Highly Efficient and Stereoselective Radical Addition of Tertiary Amines to Electron-Deficient Alkenes − Application to the Enantioselective Synthesis of Necine Bases

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A convenient and highly efficient method for the regio- and stereoselective addition of tertiary amines to electron-deficient alkenes has been elaborated. It is based on a radical chain reaction of α-aminyl radicals with alkenes, induced by a photoelectron transfer process between tertiary amines **2a**–**j** and excited electron donor substituted phenyl ketones. The influence of the nature of the amino substituents and of the alkene on the reaction have been examined. In the presence of (5*R*)-5-menthyloxy-2-(5*H*)-furanone (**1**) as electron-deficient alkene, the addition of *N*-alkylpyrrolidines **2a**–**e** occurred with a complete facial selectivity and up to 94% isolated yields. This method has been applied to a fast, efficient and enantioselective synthesis of necine bases.

Introduction

During the past twenty years, there has been a considerable increase in activity in the field of synthetic applications of functionalized radicals.[1] From retrosynthetic analyses, it appears that sequences involving radicals for the formation of C−C bonds can be introduced in the synthesis of many nitrogen-containing molecules, alkaloids, and amino acids. Among the numerous possibilities, α-aminoalkyl radicals, which possess an electron-rich or nucleophilic character, should be particularly interesting species for selective additions to electron-deficient alkenes and for synthetic applications.[2]

Despite their synthetic potential, there has not been considerable activity in the intermolecular addition of α-aminoalkyl radicals to alkenes,[1] even if several methods have been proposed for the preparation of these radicals. For example, α-aminoalkyl radicals can be obtained by homolysis of C−X bonds in the α-position relative to the nitrogen atom.[3] The instability of precursors might explain the relatively few reports and the need for new selective methods to initiate radical additions of tertiary amines to alkenes. Due to the low dissociation energy of α-amino C−H bonds, the formation of α-aminoalkyl radicals directly from tertiary amines should be very favourable.[4] In agreement with this energetic aspect, the direct addition of tertiary amines to alkenes involving a radical chain process, initiated in the presence of peroxides, was already reported more than forty years ago.[5] Unfortunately, the low chemical yields and a large amount of oligomerization products[6] precluded this approach for synthetic applications. α-Aminoalkyl radicals are also produced by electron transfer between arenes and amines[7] or by one-electron reduction of imines or imonium ions.[2]

Another access to α-aminoalkyl radicals, which has led to many mechanistic investigations, can be realized through the photoreduction of aromatic ketones in the presence of tertiary amines.[8,9] In contrast to the numerous applications of the reactivity of ketyl radicals and corresponding radical anions[10] and except for initiating polymerisations, few synthetic applications involving the amino radical cation or the corresponding α-amino radical intermediates, had been described until recently.[6,11]

In the absence of synthetic applications involving a direct intermolecular addition of tertiary amines to electron-deficient alkenes, we started a program in order to develop an efficient and highly stereoselective way of production and addition of electron-rich α-aminoalkyl radicals to electron-deficient alkenes and especially to the chiral furanone **1**.[12] The similar nucleophilic character of α-aminoalkyl and ketyl radicals[13] led us to anticipate that the low chemical yields usually observed in the intermolecular addition of tertiary amines with alkenes in the presence of benzophenone as sensitizer, might be due to oligomerization processes and by-products involving the sensitizer as well.[14]

We decided to carefully examine the role of the sensitizer. We will also discuss the limits and the conditions required for a general, efficient, and stereoselective addition of tertiary and secondary amines to electron-deficient alkenes through a radical chain mechanism.[15] The high efficiency and stereoselectivity available, made our procedure very attractive for synthetic applications in the field of natural products. This aspect will also be illustrated by a rapid and high-yielding synthesis of enantiopure necine alkaloids.

Results and Discussion

When menthyloxyfuranone **1** (0.2 mol L^{-1}) in acetonitrile was irradiated at 350 nm, in the presence of *N*-methyl-

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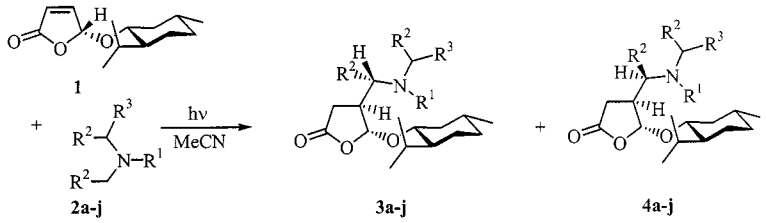


Scheme 1. Radical addition of tertiary amines **2a−j** to (5*R*)-5-menthyloxy-2(5*H*)-furanone (**1**)

pyrrolidine (**2a**) (5 equiv.) and benzophenone (1 equiv.), as described in the literature, two diastereomeric adducts **3a** (18%) and **4a** (15%) could be isolated from a complex reaction mixture (Scheme 1).[11b,11c] The structure of the adducts was determined from NMR data and the stereochemistry could be proved by chemical correlation (see later). For the addition step, the approach of the furanone ring takes place exclusively from the less-hindered side. Unfortunately, only little selectivity was observed for the second asymmetric carbon atom created in α-position of the nitrogen atom. Similar results and an extensive degradation of the starting material were also obtained, when acetophenone was used as sensitizer. According to the literature, the electron transfer process is an energetically favoured process when aromatic ketones are irradiated in the presence of trialkylamines. Furthermore, α-aminoalkyl radicals and ketyl radicals can be obtained from ketones having a lowest ($n \rightarrow \pi^*$) or ($\pi \rightarrow \pi^*$) excited state and even from aromatic ketones in a charge transfer excited state such as Michler's ketone.

To avoid coupling products involving the sensitizer, we examined the effect of electron-donating substituents in the *p*-position on the benzene ring which might prevent additions on the aromatic ring and stabilize the ketyl intermediates. We were satisfied to see that the replacement of benzophenone by its substituted derivatives not only simplified the reaction mixture but also considerably improved the isolated yields. From the results summarized in Table 1 and under the same irradiation conditions as for the preliminary experiments, 4,4′-dimethoxybenzophenone and 4,4′-dimethylaminobenzophenone could be considered as the best sensitizers. In order to optimize the reaction and to minimize the oligomerization process, we examined the effect of the concentration of the reagents on the chemical yields in the presence of 4,4′-dimethoxybenzophenone as sensitizer. Little change was observed when the concentration of the sensitizer was decreased from 1 to 0.05 mol-equiv. of **1**, but the chemical yield increased, as expected, with an increase in the concentration of the amine or a decrease in the concentration of **1**. When the starting concentration of **1** was $5 \cdot 10^{-3}$ mol L^{-1} and when 100 equiv. of **2a** were used, **3a** and **4a** could be isolated with a yield of 94%.

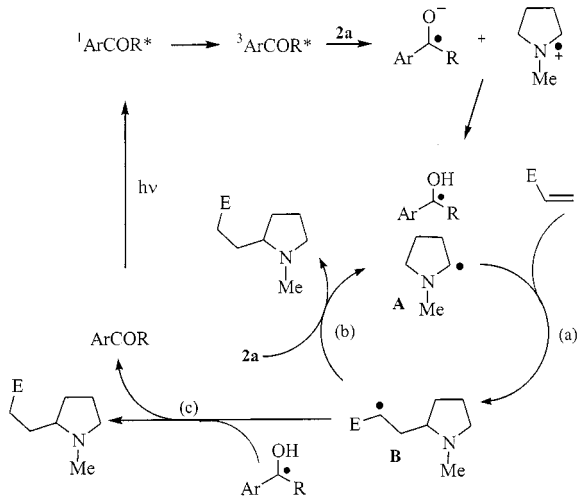
Using the photodecomposition of butyrophenone in ethylene and acetophenone as actinometer,[18] we determined a quantum yield of 4 for the addition of *N*-methylpyrrolidine to **1**, indicating that a radical chain process was involved during the reaction. This was particularly interesting if we consider the preparative aspect, the rapidity of the conversion and the almost complete absence of oligomers from the reaction mixture. Several grams of adducts could be produced in less than 1 h, with conventional irradiation sources. Furthermore, we observed that the catalytic amounts of the sensitizers used in the reaction could be recovered almost unchanged under these conditions. This can be considered as an important improvement, if we consider that stoichiometric amounts of benzophenone are usually needed in the sensitized photoadddition of tertiary amines to electron-deficient alkenes.[11b,11c,14] The radical chain process can be explained according to Scheme 2.

