (40%). The further transformation to **39** can be realized by the following sequence: (1) Finkelstein reaction to the corresponding bromide (85% yield), followed by substitution with sodium benzenesulfinate in hexamethylphosphoramide (57% yield); or (2) substitution with potassium thiophenolate followed by *m*-chloroperbenzoic acid oxidation (58% over all yield). Cleavage of the sulfonamide required rather harsh conditions: treatment with hydrobromic acid in ethyl acetate in the presence of a large excess of phenol (70 °C, steel vessel, 72 h) led to **40** in 81% yield. Final reductive amination (formaldehyde, sodium cyanoborohydride in acetic acid/acetonitrile) gave **6** in 88% yield (Scheme 9).[37] An almost identical sequence for the conversion of **37** into **6** has been described before for the desmethyl-**6** derivative.[4a]

Next to this rather unattractive sequence we also developed the synthesis of benzyl protected piperidine **49** in the required enantiomeric form. Whereas debenzylation of the latter (sodium, liquid ammonia, –30 °C) led to **37**, an intermediate in the previous synthesis, a more useful application involves its further transformation into **52** and **53**, intermediates described by Hart and Kozikowski.[6] Our sequence (Scheme 10) is useful for large scale application and rests on the methodology that was developed by Taber and co-workers for a synthesis af (*R,R*)-Solenopsin B (cf. **44** to **49**).[38] The synthesis starts from commer-

cially available oxirane **43**, which is also readily obtained from (*R*)-(+)-glycidol **42** via treatment with benzyl bromide in dimethylformamide (72% yield). Subsequent reaction of **43** with the Grignard derivative of 4-bromobut-1-ene in the presence of lithium tetrachlorocuprate in diethyl ether gave **44** in 89% yield.[23] Mitsunobu substitution with zinc diazide bipyridine (diisopropyl azo-dicarboxylate, triphenylphosphine, dichloromethane, –78°C) led to inverted **45** in 90% yield.[39] Thermolysis of the latter (*o*-dichlorobenzene, 165°C, 3 h) led directly to imine **48** (95% crude yield). This transformation involves a [2,3]-cycloaddition with formation of an unstable triazo-line which further decomposes in situ.[40] Subsequent reduction according to Yamamoto's findings (lithium aluminum hydride/trimethylaluminum; –78°C to 0°C) gave the desired *trans*-derivative **49** in 75% yield (ratio **49**:**50** better than 95:5).[41] It is interesting to note that when the *tert*-butyldimethylsilylated derivative **46** (obtained in an analogous way as **48**) was reduced under the same conditions a mixture of **37** and **47** was obtained (ratio 1:3). Presumably the reaction proceeds in this case via prior desilylation. The further transformation to **52** and **53** involves *N*-Boc protection (di-*tert*-butyl dicarbonate, dichloromethane, 97% yield) followed by debenzylation (palladium on carbon, EtOH, quantitative). The stereochemical integrity of the sequence was proven by comparision of the $[\alpha]_D$ values for alcohol **52** found by Hart and Kozikowski[6] and our pathway (+45.4 for c = 0.97 in $CHCl_3$ vs +45.04 for c = 1.07 in $CHCl_3$, respectively).



a) BnBr/NaH/DMF, 72%; b) Mg/4-bromobut-1-ene/Li_2CuCl_4/Et_2O, –78°C to r.t., 89%; c) zinc diazide bipyridine adduct/diisopropyl azodicarboxylate/Ph_3P/CH_2Cl_2, 90%; d) *o*-dichlorobenzene, 165°C, 95%; e) $LiAlH_4$, Me_3Al, THF, –78°C to 0°C, 75%; f) $(Boc)_2O$, CH_2Cl_2, 97%; g) H_2/Pd-C/EtOH, quant.; h) tetrapropylammonium perruthenate/4-methylmorpholine *N*-oxide/powdered molecular sieves/CH_2Cl_2, 98%

Scheme 10

Despite extensive experimentation we have not been able to couple the anion of sulfone **6** with the aldehyde **5** in a synthetically useful way. Deprotonation of the sulfone with butyllithium followed by the addition of **5** and acetic anhydride quench led to recovery of starting material. Also the use of excess of base,[42] or addition of ethylmagnesium bromide gave no reaction.[43] When boron trifluoride etherate was used decomposition was observed.[44]

Only when Ichihara's conditions were applied, in particular the use of hexane/diethyl ether as solvent system (lithium diisopropylamide as the base), could a product be isolated (diastereomeric mixture by ^1H NMR) that showed a satisfactory mass spectrum.[45] However, due to the very low isolated yield (10%) we decided not to pursue this route any further. It is somewhat comforting to note that Hart and Kozikowski also investigated the same Julia coupling without success. They showed however that a reversal of the polarity of the coupling partners, i. e. aldehyde **53** and the anion of a sulfone that was originally derived from thioester **28** (cf. scheme 7), eventually led to the successful synthesis of (+)-himbacine **(1)**.

^1H NMR spectra were recorded on a 500 MHz Bruker AN-500 or a 200 MHz Varian Gemini spectrometer. ^{13}C NMR spectra were recorded on a 360 MHz Bruker WH-360 or a 200 MHz Varian Gemini spectrometer. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hertz, using TMS as internal standard. Optical rotations were recorded at 20°C with a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer. Mass spectra were recorded with a AEI MS-50, a Finnigan 4000 or a Hewlett-Packard 5988 A spectrometer. All solvents were distilled before use; all reagents were of reagent grade, unless otherwise stated.