The formation of the α-aminoalkyl radical **A** involves a well-established photoelectron transfer process, followed by an addition to the electron-deficient alkene according to step (a). The fate of the electron-poor radical **B** obtained in step (a), involves a hydrogen transfer from the starting amine with regeneration of the stabilized radical **A** and formation of the adducts. This abstraction process step (b), which is kinetically favoured due to the high concentration of the amine, will also regenerate a thermodynamically fa-

Table 1. Influence of the sensitizer on the photoinduced addition of tertiary amines **2a** to **1** (see Scheme1)

Sensitizer	Triplet E_T [kcal mol^{-1}]	Irradiation time [min]	Isolated yield (%)[a]
Benzophenone	69.2[b]	10	44
Acetophenone	74[b]	10	41
4-*tert*-Butylacetophenone	72.1[c]	10	67
4-Methoxyacetophenone	70.1[c]	7	78
Xanthone	74.1[b]	10	80
4,4′-Dimethoxybenzophenone	69.4[c]	5	85
4,4′-Dimethoxybenzophenone	69.4[c]	5	94[d]
4,4′-Bis(dimethylamino)benzophenone	62[b]	5	83[e]
4-(Dimethylamino)benzaldehyde	70[b]	12	73

[a] Yields of purified products **3** and **4**. − [b] Ref.[16] − [c] Ref.[17] − [d] **1** (0.125 mmol), acetonitrile (25 mL), **2a** (50 mmol). − [e] Irradiation with visible light (halogen lamp, 500 W).



Scheme 2. Mechanism of the radical addition of tertiary amines to electron-deficient alkenes; electron donor substituted aromatic ketones are used as sensitizers in the photochemically induced radical chain process

voured α -aminoalkyl radical. The almost absent oligomerization process is not favoured by the low concentration of alkene in the reaction mixture nor by the unfavourable character of an addition process between the electron-poor radical **B** and an electron-deficient alkene. As already indicated, this new procedure is characterized by an absence of reduction products from the aromatic ketone or the electron-deficient alkene and the need for only minute amounts of the sensitizer to induce the total conversion of the alkene. To explain these facts, especially the recycling of the sensitizer, a dismutation between the ketyl radical and **B** has to be considered (Step c). Recently, a similar mechanism has been described for the addition of 1,3-dioxolane to electron-deficient alkenes.[19]

The reaction between **2a** and **1** indicated a preference for an abstraction of a secondary hydrogen from the *N*-methyl substituent. To further examine the influence of the nature of the amine on the selectivity and on the addition process and in order to investigate a possible generalization of the addition to secondary amines, we examined the addition of amines **2b**−**2j** to **1** (Scheme 1, Table 2). Similar results were obtained from tertiary amines **2a**−**2d** and *N*-alkyl substituents did not influence the regioselectivity of the H abstraction from the amine. In all cases, the isolated products involve a selective hydrogen abstraction from the pyrrolidine residue. Even with the *N*-isopropylpyrrolidine **2c**, we observed the cleavage of a secondary rather than a tertiary C−H bond. Similarly with the acyclic amine **2j**, the products result from hydrogen abstraction from an ethyl rather than an isopropyl group and formation of a secondary rather than a tertiary radical. As there is not an important contribution to the stabilization energy of α-aminyl radicals by substitution, the regioselectivity might indicate that the hydrogen abstraction is kinetically controlled.[9b] If we assume an almost planar structure of the nitrogen of diisopropylethylamine **2j** and *N*-alkylpyrrolidines, the regioselective formation of the radical might result from a better overlap of the cleaved C−H bond with the half-filled nitrogen orbital.[4a,20] However, stereoelectronic and other factors, which influence the deprotonation step of the radical cation intermediate, are still under discussion.[21] Introduction of a benzyl group on the nitrogen atom should favour the formation of α-amino radicals. Unfortunately, the *N*-benzyl derivative **2f** was found to be unreactive and was recovered unchanged under similar conditions. With *N*-methylpiperidine (**2i**), a decrease in the efficiency and an increase in the selectivity with the formation of only one stereoisomer, were observed. The better stereoselectivity observed with the *N*-methylpiperidine can be explained on the basis of the steric interactions developed in the transition states leading to the two possible stereoisomers. The isolated stereoisomer should result from the less hindered transition state **TS1** as shown in (Figure 1).

In order to extend the scope of the reaction to secondary amines, we examined the reactivity of pyrrolidine and various *N*-protected pyrrolidines. Although the direct radical addition of secondary amines with non activated alkenes is possible,[22] the Michael addition product **5** of the secondary amine **2k** to the furanone ring of **1**, was the only observed product (Scheme 3).[23] The reaction was complete within seconds at room temperature. Under similar conditions, **5** was also the only isolated product when **1** was irradiated in the presence of excess allyl derivative **2g**. The difference in reactivity between the *N*-benzyl- (**2f**) and *N*-allylpyrrolidine (**2g**), respectively, and the origin of pyrrolidine during the irradiation of **2g** remain unexplained. When the

Table 2. Influence of the nitrogen substituents on the photoinduced addition of tertiary amines **2** to **1** (Scheme 1)

Starting amine	R^1	R^2, $R^{2[a]}$	Irradiation time [min]	Isolated yield (%)[b]
2a	Me	$(CH_2)_2$	5	94
2b	Et	$(CH_2)_2$	5	81
2c	*i*Pr	$(CH_2)_2$	5	82
2d	*t*Bu	$(CH_2)_2$	5	81
2e	*t*BuMe_2Si	$(CH_2)_2$	12	77
2f	Benzyl	$(CH_2)_2$	120	0
2g	allyl	$(CH_2)_2$		[c]
2h	BOC	$(CH_2)_2$	20	0
2i	Me	$(CH_2)_3$	20	46[d]
2j[e]	*i*Pr	Me	15	78

[a] R^3 = H except when indicated. − [b] Yields of purified products **3** and **4** as a 55:45 mixture. − [c] **5** was the only isolated product (53%) (Scheme 3). − [d] **3i** was isolated with a diastereoisomeric excess higher than 90%. − [e] R^3 = Me.

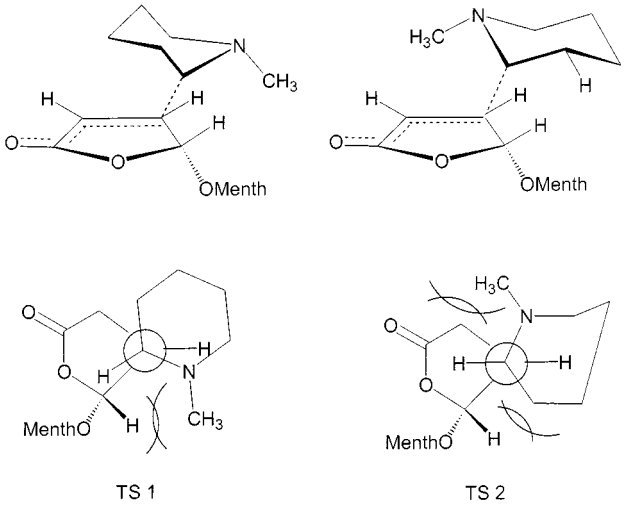
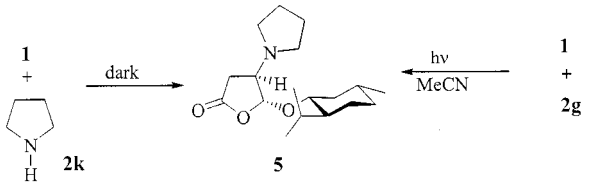


Figure 1. Transition states for the addition of 2-(*N*-methylpiperidinyl) radicals to (5*R*)-5-menthyloxy-2(5*H*)-furanone (**1**)

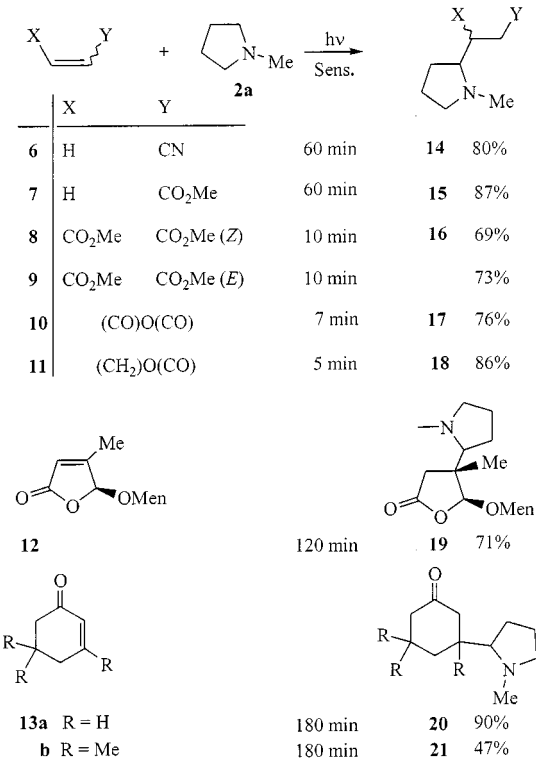
nitrogen atom was protected by silyl groups, the products were derived from a hydrogen atom from the pyrrolidine group and the addition reaction was observed, even if the lability of the trimethylsilyl (TMS) substituent of **2** led to degradation products. This decomposition problem could easily be overcome by using **2e**, substituted with the more stable *tert*-butyldimethylsilyl group instead of TMS on the nitrogen atom. When the nitrogen atom was substituted by an electron-withdrawing group, the electron transfer process should be a much slower process and no addition could be observed with the carbamate **2h**.