[(6-Bromohexyl)oxy]-*tert*-butyldimethylsilane (9):
tert-Butyldimethylsilyl chloride (22.90 g, 152.1 mmol) was added to a solution of 6-bromohexan-1-ol (25.00 g, 138.2 mmol), 4-dimethylaminopyridine (1.00 g, 8.2 mmol) and triethylamine (34.85 g, 334.0 mmol) in anhyd CH_2Cl_2 (600 mL) under N_2 atmosphere. After stirring for 16 h, the mixture was poured into satd NH_4Cl solution (500 mL) and extracted with CH_2Cl_2 (3 × 400 mL). The organic phase was washed with H_2O (500 mL), satd $NaHCO_3$ solution (500 mL) and brine (500 mL). After drying ($MgSO_4$) and concentration under vacuum, pure **9** was obtained as a colourless oil (38.71 g, 131.2 mmol, 95%); R_f (hexane/EtOAc, 7:3) 0.75.
IR (film): ν = 2931, 2895, 2857, 1471, 1762, 1388, 1360, 1255, 1130, 836, 775, 662 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.90 (s, 9 H), 1.32–1.40 (m, 2 H), 1.42–1.60 (m, 4 H), 1.85 (tt, 2 H, J = 7.1, 6.9), 3.40 (t, 2 H, J = 6.9), 3.60 (t, 2 H, J = 6.5).
MS: m/z (rel.intensity, %) = 295 ($[M]^{+\cdot}$, 1), 149 (12), 105 (7), 83 (100), 75 (28), 55 (80).

(Oct-7-ynyl)-*tert*-butyldimethylsilane (10):
To a solution of lithium acetylide, ethylenediamine complex (9.55 g, 103.8 mmol) in anhyd DMSO (50 mL) at 8°C under argon atmosphere, was added dropwise bromide **9** (25.0 g, 84.7 mmol) over 2 h. The resulting brown suspension was stirred for 1 h, while the temperature was allowed to rise to r.t. H_2O (25 mL) was added very carefully, after which the solution was poured into H_2O (120 mL). After extraction with hexane (3 × 120 mL), drying of the organic phase ($MgSO_4$) and removal of the solvents under reduced pressure, the crude product was purified by distillation (75°C/0.05 Torr) to give **10** as a colourless oil (18.72 g, 95.50 mmol, 92%); R_f (hexane/EtOAc, 9:1) 0.77.

IR (film): ν = 3310, 2934, 2858, 2160, 1460, 1255, 1099, 835, 774, 631 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.89 (s, 9 H), 1.30–1.45 (m, 4 H), 1.52 (m, 4 H), 1.93 (t, 1 H, *J* = 2.6), 2.18 (td, 2 H, *J* = 7.1, 2.6), 3.60 (t, 2 H, *J* = 6.5).
MS: *m/z* (rel.intensity, %) = 240 ($[M]^{+\cdot}$, 1), 200(5), 173 (6), 147 (42), 112 (18), 83 (20), 75 (100), 53 (50).

Methyl 9-(*tert*-Butyldimethylsilyloxy)non-2-ynoate (11):
To a solution of acetylene **10** (27.00 g, 112.5 mmol) in anhyd Et_2O (500 mL) was added dropwise BuLi (51.4 mL, 2.34 M in hexanes, 120.3 mmol) at –78°C under N_2 atmosphere. After stirring for 30 min, dry CO_2 gas was bubbled through the solution for 15 min. The mixture was then poured into 10% citric acid solution (500 mL) at 0°C, and extracted with Et_2O (3 × 350 mL). After drying of the organic phase ($MgSO_4$), the solvent was removed under reduced pressure. The crude acid so obtained was used directly for the next step.
To a solution of KOH (10.0 g, 178 mmol) in H_2O (15 mL) and EtOH (50 mL) at 65°C was added dropwise a solution of Diazald (43.0 g, 200 mmol) in Et_2O (300 mL). The diazomethane liberated was distilled into a solution of the above carboxylic acid (30.0 g, 105.1 mmol) in Et_2O (300 mL) at –10°C. After destruction of the excess of diazomethane with silica gel, the mixture was filtered, and the solvent removed under reduced pressure to give the ester **11** as a pure colourless oil (25.14 g, 84.38 mmol, 75%); R_f (hexane/EtOAc, 95:5) 0.30.
IR (film): ν = 2933, 2858, 2238, 1720, 1475, 1435, 1388, 1360, 1255, 1100, 1006, 938, 836, 776, 753, 662 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.89 (s, 9 H), 1.31–1.45 (m, 4 H), 1.45–1.62 (m, 4 H), 2.33 (t, 2 H, *J* = 7.1), 3.60 (t, 2 H, *J* = 6.5), 3.76 (s, 3 H).
MS: *m/z* (rel.intensity, %) = 283 ($[M–15]^{+\cdot}$, 3), 267 (7), 241 (88), 209 (20), 135 (18), 89 (100), 75 (67).

Methyl (*Z*)-9-(*tert*-Butyldimethylsilyloxy)non-2-enoate (12):
To a solution of 10% Pd/$BaSO_4$ (440 mg) in Et_2O (650 mL) was added quinoline (392 μL). The mixture was stirred for 30 min under H_2 atmosphere, after which ynoate **11** (22.1 g, 74.23 mmol) was added. After 16 h, the mixture was filtered over Celite, and the solvent removed under reduced pressure. The crude enoate was purified by column chromatography (hexane/EtOAc, 95:5) to give **12** as a colourless oil (20.2 g, 66.81 mmol, 90%); R_f (hexane/EtOAc, 95:5) 0.35.
IR (film): ν = 2930, 2857, 1727, 1645, 1471, 1437, 1407, 1387, 1360, 1255, 1195, 1175, 1101, 1005, 836, 775, 724, 661 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.30–1.35 (m, 4 H), 1.40–1.55 (m, 4 H), 2.64 (dt, 2 H, *J* = 7.5, 7.4), 3.59 (t, 2 H, *J* = 6.6), 3.70 (s, 3 H), 5.76 (d, 1 H, *J* = 11.5), 6.23 (dt, 1 H, *J* = 11.5, 7.5).
MS: *m/z* (rel.intensity, %) = 269 (7), 243 (43), 211 (42), 147 (27), 89 (100), 67 (75).