Scheme 3

As already indicated, the efficiency and the regioselectivity of the hydrogen abstraction made this addition of α-aminoalkyl radicals to furanone **1** very attractive for preparative chemistry. The possibility of easily producing various γ-aminobutyric derivatives and γ-amino ketones, led us to examine the photosensitized addition of *N*-methylpyrrolidine as a model for tertiary amines with other electron-deficient alkenes and the results are summarized in Scheme 4.

When a solution of **2a** and alkenes **8**−**11** in acetonitrile was irradiated at 350 nm in the presence, of small quantities of 4,4′-dimethoxybenzophenone, the corresponding adducts **16**−**18** were formed rapidly and isolated in good yields. However, in acetonitrile polymerization was observed with the less hindered alkenes **6** and **7** and the reaction was of no preparative interest. Fortunately, we observed that a polar solvent was not required in the reaction and we could isolate the corresponding adducts **14**−**15** in good yields as soon as the reaction was carried out in the

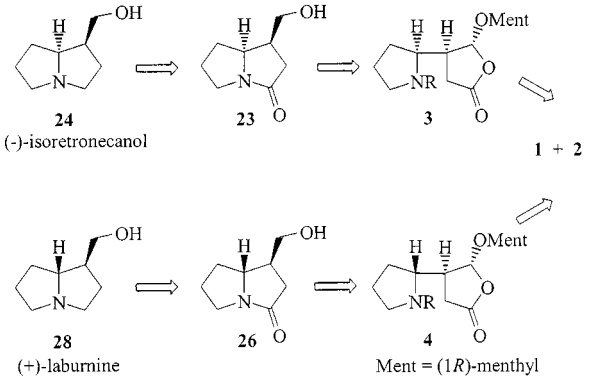


Scheme 4. Addition of *N*-methylpyrrolidine (**2a**) to various electron-deficient alkenes; the reaction of **6** and **7** has been carried out in neat **2a**; the reaction of **13a** and **13b** was carried out by irradiation with visible light and in the presence of 4,4′-(dimethylamino)-benzophenone; for further details see text and experimental section

neat amine. With β-substituted alkenes, two asymmetric centres were created and the diastereoisomers were formed in almost the same amounts. The composition (55:45) of the mixture of diastereoisomers **16**−**21** did not depend on the nature of substituents. As expected for an addition of radicals to β-disubstituted alkenes, the addition process became slower with isophorone (**13b**) and β-substituted furanone **12**. The starting stereoisomers **8**−**9**, which produce a common radical intermediate, led to the same mixture of diastereoisomers. Surprisingly, in addition to the expected adducts, some dimerization products of **13** could be characterized.[24] The formation of photodimers implied that some excitation process of the enone had been possible under the irradiation conditions. This contrasts with the absence of photoproducts different to the expected adducts, when the reaction was carried out in the presence of conjugated esters and lactones. The difference could be attributed to some residual absorption at 350 nm wavelength by the enone. Although the unsaturated esters and lactones did not absorb at this wavelength, the low concentration of the sensitizer (0.01 equiv.) used in this study allowed a competitive absorption by enones. We anticipated that a selective excitation of the sensitizer should suppress the dimeric by-products. The formation of these dimers could be suppressed indeed and a clean addition was again observed, by using an excitation with visible light and Michler's ketone as sensitizer.

The high efficiency of the addition of tertiary amines to the easily available furanone **1** led us to test its application to a simple, very fast and enantioselective synthesis of some necine bases. Furthermore, a comparison of the synthetic alkaloids with authentic samples, should prove the configuration of the asymmetric centres of the diastereoisomers **3** and **4** created in the photosensitized reaction of tertiary amines with menthyloxyfuranone **1**.

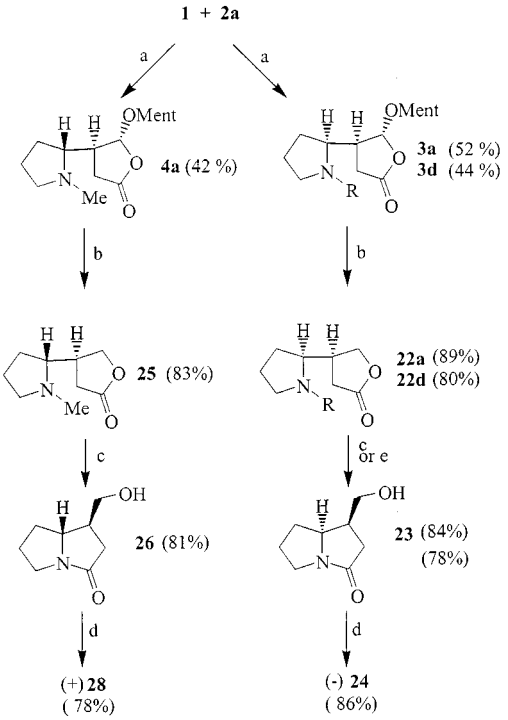
Pyrrolizidine alkaloids (−)-isoretronecanol (**24**) and (+)-laburnine (**28**), which had already inspired several total syntheses mainly developed to test new methodologies, appeared as good candidates to show the efficiency of our approach.[25] According to Scheme 5, these alkaloids might result from selective transformations of the two diastereoisomers **3** and **4** involving a sequence of cyclization and reduction steps. The necine bases might be obtained by a reduction of the corresponding lactams **23** and **26**. The lactam and the primary alcohol functions might result from a spontaneous cyclization of deprotected pyrrolidine with a lactone formed by a selective reduction of the acetal function of the corresponding adducts **3** and **4**.



Scheme 5

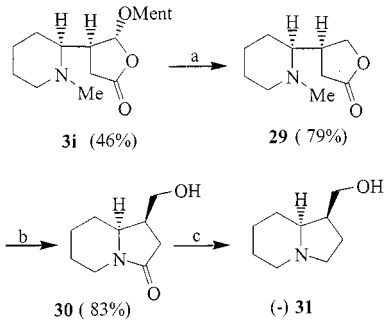
Two reduction steps are involved in the retrosynthetic scheme. In order to simplify the synthesis, we tested the following sequence: deprotection of the amine function as described below and hydrolysis of the acetal function followed by only one reduction procedure. Unfortunately, due to the lability of the polyfunctional intermediates, a complex mixture of products was produced which was not characterized. To minimize side reactions, we first decided to carry out the reduction of the acetal function (Scheme 6).

The same sequence of reactions applied to the two diastereoisomers **3** and **4** allowed for a selective synthesis of (−)-**24** and (+)-**28**. Pure amino lactones **22** and **25** were obtained by reduction of the acetal group of the corresponding photoadducts with sodium tetrahydroborate. The demethylation of the *N*-methylpyrrolidines was conveniently carried out by a photosensitised oxidation.[26] During the isolation of the products, we noticed that a spontaneous transformation into bicyclic lactams **23** and **26** had occurred. Finally, reduction of lactams **23** and **26** produced (−)-isoretronecanol **24** and (+)-laburnine **28** in high yield. From the comparison of specific rotations of the synthetic and authentic samples of the corresponding necine bases,[27]



Scheme 6. Synthesis of laburnine (**28**) and isoretronecanol (**24**): (a) hν (300 nm), 4,4′-dimethoxybenzophenone, MeCN; (b) $NaBH_4$, MeOH; (c) hν, DCN, $LiClO_4$, O_2; (d) $LiAlH_4$; (e) TFA, CH_2Cl_2

the configuration of the asymmetric centres created in the photosensitized addition of *N*-methylpyrrolidine with **1** was established without ambiguity. The synthetic samples were also shown to be almost pure enantiomers by chiral gas chromatography. Interestingly, we determined that the *N*-*tert*-butyl group of **22d** could be removed efficiently by treatment with trifluoroacetic acid. According to this synthetic scheme, (−)-isoretronecanol (**24**) and (+)-laburnine (**28**) were available in four steps from the readily available menthyloxyfuranone[12] and in 33% and 22% overall yield, respectively. Furthermore, it would be possible to prepare the enantiomers of **24** and **28** with the same efficiency, just by changing the enantiomer of menthol introduced in the starting furanone **1**.



Scheme 7. (a) $NaBH_4$, MeOH; (b) hν, DCN, $LiClO_4$, O_2; (c) $LiAlH_4$

A similar strategy could be applied to indolizidines. The synthesis of one enantiomer of the bicyclic skeleton of stellenamide A[28] was carried out to illustrate the generality of the approach. The same reaction sequence previously used

for the pyrrolizidine analogues, allowed for the synthesis of the enantiopure indolizidine (−)-**31** in four steps and with an overall yield of 27%, from **1** and *N*-methylpiperidine via **3k** (Scheme 7). The relative configuration of **3i** and **29** has been established by comparison of their NMR data with those of **3a** and **22a**, respectively. The data are very similar for the furanone moieties. The NMR data of **3i** and **29** are significantly different to those of **4a** and **25**.

Experimental Section

General Procedures: ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker AC 250. (250 MHz and 62 MHz, respectively, coupling constants are reported in Hz.) Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard. − IR spectra were recorded with a MIDAC Prospect IR (FTIR). − Mass spectra were recorded with a JOEL D-300. − Preparative chromatography was carried out with Merck art 9385 Kieselgel 60. GC was carried out with a Hewlett-Packard 6890HP with a capillary column (HP-1). − Optical rotations were measured with a Perkin−Elmer 241 Polarimeter. The enantiomeric excess was determined by GC on a chiral column (CP-Cyclodextrin-B-236-M-19) from Chrompack. − Acetonitrile was dried with calcium hydride, then with magnesium sulfate before distillation. Starting amines were dried and distilled from calcium hydride. − (5*R*)-5-menthyloxy-2(5*H*)-furanone was prepared from furfural and (−)-menthol according to a literature procedure.[12] (5*S*)-5-Mentyloxy-4-methyl-2(5*H*)-furanone was also prepared according to a literature procedure.[29] Cyclohex-2-enone, isophorone, compounds **6**−**11**, and amines **2a**, **2i**, and **2j** were purchased from Aldrich and used without further purification. − Irradiation of the solutions in pyrex tubes (Φ = 1 cm) was carried out at 350 nm with Rayonet® model RPR-100 from the Southern New England Ultraviolet Company. Irradiations with visible light were performed with a 500-W halogen lamp.

Addition of Tertiary Amines to 1: Except where indicated, a solution of **1** (120 mg, 0.5 mmol, 1 equiv.), the amine **2** (10 mmol, 20 equiv.), 4,4′-dimethoxybenzophenone (12 mg, 0.05 mmol, 0.1 equiv.) or another sensitizer (0.05 mol, 0.1 equiv., Table 1) in acetonitrile (25 mL) was irradiated at 350 nm, until conversion of **1** was complete. The excess amine and the solvent were evaporated and the residue was purified by chromatography on silica gel with petroleum ether/ethyl acetate (2:1) as eluant.

Formation of 3a and 4a

(−)-(4*S*,5*R*,2′*S*)-5-Menthyloxy-4-(1′-methylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (3a): Yield: 82 mg (51%). − M.p. 116 °C. − R_f = 0.44 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −123.0; $[\alpha]_{578}^{21}$ = −127.3; $[\alpha]_{546}^{21}$ = −143.4; $[\alpha]_{436}^{21}$ = −239.5; $[\alpha]_{365}^{21}$ = −361.2 (*c* = 0.84, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.74−1.09 (m, 3 H), 1.11−1.58 (m, 4 H), 1.62−1.89 (m, 4 H), 2.01−2.34 (m, 2 H), 2.31 (s, 3 H), 2.50−2.61 (m, 4 H), 2.80 (dd, *J* = 17.6, 10.5 Hz, 1 H), 3.05 (m, 1 H), 3.52 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.60 (d, *J* = 1.9 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.5, 20.7, 22.2, 22.4, 23.1, 25.3, 28.7, 28.7, 31.1, 34.3, 39.7, 40.7, 42.8, 47.7, 57.0, 65.2, 77.1, 102.3, 176.4. − IR (KBr): ṽ [cm^{-1}] = 2935, 2790, 1785, 1460, 1370, 1250, 1165, 955. − MS (70 eV); *m*/*z* (%): 323 (23) [M^+], 322 (100), 243 (45), 184 (76), 135 (83), 110 (24). − $C_{19}H_{33}NO_3$ (323.2): calcd. C 70.53, H 10.29, N: 4.33; found C 70.30, H 10.08, N .39.

(−)-(4*S*,5*R*,2′*R*)-5-Menthyloxy-4-(1′-methylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (4a): Yield: 67 mg (41%). − M.p. 122 °C. − R_f = 0.30 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −136.0; $[\alpha]_{578}^{21}$ = −140.7; $[\alpha]_{546}^{21}$ = −159.2; $[\alpha]_{436}^{21}$ = −261.4; $[\alpha]_{365}^{21}$ = −391.4 (*c* = 0.98, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.79 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.74−1.02 (m, 3 H), 1.13−1.49 (m, 4 H), 1.60−1.84 (m, 4 H), 2.03−2.72 (m, 7 H), 2.29 (s, 3 H), 3.06 (m, 1 H), 3.54 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.40 (d, *J* = 1.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.6, 20.9, 22.2, 22.4, 23.1, 25.4, 25.9, 28.8, 31.3, 34.3, 39.8, 40.5, 42.7, 47.7, 56.8, 65.4, 76.7, 103.0, 176.4. − IR (KBr): ṽ [cm^{-1}] = 2965, 2865, 1780, 1455, 1375, 1240, 1160, 950. − MS (70 eV); *m*/*z* (%): 323 (10) [M^+], 322 (44), 184 (100), 170 (21), 135 (22), 110 (17). − $C_{19}H_{33}NO_3$ (323.2): calcd. C 70.53, H 10.29, N 4.33; found C 70.11, H 10.41, N 4.46.

Formation of 3b and 4b: *N*-Ethylpyrrolidine was prepared according to ref.[30]

(−)-(4*S*,5*R*,2′*S*)-4-(1′-Ethylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (3b): Yield: 75 mg (45%). − M.p. 91 °C. − R_f = 0.42 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −139.3; $[\alpha]_{578}^{21}$ = −147.7; $[\alpha]_{546}^{21}$ = −169.6; $[\alpha]_{436}^{21}$ = −273.6; $[\alpha]_{365}^{21}$ = −412.6 (*c* = 1.02, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ= 0.79 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.74−1.02 (m, 3 H), 1.08 (t, *J* = 6.3 Hz, 3 H), 1.13−1.49 (m, 4 H), 1.60−1.84 (m, 4 H), 2.03−2.72 (m, 7 H), 2.36 (dq, *J* = 14.2, 6.3 Hz, 1 H), 2.41 (dq, *J* = 14.2, 6.3 Hz, 1 H), 3.06 (m, 1 H), 3.54 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.60 (d, *J* = 1.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 14.6, 15.7, 20.8, 22.2, 22.4, 23.1, 25.4, 26.1, 28.3, 31.4, 34.3, 39.9, 42.8, 47.5, 47.7, 56.0, 63.2, 76.8, 103.0, 176.8. − IR (KBr): ṽ [cm^{-1}] = 2970, 2865, 1775, 1465, 1370, 1245, 1155, 960. − MS (70 eV); *m*/*z* (%): 337 (8) [M^+], 336 (56), 198 (100), 135 (30), 110 (21). − $C_{20}H_{35}NO_3$ (337.5): calcd. C 71.18, H 10.45, N 4.15; found C 71.11, H 10.41, N 3.95.