3-[(*E*)-7-(*tert*-Butyldimethylsilyloxy)hept-1-enyl]-2,5-dihydro-5-methylfuran-2-one (13):
To a solution of diisopropylamine (1.14 mL, 8.14 mmol) in THF (70 mL) was added dropwise BuLi (3.12 mL, 2.5 M in hexane, 7.78 mmol) at –78°C under argon atmosphere. Then hexamethylphosphoramide (1.47 mL, 8.48 mmol) was added, followed by the dropwise addition of a solution of the enoate **12** (2.01 g, 7.07 mmol) in THF (10mL) over 40 min. After stirring for 30 min 2-acetoxypropanal (1.15 g, 9.90 mmol) was added, and the mixture was stirred for 6 h. After slowly warming to –53°C, the mixture was stirred for an additional 90 h at this temperature. Then satd NH_4Cl solution (30 mL) was added, and after warming to r.t., the mixture was extracted with Et_2O (3 × 70 mL). The organic phase was dried ($MgSO_4$), the solvent removed under vacuum and the crude butenolide was purified by HPLC (hexane/EtOAc, 82:18) to give butenolide **13** as a colourless oil (1.49 g, 4.60 mmol, 65%); R_f (hexane/EtOAc, 7:3) 0.58.
IR (film): ν = 2931, 2856, 1758, 1472, 1385, 1318, 1255, 1096, 1029, 975, 836, 775, 668 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.88 (s, 9 H), 1.42 (d, 3 H, *J* = 6.6), 1.30–1.70 (m, 6 H), 2.18 (dt, 2 H, *J* = 7.1, 7.0), 3.59 (t, 2 H, *J* = 6.6), 5.02 (br q, 1 H, *J* = 6.6), 6.09 (d, 1 H, *J* = 16.0), 6.78 (dt, 1 H, *J* = 16.0, 7.0), 7.03 (d, 1 H, *J* = 1.5).
MS: *m/z* (rel.intensity, %) = 309 ($[M–15]^{+\cdot}$, 3), 267 (85), 237 (6), 175 (8), 147 (20), 105 (20), 91 (15), 75 (100), 55 (18).
Side-product **14** (see text): R_f (hexane/EtOAc, 7:3) 0.43.
^1H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.88 (s, 9 H), 1.28 (d, 3 H, *J* = 6.3), 1.30–1.40 (m, 4 H), 1.50 (m, 2 H), 2.02 (s, 3 H), 2.05 (dt, 2 H, *J* = 7.1, 6.7), 2.80 (d, 1 H, *J* = 3.0), 3.15 (dd, 1 H, *J* = 9.2, 4.7), 3.58 (t, 2 H, *J* = 6.6), 3.71 (s, 3 H), 3.93 (ddd, 1 H, *J* = 6.8, 4.7, 3.0), 4.74 (dq, 1 H, *J* = 6.8, 6.3), 5.49 (dd + long range, 1 H, *J* = 15.4, 9.2), 5.60 (dt, 1 H, *J* = 15.4, 6.6).

3-[(*E*)-7-Hydroxyhept-1-enyl)-2,5-dihydro-5-methylfuran-2-one (7):
To a solution of *tert*-butyldimethylsilyl ether **13** (2.11g, 6.51 mmol) in MeCN (50 mL) was added dropwise a 48% aq solution of HF (0.47 mL, 13.00 mmol). After 30 min the mixture was poured into satd $NaHCO_3$ solution and extracted with Et_2O (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuum, and the product purified by HPLC (hexane/EtOAc, 1:1) to give **7** as a colourless oil (1.35 g, 6.43 mmol, 99%); R_f (hexane/EtOAc, 55:45) 0.25.
IR (film): ν = 3427, 2933, 2857, 1740, 1454, 1317, 1205, 1083, 981 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.40 (d, 3 H, *J* = 6.8), 1.32-1.58 (m, 6 H), 2.16 (dt, 2 H, *J* = 7.2, 7.0), 3.61 (t, 2 H, *J* = 6.6), 5.01 (br q, 1 H, *J* = 6.8), 6.08 (d, 1 H, *J* = 16.0), 6.75 (dt, 1 H, *J* = 16.0, 7.0), 7.03 (d, 1 H, *J* = 1.7).
MS: *m/z* (rel.intensity, %) = 210 ($[M]^{+\cdot}$, 5), 192 (7), 174 (7), 163 (6), 147 (10), 135 (9), 119 (9), 105 (11), 91 (20), 79 (28), 67 (23), 55 (30), 43 (100).

(5*S*)-3-[(E)-(7-Hydroxyhept-2-enyl)-2,5-dihydro-5-methylfuran-2-one (18):
(*S*)-Ethyl 4-hydroxypent-2-ynoate (1.300 g, 9.15 mmol) and hept-6-en-1-ol (1.140 g, 10.00 mmol) were dissolved in anhyd and degassed MeOH under argon atmosphere. Cp(COD)RuCl (5 mol %) was added and the mixture was refluxed for 3 h. The orange solution was then cooled to r.t., filtered through a pad of silica gel and washed several times with EtOAc. After concentration in vacuum, purification was effected by column chromatography (pentane/EtOAc, 1:1) to give a mixture of two unseparable alcohols (88:12 by ^1H NMR), the major product being the desired butenolide **18**; R_f (pentane/EtOAc, 7:3) 0.23
IR (film): ν = 3382, 2933, 1748, 1650, 1453, 1321, 1198, 1057, 1023, 972, 873 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): for the major product **18,** δ = 1.40 (d, 3 H, *J* = 6.8), 1.42–1.70 (m, 4 H), 2.07 (q, 2 H, *J* = 7.1), 2.96 (br d, 2 H, *J* = 6.6), 3.24 (t, 2 H, *J* = 6.6), 5.00 (qq, 1 H, *J* = 6.9, 1.7), 5.48 (*A*Bt, 1 H, J_{AB} = 15.1, *J* = 6.6), 5.56 (A*B*t, 1 H, J_{AB} = 15.3, *J* = 6.6), 6.99 (d, 1 H, *J* = 1.6); for the minor product **17,** δ = 1.28 (t, 3 H, *J* = 6.9), 1.31 (d, 3 H, *J* = 6.5), 1.42–1.70 (m, 3 H), 2.02 (q, 2 H, *J* = 7.4), 2.13 (m, 1 H), 3.03 (dd, 1 H, *J* = 13.4, 6.6), 3.55 (dd, 1 H, *J* = 13.5, 6.0), 3.62 (t, 2 H, *J* = 6.6), 4.16 (q, 2 H, *J* = 7.1), 4.32 (br q, 1 H, *J* = 6.5), 5.40–5.60 (m, 2 H), 6.0 (br s, 1 H).