(−)-(4*S*,5*R*,2′*R*)-4-(1′-Ethylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (4b): Yield: 61 mg (36%). − M.p. 87 °C. − R_f = 0.26 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −123.6; $[\alpha]_{578}^{21}$ = −137.1; $[\alpha]_{546}^{21}$ = −161.0; $[\alpha]_{436}^{21}$ = −242.8; $[\alpha]_{365}^{21}$ = −362.6 (*c* = 1.04, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ= 0.81 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 7.6 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 0.76−1.06 (m, 3 H), 1.09 (t, *J* = 6.3 Hz, 3 H), 1.17−1.54 (m, 4 H), 1.66−1.88 (m, 4 H), 2.01−2.69 (m, 7 H), 2.31−252 (m, 2 H), 3.06 (m, 1 H), 3.54 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.41 (d, *J* = 1.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.2, 15.9, 20.9, 22.2, 22.3, 23.0, 25.3, 26.8, 30.1, 31.3, 34.3, 39.9, 42.9, 47.6, 47.8, 56.2, 64.3, 76.7, 103.9, 176.2. − IR (KBr): ṽ [cm^{-1}] = 2965, 2875, 1785, 1470, 1370, 1255, 1160, 950. − MS (70 eV); *m*/*z* (%): 337 (14) [M^+], 336 (46), 198 (100), 135 (20), 110 (12). − $C_{20}H_{35}NO_3$ (337.5): calcd. C 71.18, H 10.45, N 4.15; found C 71.03, H 10.36, N 4.01.

Formation of 3c and 4c: *N*-Isopropylpyrrolidine was prepared according to ref.[30]

(−)-(4*S*,5*R*,2′*S*)-4-(1′-Isopropylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (3c): Yield: 79 mg (45%). − M.p. 98 °C. − R_f = 0.48 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −98.3; $[\alpha]_{578}^{21}$ = −99.8; $[\alpha]_{546}^{21}$ = −111.8; $[\alpha]_{436}^{21}$ = −163.1; $[\alpha]_{365}^{21}$ = −255.8 (*c* = 0.96, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3 H), 0.80 (d, *J* = 7.6 Hz, 3 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.72−1.04 (m, 3 H), 0.92 (d, *J* = 6.7 Hz), 1.04 (d, *J* = 6.7 Hz), 1.08−1.32 (m, 2 H), 1.38−1.67 (m, 6 H), 2.00−2.23 (m, 2 H), 2.30−2.39 (m), 2.42 (dd, *J* = 15.9, 2.2 Hz, 1 H), 2.58 (dd, *J* = 15.9, 7.9 Hz, 1 H), 2.82 (m, 1 H), 3.02−3.26 (m), 3.57 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.64 (d, *J* = 0.9 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ =

15.6, 17.7, 20.9, 22.2, 23.2, 23.5, 24.9, 25.1, 28.4, 29.9, 31.3, 34.5, 40.3, 47.8, 48.2, 48.7, 50.1, 56.2, 77.4, 101.2, 176.2. − IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2975, 2865, 1775, 1450, 1365, 1235, 1155, 960. − MS (70 eV); *m/z* (%): 351 (8) [M^+], 350 (28), 336 (42), 212 (72), 112 (100). − $C_{23}H_{41}NO_3$ (351.5): calcd. C 71.75, H 10.61, N 3.98; found C 71.58, H 10.80, N 3.82.

(−)-(4*S*,5*R*,2′*R*)-4-(1′-Isopropylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (4c): Yield: 65 mg (37%). − M.p. 89 °C. − R_f = 0.43 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −94.6; $[\alpha]_{578}^{21}$ = −96.8; $[\alpha]_{436}^{21}$ = −107.8; $[\alpha]_{436}^{21}$ = −152.3; $[\alpha]_{365}^{21}$ = −233.6 (*c* = 1.00, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3 H), 0.83 (d, *J* = 7.6 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.72−1.06 (m, 3 H), 0.94 (d, *J* = 6.7 Hz), 1.02 (d, *J* = 6.7 Hz), 1.16−1.36 (m, 2 H), 1.42−1.75 (m, 6 H), 2.04−2.21 (m, 2 H), 2.30−2.39 (m,2 H), 2.38 (dd, *J* = 16.1, 2.4 Hz, 1 H), 2.68 (dd, *J* = 16.1, 7.9 Hz, 1 H), 2.82−2.97 (m, 3 H), 3.57 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.63 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.7, 17.6, 20.9, 22.1, 23.1, 23.7, 24.7, 25.3, 27.9, 30.6, 31.4, 34.4, 40.0, 47.5, 48.7, 48.9, 50.8, 58.6, 77.1, 102.4, 176.8. − IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2960, 2860, 1790, 1460, 1365, 1230, 1155, 950. − MS. (70 eV); *m/z* (%): 351 (5) [M^+], 350 (23), 336 (47), 212 (61), 112 (100). − $C_{23}H_{41}NO_3$ (351.5): calcd. C 71.75, H 10.61, N 3.98; found C 71.55, H 10.83, N 3.72.

Formation of 3d and 4d. − 1-*tert*-Butylpyrrolidine 2d: 1,4-Dibromobutane (43.2 g, 200 mmol, 1 equiv.) was added to a solution of *tert*-butylamine (21.9 g, 200 mmol, 1 equiv.) and potassium carbonate (13.8 g, 100 mmol, 0.5 equiv.) in ethanol (20 mL) and the solution was stirred at 60 °C for 3 d. Then the solution was treated with Et_2O (100 mL) and a solution of potassium hydroxide (10%, 100 mL). The ethereal solution was treated with a saturated solution of sodium chloride and was dried with magnesium sulfate. After evaporation of the solvent, the oil residue was distilled under reduced pressure. Yield 22.4 g (92%).[31]

(−)-(4*S*,5*R*,2′*S*)-4-(1′-*tert*-Butylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (3d): Yield: 82 mg (45%). − M.p. 116 °C. − R_f = 0.42 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −83.3; $[\alpha]_{578}^{21}$ = −86.9; $[\alpha]_{546}^{21}$ = −98.9; $[\alpha]_{436}^{21}$ = −162.2; $[\alpha]_{365}^{21}$ = −240.3 (*c* = 0.96, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.77 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.77−0.99 (m, 3 H), 1.04 (s, 9 H), 1.13−1.29 (m, 2 H), 1.30−1.78 (m, 6 H), 2.03−2.18 (m, 2 H), 2.25−2.35 (m, 2 H), 2.19 (dd, *J* = 18.7, 3.4 Hz, 1 H), 2.79 (dd, *J* = 18.7, 9.5 Hz, 1 H), 2.75−3.09 (m, 2 H), 3.57 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.61 (d, *J* = 2.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.6, 20.8, 22.2, 23.1, 24.8, 25.4, 27.3, 28.8, 30.9, 31.3, 34.3, 40.0, 47.4, 47.6, 54.1, 54.9, 57.9, 76.8, 103.4, 177.0. − IR: (KBr), $\tilde{\nu}$ [cm^{-1}] = 2960, 2870, 1770, 1455, 1380, 1230, 1115, 940. − MS: (70 eV); *m/z* (%): 366 (10) [11^+ + 1], 350 (18), 226 (84), 126 (100), 110 (45). − $C_{22}H_{39}NO_3$ (365.3): calcd. C 72.27, H 10.76, N 3.83; found C 72.20, H 10.24, N 3.68.

(−)-(4*S*,5*R*,2′*R*)-4-(1′-*tert*-Butylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (4d): Yield: 66 mg (36%). − M.p. 116 °C. − R_f = 0.29 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −73.2; $[\alpha]_{578}^{21}$ = −76.8; $[\alpha]_{546}^{21}$ = −86.8; $[\alpha]_{436}^{21}$ = −141.9; $[\alpha]_{365}^{21}$ = −221.5 (*c* = 1.00, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.74−1.09 (m, 3 H), 1.07 (s, 9 H), 1.13−1.34 (m, 2 H), 1.36−1.75 (m, 6 H), 2.02−2.18 (m, 2 H), 2.30−2.39 (m, 2 H), 2.38 (dd, *J* = 15.0, 2.4 Hz, 1 H), 2.67 (dd, *J* = 15.0, 9.1 Hz, 1 H), 2.76−2.97 (m, 2 H), 3.49 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.60 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.6, 20.8, 22.2, 23.1, 24.9, 25.4, 27.3, 28.6, 31.4, 31.4, 34.4, 40.3, 47.1, 47.7, 48.4, 53.9, 58.3, 77.2, 103.7, 177.4. − IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2960, 2870, 1795, 1455, 1365, 1230, 1165, 940. − MS (70 eV); *m/z* (%): 365 (1) [11^+ + 1], 350 (34), 226 (57), 170 (21), 126 (100), 110 (15). − $C_{22}H_{39}NO_3$ (365.3): calcd. C 72.27, H 10.76, N 3.83; found C 72.32, H 11.03, N 3.63.