(*E*)-7-[(5*S*)-5-Methyl-2,5-dihydro-2-oxo-3-furanyl]hept-5-enyl Acetate (19):
To a solution of acetyl chloride (190 mg, 2.41 mmol) in anhyd THF (5 mL) were added dropwise pyridine (240 mg, 3.02 mmol) and a mixture of the alcohols **17** and **18** (230 mg, 1.19 mmol) successively at 0°C. After stirring for 30 min, the white suspension was poured into 3 N aq HCl (3N, 5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with H_2O (10 mL), dried ($MgSO_4$) and concentrated in vacuum. The crude liquid was purified by column

chromatography (pentane/EtOAc, 7:3) to afford the desired acetate **19** (250 mg, 0.95 mmol, 80%); R_f (pentane/EtOAc, 1:1) 0.72
IR (film): ν = 2935, 1754, 1654, 1432, 1368, 130, 1241, 1024, 972 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.60 (m, 7 H), 1.41 (d, 3 H, *J* = 6.5), 2.00 (m, 2 H), 2.05 (s, 3 H), 2.95 (d, 2 H, *J* = 5.2), 4.05 (t, 2 H, *J* = 7.0), 5.00 (qd, 1 H, *J* = 6.5, 1.6), 5.49 (*A*Bt, 1 H, J_{AB} = 15.1, *J* = 6.6), 5.53 (A*B*t, 1 H, J_{AB} = 15.3, *J* = 6.6), 7.01 (d, 1 H, *J* = 1.56).
^{13}C NMR (90 MHz, $CDCl_3$): δ = 173.29, 170.90, 149.23, 133.20, 133.20, 126.49, 77.47, 64.22, 31.82, 28.28, 27.94, 25.50, 20.93, 19.53.

(5*S*)-3-[(*E*)-7-Hydroxyhept-1-enyl]-2,5-dihydro-5-methylfuran-2-one (7):
Wilkinson's catalyst (120 mg, 0.17 mmol) and a 0.1 M aq suspension of HCl in $CHCl_3$ (60 μL) were added to a solution of **18** (360 mg, 1.71 mmol) in anhyd $CHCl_3$ (12 mL) under argon atmosphere. After stirring for 17 h at 80°C, the mixture was cooled to r.t., poured into satd Na_2CO_3 solution (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with H_2O, dried ($MgSO_4$), and after removal of the solvents under vacuum, a mixture of isomers was obtained. The crude mixture (consisting of the desired alcohol **7** besides other alcohols **20** and aldehyde **21** as deduced by ^1H NMR of the mixture) was purified by column chromatography (pentane/EtOAc, 1:1) on silica gel activated with $AgNO_3$ to afford the desired butenolide **7** (0.107g, 0.51 mmol, 30%) as a colourless oil; $[\alpha]_D$ +25.02 (*c* = 0.34, $CHCl_3$).
The other experimental data were identical to those described for racemic **7** (vide supra).

(*E*)-7-(5-Methyl-2,5-dihydro-2-oxo-3-furanyl)hept-6-enal (22):
To a solution of oxalyl chloride (2.16 mL, 24.76 mmol) in anhyd CH_2Cl_2 (100 mL) at –60°C under argon atmosphere was added a solution of DMSO (3.50 mL, 49.42 mmol) in CH_2Cl_2 (15 mL). After stirring for 5 min, a solution of alcohol **7** (2.60 g, 12.38 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The mixture was stirred for 1 h, after which Et_3N (14 mL, 100 mmol) was added very slowly (the temperature was kept between –60 and –55°C). After removal of the cooling bath, the mixture was stirred another 30 min, and then poured into a mixture of a 10% citric acid solution (65 mL) and satd aq NH_4Cl solution (65 mL). After extraction with CH_2Cl_2 (3 × 100 mL), washing with satd NH_4Cl solution, drying ($MgSO_4$) and concentration of the solvent, the crude aldehyde was purified by column chromatography (hexane/EtOAc, 6:4) to give the aldehyde **22** as a colourless oil (2.15 g, 20.80 mmol, 84%); R_f (hexane/EtOAc, 1:1) 0.42.
IR (film): ν = 3155, 2985, 2935, 2861, 1741, 1684, 1661, 1558, 1463, 1376, 1319, 1216, 1165, 1094, 1029, 924, cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 6.6), 1.42–1.52 (m, 2 H), 1.60–1.70 (m, 2 H), 2.18 (dt, 2 H, *J* = 7.1, 7.0), 2.44 (dt, 2 H, *J* = 7.3, 1.6), 5.02 (br q, 1 H, *J* = 6.6), 6.09 (d, 1 H, *J* = 16.0), 6.78 (dt, 1 H, *J* = 16.0, 7.0), 7.04 (d, 1 H, *J* = 1.5), 9.75 (t, 1 H, *J* = 1.6).
MS: *m*/*z* (rel.intensity, %) = 208 ($[M]^{+\cdot}$, 2), 190 (10), 164 (5), 137 (4), 119 (12), 105 (8), 91 (16), 79 (16), 67 (22), 55 (17), 43 (100).

Ethyl (2*E*,8*E*)-9-[(5*S*)-5-Methyl-2,5-dihydro-2-oxo-3-furanyl]nona-2,8-dienoate (23):
To a stirred suspension of LiCl (57.6 mg, 1.36 mmol) in anhyd MeCN (12 mL) under N_2 atmosphere were added dropwise triethyl phosphonoacetate (270 µL, 1.36 mmol), DBU (168 µL, 1.12 mmol) and a solution of the aldehyde **22** (237 mg, 1.13 mmol) in MeCN (1 mL). After 2 h, the mixture was poured into satd aq NH_4Cl solution and extracted with Et_2O (3 × 15 mL). After washing with brine, the solvents were removed under reduced pressure and the product was purified by HPLC (hexane/EtOAc, 78:22) to give **23** as a colourless oil (235 mg, 0.85 mmol, 75%); R_f (hexane/EtOAc, 7:3) 0.32.
IR (film): ν = 2981, 2932, 2857, 1755, 1717, 1654, 1448, 1368, 1318, 1267, 1184, 1147, 1084, 1041, 978 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, *J* = 7.1), 1.42 (d, 3 H, *J* = 7.0), 1.47 (m, 4 H), 2.14–2.25 (m, 4 H), 4.17 (q, 2 H, *J* = 7.1), 5.02 (br q, 1 H, *J* = 7.0), 5.80 (dt, 1 H, *J* = 15.6, 1.4), 6.09 (d, 1 H, *J* = 15.7), 6.78 (dt, 1 H, *J* = 15.7, 7.0), 6.95 (dt, 1 H, *J* = 15.6, 7.0), 7.04 (d, 1 H, *J* = 1.3).
MS: *m*/*z* (rel.intensity, %) = 278 ($[M]^{+\cdot}$, 3), 260 (2), 232 (18), 214 (10), 204 (19), 187 (6), 171 (5), 161 (14), 136 (13), 119 (8), 105 (10), 94 (22), 81 (32), 67 (25), 55 (20), 43 (100).

Diels–Alder Adducts Ethyl (3*S*,3a*R*,4*R*,4a*S*,8a*R*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxobenzo[*f*]isobenzofuran-4-carboxylate (24) and Ethyl (3*S*,3a*R*,4*S*,4a*R*,8a*R*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxobenzo[*f*]isobenzofuran-4-carboxylate (25) and Their Enantiomers:
A solution of **23** (100 mg, 0.36 mmol) and di-*tert*-butylcresol (10 mg) in toluene (12 mL) was heated in a steel vessel at 170°C for 48 h. After cooling to r.t., filtering and removal of the solvent, the mixture was purified by HPLC (hexane/EtOAc, 3:1) to give a 1:1 mixture of adducts **24** and **25** (83 mg, 0.30 mmol, 83%); R_f (hexane/EtOAc, 7:3) 0.23.
IR (film): ν = 2928, 2856, 1766, 1730, 1684, 1450, 1387, 1260, 1223, 1174, 1036, 954, 931, 866, 799, 742 cm^{-1}.
MS: *m*/*z* (rel.intensity, %) = 278 ($[M]^{+\cdot}$, 11), 260 (10), 250 (5), 235 (10), 205 (12), 187 (9), 177 (46), 166 (29), 149 (20), 133 (33), 119 (12), 105 (18), 91 (47), 79 (22), 69 (27), 55 (42), 43 (100).
^1H NMR (500 MHz, $CDCl_3$): *exo*-adduct **25**: δ = 1.00–1.20 (m, 4 H), 1.30 (t, 3 H, *J* = 7.2), 1.40 (d, 3 H, *J* = 6.1), 1.50–1.70 (m, 4 H), 2.17 (m, 1 H), 2.46 (m, 1 H, Σ*J* = 23.0), 2.50 (dd, 1 H, *J* = 11.3, 10.5), 2.93 (ddd, 1 H, *J* = 12.5, 10.5, 2.6), 4.13 (q, 2 H, *J* = 7.2), 4.26 (dq, 1 H, *J* = 9.2, 6.1), 6.70 (dd, 1 H, *J* = 3.5, 2.6); *endo*-adduct **24**: δ = 1.00–1.20 (m, 4 H), 1.30 (t, 3 H, *J* = 7.2), 1.36 (d, 3 H, *J* = 6.1), 1.50–1.72 (m, 4 H), 1.80 (m, 1 H), 2.05 (m, 1 H), 2.73 (dd, 1 H, *J* = 11.0, 10.5), 2.81 (ddd, 1 H, *J* = 11.0, 10.5, 2.9), 4.20 (q, 2 H, *J* = 7.2), 4.38 (dq, 1 H, *J* = 9.2, 6.1), 6.65 (dd, 1 H, *J* = 3.8, 2.9).

(2*E*,8*E*)-9-(2,5,Dihydro-5-methyl-2-oxo-3-furanyl)nona-2,8-dienal (4):
To a solution of $ZnBr_2$ (590 mg, 4.05 mmol) and aldehyde **22** (710 mg, 3.38 mmol) in anhyd THF (50 mL) was added 2,2-bis(trimethylsilyl)-*tert*-butylacetaldimine (5.7 g, 23.6 mmol) at 10°C under N_2 atmosphere. The mixture was warmed to r.t. and stirred for 16 h. An aqueous solution of oxalic acid (5% w/w) was added until pH = 4, and the mixture was stirred for another 16 h. The mixture was extracted with Et_2O (3 × 50 mL), washed with brine and dried ($MgSO_4$). After removal of the solvents, the crude product was purified by HPLC (hexane/EtOAc, 55:45) to give the unsaturated aldehyde **4** (522 mg, 2.67 mmol, 66%); R_f (hexane/EtOAc, 7:3) 0.21.
IR (CH_2Cl_2): ν = 2934, 2859, 1754, 1688, 1432, 1362, 1320, 1251, 1223, 1161, 1122, 1085, 1029, 975, 909, 768, 738 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 6.8), 1.49–1.58 (m, 4 H), 2.20 (dt, 2 H, *J* = 7.0, 6.7), 2.35 (dtd, 2 H, *J* = 7.0, 6.3, 1.3), 5.03 (br q, 1 H, *J* = 6.8), 6.10 (br d, 1 H, *J* = 15.8), 6.13 (ddd, 1 H, *J* = 15.6, 7.9, 1.4), 6.80 (dt, 1 H, *J* = 15.8, 7.0), 6.85 (dt, 1 H, *J* = 15.6, 6.8), 7.03 (d, 1 H, *J* = 1.7), 9.50 (d, 1 H, *J* = 7.9).
MS: *m*/*z* (rel.intensity, %) = 216 ($[M–18]^{+\cdot}$, 4), 187 (6), 171 (7), 137 (10), 119 (16), 110 (23), 95 (32), 67 (40), 43 (100).