Formation of 3e and 4e. − 1-(*tert*-Butyldimethylsilyl)pyrrolidine (2e): *tert*-Butyldimethylsilyl chloride (11.5 g; 74 mmol; 1.1 equiv.) was added to a solution of pyrrolidine (7.34 g; 67 mmol; 1 equiv.) and triethylamine (7.4 g; 74 mmol; 1.1 equiv.) in toluene (40 mL) under argon. The resulting solution was stirred at room temperature for 3 h. A mixture of diethyl ether and petroleum ether (1:1; 100 mL) was added. The resulting suspension was filtered through Celite. The solvents were removed under reduced pressure. Yield: 11.4 g (92%).

(−)-(4*S*,5*R*,2′*S*)-4-(1′-*tert*-Butyldimethylsilylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (3e): Yield: 89 mg (42%). − M.p. 139 °C. − R_f = 0.77 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −120.2; $[\alpha]_{578}^{21}$ = −134.6; $[\alpha]_{546}^{21}$ = −14.5; $[\alpha]_{436}^{21}$ = −249.9; $[\alpha]_{365}^{21}$ = −310.0 (*c* = 1.02, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 6 H), 0.78 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 7.6 Hz, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H), 0.94 (s, 9 H), 0.74−1.09 (m, 3 H), 1.13−1.36 (m, 2 H), 1.38−1.75 (m, 6 H), 1.83−2.12 (m, 2 H), 2.30−2.52 (m, 2 H), 2.54 (dd, *J* = 15.0, 3.4 Hz, 1 H), 2.67 (dd, *J* = 15.0, 9.1 Hz, 1 H), 2.76−2.97 (m, 2 H), 3.41 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.60 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −3.6, 15.5, 20.9, 21.0, 22.2, 23.0, 25.4, 25.6, 27.5, 30.0, 31.2, 31.7, 34.2, 39.9, 47.7, 49.3, 49.9, 60.5, 77.5, 101.9, 176.3. − IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2965, 2870, 1785, 1455, 1370, 1225, 1170, 965. − S.M. (70 eV); *m/z*: 423 (7) [M^+], 422 (29), 328 (15), 226 (100), 139 (16). − $C_{24}H_{45}NO_3Si$ (423.7): calcd. C 68.03, H 10.70, N 3.31; found C 67.85, H 10.57, N 3.19.

(−)-(*4S*,5*R*,2′*R*)-4-(1′-*tert*-Butyldimethylsilylpyrrolidin-2′-yl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (4e): Yield: 74 mg (35%). − M.p. 133 °C. − R_f = 0.77 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −122.3; $[\alpha]_{578}^{21}$ = −136.6; $[\alpha]_{546}^{21}$ = −170.6; $[\alpha]_{436}^{21}$ = −241.9; $[\alpha]_{365}^{21}$ = −298.5 (*c* = 1.00, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 6 H), 0.76 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 7.6 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.94 (s, 9 H), 0.74−1.05 (m, 3 H), 1.09−1.37 (m, 2 H), 1.38−1.75 (m, 6 H), 1.83−2.14 (m, 2 H), 2.24−2.48 (m, 2 H), 2.56 (dd, *J* = 16.1, 3.4 Hz, 1 H), 2.69 (dd, *J* = 16.1, 9.1 Hz, 1 H), 2.74−2.98 (m, 2 H), 3.42 (td, *J* = 10.7, 4.2 Hz, 1 H), 5.17 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = −3.6, 15.4, 20.6, 20.8, 22.2, 23.0, 25.4, 25.6, 27.3, 30.0, 31.3, 31.7, 34.2, 39.8, 47.7, 49.3, 50.3, 60.0, 75.7, 103.4, 175.9. − IR (KBr): $\tilde{\nu}$ [cm^{-1}] = 2960, 2870, 1795, 1465, 1370, 1230, 1170, 955. − MS (70 eV); *m/z* (%): 423 (7) [M^+], 422 (21), 328 (7), 226 (100), 139 (7). − $C_{24}H_{45}NO_3Si$ (423.7): calcd. C 68.03, H 10.70, N 3.31; found C 67.82, H 10.52, N 3.35.

Formation of 3i: A solution of **1** (240 mg, 1 mmol, 1 equiv.), *N*-methylpiperidine (**2i**) (6.0 g, 60 mmol, 60 equiv.) and 4,4′-dimethoxybenzophenone (24 mg, 0.1 mmol, 0.1 equiv.) in acetonitrile (50 mL) was irradiated for 20 min at 350 nm. After evaporation of the solvent and excess amine, the residue was purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant.

(−)-(4*S*,5*R*,2′*S*)-5-Menthyloxy-4-(1-methylpiperidin-2-yl)-4,5-dihydrofuran-2(3*H*)-one (3i): Yield: 155 mg (46%). − M.p. 132 °C. − R_f = 0.40 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −116.2; $[\alpha]_{578}^{21}$ = −120.3; $[\alpha]_{546}^{21}$ = −142.8; $[\alpha]_{436}^{21}$ = −236.4; $[\alpha]_{365}^{21}$ = −249.6 (*c* = 0.84, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 7.6 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.74−1.09 (m, 3 H), 1.11−1.58 (m, 4 H), 1.62−1.89 (m, 4 H),

2.01−2.34 (m, 2 H), 2.31(s, 3 H), 2.50−2.61 (m, 4 H), 2.80 (dd, J = 17.6, 10.5 Hz, 1 H), 3.05 (m, 1 H), 3.52 (td, J = 10.7, 4.2 Hz, 1 H), 5.60 (d, J = 1.9 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.6, 20.9, 22.2, 23.1, 24.1, 24.6, 24.9, 25.5, 28.2, 31.4, 34.3, 39.8, 42.2, 42.8, 47.8, 56.9, 63.3, 76.5, 102.3, 176.9 − IR (KBr): ṽ [cm^{-1}] = 2930, 2865, 1785, 1455, 1370, 1165, 940. − MS (70 eV); *m/z* (%): 337 (1.5) [M^+], 322 (0.2), 238 (0.3), 198 (100), 124 (7). − $C_{20}H_{35}NO_3$ (337.5): calcd. C 71.18, H 10.45, N 4.15; found C 70.91, H 10.18, N 3.99.

Formation of 3j and 4j: A solution of **1** (360 mg, 1.5 mmol, 1 equiv.), diisopropylethylamine (**2j**) (3.87 g, 30 mmol, 20 equiv.) and 4,4′-dimethoxybenzophenone (36 mg, 0.15 mmol, 0.1 equiv.) in acetonitrile (75 mL) was irradiated for 15 min at 350 nm. After evaporation of the solvent and excess amine, the residue was purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant.

(−)-(4*S*,5*R*,2′*S*)-4-(1′-Diisopropylaminoethyl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (3j): Yield: 237 mg (43%). − M.p. 112 °C. − R_f = 0.62 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −103.4; $[\alpha]_{578}^{21}$ = −107.4; $[\alpha]_{546}^{21}$ = −122.1; $[\alpha]_{436}^{21}$ = −201.0; $[\alpha]_{365}^{21}$ = −298.1 (*c* = 1.02, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.64 (d, J = 6.8 Hz, 3 H), 0.80 (d, J = 6.9 Hz, 3 H), 0.82 (d, J = 7.6 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.12 (d, J = 7.0 Hz, 3 H), 0.62−1.67 (m, 7 H), 1.99−2.33 (m, 4 H), 2.52 (dd, J = 15.8, 8.1 Hz, 1 H), 2.61 (dddd, J = 8.1, 7.0, 4.3, 1.5 Hz,1 H), 2.70(dd, J = 15.8, 4.3 Hz, 1 H), 3.02 (qt, J = 7.0, 7.0 Hz, 1 H), 3.48 (td, J = 10.7, 4.2 Hz, 1 H), 5.42 (d, J = 1.5 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.5, 18.6, 20.7, 21.8, 21.8, 22.1, 22.9, 23.4, 23.4, 25.3, 31.2, 32.0, 34.2, 39.6, 44.4, 44.4, 47.2, 47.7, 49.9, 76.4, 103.4, 176.4. − IR (KBr): ṽ [cm^{-1}] = 2960, 2860, 1780, 1465, 1365, 1215, 1115, 940. − MS (70 eV); *m/z* (%): 367 (13) [M^+], 352 (43), 228 (51), 140 (26), 128 (100). − $C_{22}H_{41}NO_3$ (367.6): calcd. C 70.53, H 10.29, N 4.33; found C 70.28, H 10.24, N 4.10.