Diels–Alder Adducts (3*S*,3a*R*,4*R*,4a*S*,8a*R*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxobenzo[*f*]isobenzofuran-4-carbaldehyde (5) and (3*S*,3a*R*,4*S*,4a*R*,8a*R*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxobenzo[*f*]isobenzofuran-4-carbaldehyde (26) and Their Enantiomers:
A solution of **4** (350 mg, 1.49 mmol) and di-*tert*-butylcresol (70 mg) in toluene (15 ml) was heated in a steel vessel at 170°C for 24 h. After cooling to r.t., filtering and removal of the solvent, a mixture of 4 adducts in a 10:8:1:6 ratio was obtained (83 mg, 0.30 mmol, 83%). Purification by HPLC (hexane/EtOAc, 3:1) gave pure adducts **5** and **26**

in 40% (140 mg, 0.60 mmol), and 25% (87.5 mg, 0.37 mmol) isolated yield, respectively; R_f (hexane/EtOAc, 7:3) 0.25.
IR (film): ν = 2930, 2857, 1756, 1686, 1447, 1387, 1326, 1222, 1051, 1032, 922, 908, 759, 718, 689 cm^{-1}.
MS: *m*/*z* (rel.intensity, %) = 234 ($[M]^{+\cdot}$, 6), 219 (3), 216 (16), 190 (31), 173 (10), 161 (100), 145 (18), 133 (21), 105 (32), 91 (70), 77 (25), 65 (13), 43 (16).
^{1}H NMR (500 MHz, $CDCl_3$): *endo*-adduct **5**: δ = 1.10–1.40 (m, 3 H), 1.41 (d, 3 H, *J* = 6.1), 1.49–1.75 (m, 3 H), 1.80 (m, 2 H), 2.31 (m, 1 H), 2.46 (m, 1 H, ΣJ = 29.0), 2.55 (ddd, 1 H, *J* = 10.9, 9.3, 4.4), 2.93 (ddd, 1 H, *J* = 9.3, 9.2, 3.2), 4.15 (dq, 1 H, *J* = 9.2, 6.1), 6.72 (dd, 1 H, *J* = 3.8, 3.2), 9.74 (d, 1 H, *J* = 4.4); *exo*-adduct **26**: δ = 1.10–1.40 (m, 5 H), 1.45 (d, 3 H, *J* = 6.1), 1.80 (m, 4 H), 2.12 (m, 1 H, ΣJ = 25.0), 2.73 (ddd, 1 H, *J* = 10.6, 10.4, 4.3), 2.88 (ddd, 1 H, *J* = 10.4, 9.2, 3.4), 4.42 (dq, 1 H, *J* = 9.2, 6.1), 6.72 (dd, 1 H, *J* = 3.4, 3.0), 9.69 (d, 1 H, *J* = 4.3).

(2*S*)-1-(Benzyloxy)hept-6-en-2-ol (44):
To a suspension of Mg (4.007 g, 164.84 mmol) in Et_2O (10 mL) was added dropwise under argon atmosphere a solution of 4-bromobut-1-ene (20.230 g, 149.85 mmol) in Et_2O (100 mL). After 30 min, the mixture was cooled to –78°C, and a 0.1 M THF solution of lithium tetrachlorocuprate (50 mL, 5.00 mmol) was added, followed by the dropwise addition of **43** (7.710 g, 49.95 mmol). The mixture was stirred overnight, while the temperature was allowed to warm to r.t. The dark solution was cooled to 0°C, and a satd aq solution of NH_4Cl (200 mL) was added carefully. The mixture was extracted with Et_2O (3 × 250 mL), the combined organic phases were dried ($MgSO_4$) and the solvent was removed under vacuum. The product was further purified by distillation (137°C/ 0.7 Torr) to give **44** as a colourless oil (9.794 g, 44.46 mmol, 89%); R_f (isooctane/EtOAc, 4:1) 0.32;
$[\alpha]_D$ –3.65 (*c* = 1.07, $CHCl_3$).
IR (film): ν = 3445, 3065, 3030, 2929, 2860, 1640, 1496, 1454, 1364, 1310, 1255, 1206, 1098, 1028, 997, 911, 737, 698 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40–1.60 (m, 4 H), 2.07 (m, 2 H), 3.33 (*AX*d, 1 H, J_{AX} = 9.3, *J* = 7.9), 3.51 (A*X*d, 1 H, J_{AX} = 9.4, *J* = 3.0), 3.82 (m, 1 H), 4.56 (s, 2 H), 4.89 (br d, 1 H, *J* = 17.0), 5.01 (br d, 1 H, *J* = 10.2), 5.80 (ddt, 1 H, *J* = 16.9, 10.2, 6.7), 7.29–7.38 (m, 5 H).
^{13}C NMR + DEPT (50 MHz, $CDCl_3$): δ = 24.75 (CH_2), 32.48 (CH_2), 33.67 (CH_2), 70.25 (CH), 73.32 (CH_2), 74.58 (CH_2), 114.65 (CH_2), 127.72 (CH), 127.78 (CH), 128.45 (CH), 137.94 (C), 138.57 (CH).
MS: *m*/*z* (rel.intensity, %) = 220 ($[M]^{+\cdot}$, 1), 189 (1), 171 (1), 129 (1), 122 (5), 121 (4), 107 (13), 91 (100), 81 (51), 65 (18), 55 (26).

(6*R*)-6-Azido-7-(benzyloxy)hept-1-ene (45):
Zinc diazide bipyridine adduct (9.310 g, 30.27 mmol), prepared as described by Viaud and Rollin,[39] was added to a solution of **44** (8.890 g, 40.35 mmol) and PPh_3 (21.167 g, 80.70 mmol) in anhyd toluene (250 mL) under argon atmosphere. Diisopropyl azodicarboxylate (16.318 g, 80.70 mmol) was added dropwise to the above mixture, causing a slight exothermic reaction. After 3 h, the mixture was filtered over silica gel. Further purification was effected by column chromatography (pentane/EtOAc, 19:1) which gave **45** as a colourless oil (8.909 g, 36.32 mmol, 90%); R_f (isooctane/EtOAc, 9:1) 0.63;
$[\alpha]_D$ –20.10 (*c* = 3.88, $CHCl_3$).
IR (film): ν = 3065, 3030, 2938, 2860, 2106, 1640, 1496, 1454, 1364, 1340, 1272, 1207, 1115, 1028, 995, 912, 737, 698, 626 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41–1.57 (m, 4 H), 2.67 (m, 2 H), 3.49 (*AB*d, 1 H, J_{AB} = 8.7, *J* = 8.6), 3.52 (m, 1 H), 3.57 (A*B*d, 1 H, J_{AB} = 8.7, *J* = 2.7), 4.58 (s, 2 H), 4.98 (br d, 1 H, *J* = 10.2), 5.02 (br d, 1 H, *J* = 17.2), 5.78 (ddt, 1 H, *J* = 17.0, 10.2, 6.7), 7.28–7.38 (m, 5 H).
^{13}C NMR + DEPT (50 MHz, $CDCl_3$): δ = 25.08 (CH_2), 30.12 (CH_2), 33.23 (CH_2), 61.60 (CH), 72.69 (CH_2), 73.14 (CH_2), 114.88 (CH_2), 127.40 (CH), 127.57 (CH), 128.28 (CH), 137.71 (C), 137.95 (CH).
MS: *m*/*z* (rel.intensity, %) = 244 ($[M]^{+\cdot}$ –1, 1), 216 (4), 186 (2), 174 (2), 148 (7), 140 (4), 105 (4), 91 (100), 65 (15), 41 (26).