(−)-(4*S*,5*R*,2′*R*)-4-(1′-Diisopropylaminoethyl)-5-menthyloxy-4,5-dihydrofuran-2(3*H*)-one (4j): Yield: 193 mg (35%). − M.p. 127 °C. − R_f = 0.56 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −102.0; $[\alpha]_{578}^{21}$ = −106.0; $[\alpha]_{546}^{21}$ = −120.2; $[\alpha]_{436}^{21}$ = −197.4; $[\alpha]_{365}^{21}$ = −293.3 (*c* = 1.02, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.78 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 7.6 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.04 (d, J = 7.0 Hz, 3 H), 0.62−1.67 (m, 7 H), 1.99−2.33 (m, 4 H), 2.48 (dd, J = 17.9, 2.1 Hz, 1 H), 2.61 (ddd, J = 8.0, 7.0, 2.1 Hz, 1 H), 2.68(dd, J = 17.9, 8.0 Hz, 1 H), 3.23 (qt, J = 7.0, 7.0 Hz, 1 H), 3.52 (td, J = 10.7, 4.2 Hz, 1 H), 5.42 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.5, 20.3, 20.9, 21.7, 22.0, 22.2, 23.1, 23.7, 23.9, 25.4, 31.3, 34.3, 35.1, 39.8, 44.8, 46.4, 47.8, 49.4, 49.6, 76.0, 102.3, 177.6. − IR (KBr): ṽ [cm^{-1}] = 2960, 2860, 1780, 1465, 1365, 1215, 1115, 940. − MS (70 eV); *m/z* (%): 367 (18) [M^+], 352 (52), 228 (43), 140 (24), 128 (100). − $C_{22}H_{41}NO_3$ (367.6): calcd. C 70.53, H 10.29, N 4.33; found C 70.13, H 10.08, N 4.03.

3-(1-Methylpyrrolidin-2-yl)propionitrile (14): A solution of acrylonitrile (530 mg, 10 mmol, 1 equiv.) and 4,4′-dimethoxybenzophenone (24 mg, 0.1 mmol, 0.01 equiv.) in *N*-methylpyrrolidine (100 mL) was irradiated at 350 nm for 1 h. After concentration, the residue was purified by chromatography on silica gel with a mixture of petroleum ether and ethyl acetate (1:1) as the eluant. Yield: 1.11 g (80%). − R_f = 0.17 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.40−2.01 (m, 8 H, 2.17 (s, 3 H), 2.20−2.49 (m, 2 H), 2.83 (ddd, J = 9.5, 6.9, 3.1 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 13.9, 22.8, 28.1, 29.6, 35.7, 53.2, 63.4, 115.3. − IR: (KBr): ṽ [cm^{-1}] = 2975, 2655, 1345. − MS (70 eV); *m/z* (%): 138 (23) [M^+], 137 (100), 84 (34). − $C_8H_{14}N_2$ (138.2): calcd. C 69.56, H 10.14, N 20.29; found C 69.35, H 10.21, N 20.06.

Methyl 3-(1-Methylpyrrolidin-2-yl)propionate (15): A solution of methyl acrylate (860 mg, 10 mmol, 1 equiv.) and 4,4′-dimethoxybenzophenone (24 mg, 0.1 mmol, 0.01 equiv.) in methylpyrrolidine (100 mL) was irradiated at 350 nm for 1 h. After concentration, the residue was distilled under reduced pressure. Yield: 1.49 g (87%). − R_f = 0.23 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.37−1.63 (m, 2 H), 1.65−1.98 (m, 4 H), 2.00−2.13 (m, 2 H), 2.20−2.43 (m, 2 H), 2.32 (s, 3 H), 3.39 (ddd, J = 9.5, 7.2, 2.3 Hz, 1 H), 3.58 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ =21.7, 28.4, 30.0, 30.6, 51.2, 57.0, 65.0, 173.8. − IR: (KBr): ṽ [cm^{-1}] = 2960, 2785, 1745, 1455, 1165. − MS (70 eV); *m/z* (%): 171 (14) [M^+], 170 (100), 156 (4), 112 (42). − $C_9H_{17}NO_2$ (171.2): calcd. C 63.13, H 10.01, N 8.18; found C 62.95, H 10.21, N 7.93.

Addition of 2a with the Other Electrophiles 8−12: A solution of the electrophilic alkene (1 mmol) and 4,4′-dimethoxybenzophenone (24 mg, 0.1 mmol, 0.01 equiv.) in a mixture of **2a** and acetonitrile (1:1, 100 mL) was irradiated at 350 nm. After evaporation of the solvent and excess amine, the residue was purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant.

Dimethyl 2-(1-Methylpyrrolidin-2-yl)succinate (16): Yield: 92 mg (40%). − R_f = 0.25 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.40−2.01 (m, 4 H), 2.27 (s, 3 H), 2.29−2.52 (m, 2 H), 2.51 (dd, J = 17.6, 4.8 Hz, 1 H), 2.56 (m, 1 H), 2.69 (dd, J = 17.6, 8.7 Hz, 1 H), 2.83 (ddd, J = 8.7, 4.8, 4.1 Hz, 1 H), 3.61 (s, 3 H), 3.64 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 24.3, 28.2, 33.6, 37.8, 42.1, 48.2, 53.2, 62.8, 63.2, 171.9, 173.4. − IR (KBr): ṽ [cm^{-1}] = 2935, 2855, 1740, 1725, 1440, 1165, 1010. − MS (70 eV); *m/z* (%): 229 (13) [M^+], 228 (39), 214 (12), 170 (100). − $C_{11}H_{19}NO_4$ (229.3): calcd. C 57.63, H 8.35, N: 6.11; found C 57.35, H 8.03, N 5.76.

Dimethyl 2-(1-Methylpyrrolidin-2-yl)succinate (16′): Yield: 76 mg (33%). − R_f = 0.25 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.43−1.97 (m, 4 H), 2.29 (s, 3 H), 2.23−2.52 (m, 2 H), 2.52 (dd, J = 17.4, 4.7 Hz, 1 H), 2.57 (m, 1 H), 2.73 (dd, J = 17.4, 8.4 Hz, 1 H), 2.85 (ddd, J = 8.4, 4.7, 3.6 Hz, 1 H), 3.63 (s, 3 H), 3.65 (s, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 24.6, 28.0, 32.9, 37.4, 42.6, 47.8, 55.1, 64.3, 65.2, 172.3, 173.5. − IR (KBr): ṽ [cm^{-1}] = 2935, 2865, 1745, 1730, 1440, 1155, 1010. − MS (70 eV); *m/z* (%): 229 (19) [M^+], 228 (48), 214 (8), 170 (100). − $C_{11}H_{19}NO_4$ (229.3): calcd. C 57.63, H 8.35, N 6.11; found C 57.32, H 8.06, N 5.74.

3-(1-Methylpyrrolidin-2-yl)dihydrofuran-2,5-dione (17): Yield: 77 mg (42%). − R_f = 0.21 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.35−1.87 (m, 4 H), 2.31 (s, 3 H), 2.26−2.57 (m, 2 H), 2.51 (dd, J = 16.9, 4.3 Hz, 1 H), 2.59 (m, 1 H), 2.66 (dd, J = 16.9, 7.9 Hz, 1 H), 2.83 (ddd, J = 7.9, 4.7, 4.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.2, 27.4, 31.9, 39.2, 39.8, 46.2, 51.9, 166.9, 167.3. − IR (KBr): ṽ [cm^{-1}] = 2935, 2855, 1740, 1725, 1440, 1165, 1010. − MS (70 eV); *m/z* (%): 183 (56) [M^+], 155 (23), 139 (100). − $C_9H_{13}NO_3$ (183.2): calcd. C 57.63, H 8.35, N 6.11; found C 57.35, H 8.03, N 5.76.

3-(1-Methylpyrrolidin-2-yl)dihydrofuran-2,5-dione (17′): Yield: 62 mg (34%). − R_f = 0.21 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.37−1.89 (m, 4 H), 2.33 (s, 3 H), 2.26−2.57 (m, 2 H), 2.49 (dd, J = 16.9, 4.3 Hz, 1 H), 2.56 (m, 1 H), 2.63 (dd, J = 16.9, 7.9 Hz, 1 H), 2.72 (ddd, J = 7.9, 4.3, 3.9 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 24.3, 28.2, 30.3, 38.6, 40.9, 45.8,

52.7, 166.3, 168.1. − IR (KBr): ṽ [cm^{-1}] = 2935, 2855, 1740, 1725, 1440, 1165, 1010. − MS (70 eV); *m/z* (%): 183 (39) [M$^+$], 155 (33), 139 (100). − $C_9H_{13}NO_3$ (183.2): calcd. C 57.63, H 8.35, N 6.11; found C 57.39, H 8.13, N 5.86.