(2*R*,6*S*)-2-[(Benzyloxy)methyl]-6-methylhexahydropyridine (49):
A solution of **45** (7.486g, 30.51 mmol) in anhyd 1,2-dichlorobenzene (50 mL) was heated for 3 h at 165°C under N_2 atmosphere. The mixture was cooled to r.t. and the solvent was removed by distillation, giving the crude imine **48**, which was used immediately in the following reduction without purification.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (m, 1 H), 1.58 (m, 1 H), 1.78 (m, 1 H), 1.85 (m, 1 H), 1.93 (s, 3 H), 2.04–2.16 (m, 2 H), 3.38 (*AX*d, 1 H, J_{AX} = 8.7, *J* = 8.1), 3.53 (m, 1 H), 3.74 (A*X*d, 1 H, J_{AX} = 9.1, *J* = 4.8), 4.55 (*AB*, 1 H, J_{AB} = 12.3), 4.61 (A*B*, 1 H, J_{AB} = 12.3), 7.28–7.36 (m, 5 H).
To a suspension of $LiAlH_4$ (8.535 g, 213.61 mmol) in anhyd THF (250 ml) at –78°C under N_2 atmosphere was slowly added a solution of **48** in THF (50 mL), followed by the dropwise addition of a 2 M hexane solution of Me_3Al (106.8 mL, 213.61 mmol) over 30 min. The mixture was stirred for 30 min at –78°C, 1 h at –45°C, 1 h at –20°C and finally 1 h at 0°C. Still at 0°C, the solution was diluted with Et_2O (200 mL), after which NaF (35.875 g, 854.4 mmol) was added. Then H_2O (11.54 g, 640.8 mmol) was added very carefully, after which the slurry was stirred for 15 min. After filtration over Celite, the residue was dried ($MgSO_4$). The crude product was purified by column chromatography (Et_2O/Et_3N, 99:1) to afford **49** (5.018 g, 22.88 mmol, 75%) as a colourless oil; R_f (Et_2O/Et_3N, 99:1) 0.31; $[\alpha]_D$ +8.92 (*c* = 1.11, $CHCl_3$). The *cis*-piperidine **50** was obtained when no Me_3Al was used in the reaction.
IR (film): ν = 3322, 3088, 3030, 2929, 2861, 1496, 1454, 1367, 1330, 1207, 1098, 1028, 946, 736, 680 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): 2,6-*trans*-piperidine **49**: δ = 1.07 (d, 3 H, *J* = 6.2), 1.23 (m, 1 H), 1.32 (m, 1 H), 1.44 (m, 1 H), 1.54–1.63 (m, 3 H), 3.01 (qdd, 1 H, *J* = 6.6, 6.2, 3.2), 3.20 (m, 1 H), 3.35 (dd, 1 H, *J* = 9.1, 4.3), 3.54 (app t, 1 H, *J* = 9.1), 4.52 (*AB*, 1 H, *J* = 12.1), 4.54 (A*B*, 1 H, *J* = 12.1), 7.27–7.37 (m, 5 H); *cis*-piperidine **50**: δ = 1.07 (d, 3 H, *J* = 6.3), 1.27–1.41 (m, 2 H), 1.50 (m, 1 H), 1.59 (m, 1 H), 1.78 (m, 1 H), 1.85 (m, 1H), 2.62 (qdd, 1 H, *J* = 6.3, 4.7, 2.6), 2.84 (ddt, 1 H, *J* = 11.3, 8.7, 2.8), 3.33 (*AX*d, 1 H, J_{AX} = *J* = 8.9), 3.46 (A*X*d, 1 H, J_{AX} = 9.0, *J* = 3.4), 4.47 (*AB*, 1 H, J_{AB} = 11.8), 4.55 (A*B*, 1 H, J_{AB} = 11.8), 7.26–7.37 (m, 5 H).
^{13}C NMR + DEPT (50 MHz, $CDCl_3$): *trans*-piperidine **49**: δ = 19.50 (CH_2), 20.95 (CH_3), 26.94 (CH_2), 32.34 (CH_2), 45.28 (CH), 50.03 (CH), 71.72 (CH_2), 72.92 (CH_2), 127.30 (CH), 127.35 (CH), 128.08 (CH), 138.16 (C).
MS: *m*/*z* (rel.intensity, %) = 219 ($[M]^{+\cdot}$, 1), 218 ($[M]^{+\cdot}$ –1, 1), 204 (2), 199(2), 126 (3), 113 (4), 111 (5), 105 (4), 98 (100), 91 (34), 65 (12), 55 (18).

(2*R*,6*S*)-(6-Methylhexahydro-2-pyridinyl)methanol (37):
Ammonia (20 mL) was distilled into a dry flask and cooled to –78°C. Na (50 mg) was added, which turned the solution deep blue. A solution of **49** (250 mg, 1.14 mmol) in Et_2O (5 mL) was added dropwise, followed by the addition of *tert*-butyl alcohol (150 mg). The cooling bath was removed, and the mixture was refluxed at –30°C. After 2 h, solid NH_4Cl was added until the blue colour disappeared. The ammonia was removed by a stream of air, after which the residue was taken up in CH_2Cl_2 and filtered over Celite. After removal of the solvents, the amino alcohol **37** (127 mg, 0.983 mmol, 86%) was obtained as a light yellow oil; R_f [hexane/acetone (2% aq NH_3), 55:45] 0.11.
IR (film): ν = 3299, 2930, 2864, 1633, 1442, 1378, 1330, 1125, 1051, 955, 824 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.08 (d, 3 H, *J* = 6.6), 1.15–1.70 (m, 6 H), 3.00 (m, 2 H), 3.42 (dd, 1 H, *J* = 10.3, 4.7), 3.62 (dd, 1 H, *J* = 10.3, 9.6).
MS: *m*/*z* (rel.intensity, %) = 129 ($[M]^{+\cdot}$, 6), 128 (8), 114 (10), 106 (10), 98 (100), 81 (9), 70 (10), 56 (20), 44 (20).

***tert*-Butyl (2*R*,6*S*)-2-[(Benzyloxy)methyl]-6-methylhexahydro-1-pyridinecarboxylate (51):**
To a solution of di-*tert*-butyl dicarbonate (3.497 g, 16.02 mmol) in anhyd CH_2Cl_2 (100 mL) at 0°C under N_2 atmosphere was added the pi-

peridine **49** (3.195 g, 14.56 mmol), and the mixture was stirred overnight, while the temperature was allowed to rise to r.t. The mixture was poured into satd aq NH_4Cl solution (150 mL), extracted with CH_2Cl_2 (3 × 100 mL) and dried ($MgSO_4$). After removal of the solvent, the product was purified by column chromatography (isooctane/EtOAc, 9:1) to give **51** as a colourless oil (4.512 g, 14.12 mmol, 97%); R_f (isooctane/EtOAc, 85:15) 0.42; $[\alpha]_D$ +50.0 (*c* = 2.04, $CHCl_3$).
IR (film): ν = 2971, 2871, 1810, 1757, 1689, 1454, 1390, 1365, 1323, 1254, 1178, 1092, 880, 773, 737, 698 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, 1 H, *J* = 6.7), 1.44 (s, 9 H), 1.51–1.96 (m, 6 H), 3.47 (*A*Bd, 1 H, J_{AB} = *J* = 9.4), 3.56 (A*B*d, 1 H, J_{AB} = 9.0, *J* = 3.9), 3.99 (m, 2 H), 4.51 (*A*B, 1 H, J_{AB} = 12.0), 4.59 (A*B*, 1 H, J_{AB} = 12.0), 7.28–7.34 (m, 5 H).
^{13}C NMR + DEPT (50 MHz, $CDCl_3$): δ = 13.40 (CH_2), 20.39 (CH_3), 21.50 (CH_2), 26.97 (CH_2), 28.49 (CH_3), 46.90 (CH), 50.35 (CH), 71.39 (CH_2), 72.89 (CH_2), 79.18 (C), 127.51 (CH), 127.59 (CH), 128.32 (CH), 138.52 (C), 155.10 (C).

***tert*-Butyl (2*R*,6*S*)-2-(Hydroxymethyl)-6-methylhexahydro-1-pyridinecarboxylate (52):**
Benzyloxypiperidine **51** (4.400 g, 13.77 mmol) was dissolved in EtOH (140 mL) and 10% Pd/C (0.22 g, 5% w/w) was added. The mixture was stirred for 3 h under an atmosphere of H_2. After filtration over Celite and concentration under vacuum, the pure alcohol **52** (3.158 g, 13.77 mmol, 100%) was obtained as white crystals. An analytical sample was obtained by HPLC (isooctane/EtOAC, 8:2); R_f (isooctane/EtOAc, 8:2) 0.28; $[\alpha]_D$ +45.04 (*c* = 1.07, $CHCl_3$).
IR (film): ν = 3434, 2972, 2875, 1670, 1457, 1379, 1365, 1328, 1253, 1176, 1126, 1091, 1050, 878, 773 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.79 (d, 3 H, *J* = 6.9), 1.45 (s, 9 H), 1.47–1.77 (m, 6 H) 3.62–3.68 (m, 2 H), 3.75 (dd, 1 H, *J* = 11.4, 7.2), 4.18 (m, 1 H).
^{13}C NMR + DEPT (50 MHz, $CDCl_3$): δ = 15.86 (CH_2), 18.50 (CH_3), 25.20 (CH_2), 27.93 (CH_2), 28.43 (CH_3), 48.33 (CH), 54.15 (CH_2), 66.16 (CH), 79.87 (C), 158.38 (C).
MS: *m*/*z* (rel.intensity, %) = 213 ($[M–16]^{+\cdot}$, 1), 198 (5), 183 (1), 169 (2), 156 (6), 143 (10), 142 (77), 98 (47), 69 (19), 57 (100).

***tert*-Butyl (2*R*,6*S*)-2-Formyl-6-methylhexahydro-1-pyridinecarboxylate (53):**
To a mixture of **52** (3.050 g, 13.30 mmol), 4-methylmorpholine *N*-oxide (2.337 g, 19.95 mmol) and powdered molecular sieves (1.525 g) in anhyd CH_2Cl_2 (6 mL) was added tetrapropylammonium perruthenate (0.234 g, 0.066mmol) under argon atmosphere, and the mixture was stirred for 2 h. After concentration under vacuum, the black mixture was dissolved in EtOAc and filtered over silica gel. The solvent was removed under vacuum and the crude product was purified by column chromatography (pentane/EtOAc, 85:15) to give **53** (2.963 g, 13.03 mmol, 98%) as a colourless oil; R_f (isooctane/EtOAc, 4:1) 0.48; $[\alpha]_D$ +127.6 (*c* = 1.46, $CHCl_3$).
IR (film): ν = 2975, 2942, 2875, 2815, 2716, 1732, 1682, 1456, 1393, 1370, 1299, 1234, 1170, 1135, 1072, 1058, 1026, 887, 777 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, 3 H, *J* = 6.8), 1.39 (m, 1 H), 1.46 (s, 9 H), 1.57–1.74 (m, 5 H), 3.62 (dt, 1 H, *J* = 12.3, 3.9), 4.27 (br s, 1 H), 9.29 (d, 1 H, *J* = 3.8).
^{13}C NMR + DEPT (50 MHz, $CDCl_3$): δ = 15.00 (CH_3), 16.00 (CH_2), 25.15 (CH_2), 27.95 (CH_3), 29.06 (CH), 47.10 (CH), 58.96 (CH), 76.90 (C), 196.34 (C).
MS: *m*/*z* (rel.intensity, %) = 198 (34), 154 (32), 142 (29), 128 (3), 98 (36), 84 (8), 69 (9), 57 (100).

We are grateful to "Fonds voor Wetenschappelijk Onderzoek–Vlaanderen" for financial support. S. H. and G. D. B. thank IWT for their scholarships.

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