4-(1-Methylpyrrolidin-2-yl)dihydrofuran-2-one (18): Yield: 80 mg (47%). − R_f = 0.17 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.30−1.97 (m, 4 H), 2.19 (s, 3 H), 2.07−2.23 (m, 2 H), 2.29 (dd, *J* = 16.9, 4.8 Hz, 1 H), 2.47 (dd, *J* = 16.9, 7.9 Hz, 1 H), 2.69 (m, 1 H), 2.89 (m, 1 H), 3.98 (dd, *J* = 14.2, 6.3 Hz, 1 H), 4.36 (dd, *J* = 14.2, 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.0, 26.4, 32.1, 36.8, 40.7, 57.0, 67.2, 71.5, 177.6. IR (KBr): ṽ [cm^{-1}] = 2920, 1760, 1440, 1165. − MS (70 eV); *m/z* (%): 169 (11) [M$^+$], 168 (31), 125 (24), 84 (100). − $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.48, H 8.62, N 8.01.

4-(1-Methylpyrrolidin-2-yl)dihydrofuran-2-one (18′): Yield: 66 mg (39%). − R_f = 0.17 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.27−1.96 (m, 4 H), 2.18 (s, 3 H), 2.07−2.23 (m, 2 H), 2.21 (dd, *J* = 16.8, 4.5 Hz, 1 H), 2.38 (dd, *J* = 16.8, 7.7 Hz, 1 H), 2.66 (m, 1 H), 2.89 (m, 1 H), 3.92 (dd, *J* = 15.5, 5.9 Hz, 1 H), 4.19 (dd, *J* = 15.5, 7.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.1, 27.2, 30.1, 38.0, 40.9, 56.9, 67.2, 69.6, 177.7. − IR (KBr): ṽ [cm^{-1}] = 2930, 1745, 1410, 1155. − MS (70 eV); *m/z* (%): 169 (16) [M$^+$], 168 (42), 125 (12), 84 (100). − $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.45, H 8.65, N 7.97.

(+)-(4*R*,5*S*,2′*R*)-5-Menthyloxy-4-methyl-4-(1′-methylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (19): Yield: 73 mg (39%). − R_f = 0.57 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = +100.1; $[\alpha]_{578}^{21}$ = +100.8; $[\alpha]_{546}^{21}$ = +114.0; $[\alpha]_{436}^{21}$ = +183.6; $[\alpha]_{365}^{21}$ = +264.9 (*c* = 0.44, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.72 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.72−1.09 (m, 3 H), 1.13−1.58 (m, 4 H), 1.20 (s, 3 H), 1.61−1.87 (m, 4 H), 1.93−2.23 (m, 2 H), 2.21 (d, *J* = 17.0 Hz, 1 H), 2.32 (s, 3 H), 2.50 (d, *J* = 17.0 Hz, 1 H), 3.02 (m, 2 H), 3.48 (m, 1 H), 3.61 (td, *J* = 10.4, 4 Hz, 1 H), 5.40 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.5, 17.2, 21.0, 22.3, 22.8, 23.1, 25.6, 28.1, 31.4, 34.4, 38.8, 39.7, 42.5, 45.7, 48.0, 58.0, 70.0, 75.1, 104.0, 175.2. − IR (KBr): ṽ [cm^{-1}] = 2930, 2765, 1785, 1455, 1370, 1240, 1155, 955. − MS (70 eV); *m/z* (%): 337 (6) [M$^+$], 279 (9), 198 (78), 182 (36), 138 (67), 124 (100). − $C_{20}H_{35}NO_3$ (337.3): calcd. C 71.18, H 10.45, N 4.15; found C 70.92, H 10.19, N 4.01.

(+)-(4*R*,5*S*,2′*S*)-5-Menthyloxy-4-methyl-4-(1′-methylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (19′): Yield: 59 mg (32%). − R_f = 0.52 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = +128.1; $[\alpha]_{578}^{21}$ = +132.9; $[\alpha]_{546}^{21}$ = +151.3; $[\alpha]_{436}^{21}$ = +252.7; $[\alpha]_{365}^{21}$ = +254.4 (*c* = 1.09, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.72 (d, *J* = 6.7 Hz, 3 H), 0.83 (d, *J* = 6.7 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H), 0.72−1.07 (m, 3 H), 1.10−1.47 (m, 4 H), 1.13 (s, 3 H), 1.52−1.58 (m, 4 H), 1.82−2.17 (m, 2 H), 2.16 (d, 15.0, 1 H), 2.29 (s, 3 H), 2.57 (d, 15.0, 1 H), 3.00 (m, 2 H), 3.48 (m, 1 H), 3.60 (td, *J* = 10.4, 4 Hz, 1 H), 5.49 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 15.7, 17.6, 20.9, 22.3, 23.1, 23.7, 25.5, 28.8, 31.3, 34.3, 39.3, 39.5, 40.1, 46.6, 47.9, 58.5, 70.7, 76.1, 103.4, 175.2. − IR (KBr): ṽ [cm^{-1}] = 2935, 2740, 1775, 1445, 1235, 1155. − MS (70 eV); *m/z* (%): 337 (2) [M$^+$], 279 (9), 198 (100), 182 (21), 138 (20), 124 (14). − $C_{20}H_{35}NO_3$ (337.3): calcd. C 71.18, H 10.45, N 4.15; found C 70.90, H 10.17, N 3.82.

Products 20 and 21: To avoid the formation of cyclohexenone dimers, the reaction procedure was modified slightly. A solution of **13a** (96 mg, 1 mmol, 1 equiv.) and bis(dimethylamino)benzophenone (27 mg, 0.1 mmol, 0.01 equiv.) in methylpyrrolidine (100 mL) was irradiated for 8 h with visible light, using a 500-W halogen lamp. After evaporation of excess amine, the residue was purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant.

3-(1-Methylpyrrolidin-1-yl)cyclohexanone (20): Yield: 80 mg (44%). − R_f = 0.27 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.31−1.86 (m, 6 H), 1.87−2.12 (m, 2 H), 2.31 (s, 3 H), 2.13−2.54 (m, 7 H), 3.02 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.1, 25.2, 29.2, 38.2, 40.8, 41.8, 41.9, 46.7, 54.1, 67.7, 211.7. − IR (KBr): ṽ [cm^{-1}] = 2925, 1745, 1460, 1150, 1010. − MS (70 eV); *m/z* (%): 181 (1) [M$^+$], 180 (100), 110 (4). − $C_{11}H_{19}NO$ (181.30): calcd. C 72.88, H 10.56, N 8.83; found C 72.95, H 10.21, N 8.43.

3-(1-Methylpyrrolidin-1-yl)cyclohexanone (20′): Yield: 65 mg (36%). − R_f = 0.27 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 1.31−1.86 (m, 12 H), 1.87−2.12 (m, 4 H), 2.31 (s, 3 H), 2.13−2.54 (m, 14 H), 2.33 (s, 3 H), 3.02 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 25.0, 25.7, 29.1, 38.5, 41.3, 41.7, 41.8, 46.8, 54.1, 67.8, 212.8. − IR (KBr): ṽ [cm^{-1}] = 2930, 1760, 1455, 1140, 1055. − MS (70 eV); *m/z* (%): 181 (4) [M$^+$], 180 (100), 110 (6). − $C_{11}H_{19}NO$ (181.30): calcd. C 72.88, H 10.56, N 8.83; found C 72.52, H 10.19, N 8.46.

3,5,5-Trimethyl-3-(1-methylpyrrolidin-1-yl)cyclohexanone (21): Yield: 58 mg (26%). − R_f = 0.23 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 0.92 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.31−1.90 (m, 4 H), 1.98−2.53 (m, 8 H), 2.38 (s, 3 H), 2.81 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.4, 24.9, 27.0, 28.6, 34.0, 35.4, 44.5, 45.2, 46.6, 47.2, 53.7, 58.4, 76.0, 212.8. − IR (KBr): ṽ [cm^{-1}] = 2950, 1775, 1430, 1155, 965. − MS (70 eV); *m/z* (%): 223 (85) [M$^+$], 190 (26), 139 (27), 124 (54), 110 (76). − $C_{14}H_{25}NO$ (223.2): calcd. C 75.28, H 11.28, N 6.27; found C 74.95, H 11.03, N 6.13.

3,5,5-Trimethyl-3-(1-methylpyrrolidin-1-yl)cyclohexanone (21′): Yield: 47 mg (21%). − R_f = 0.23 (ethyl acetate/petroleum ether, 1:2). − ^{1}H NMR ($CDCl_3$): δ = 0.93 (s, 3 H), 0.96 (s, 3 H), 1.06 (s, 3 H), 1.33−1.86 (m, 4 H), 1.98−2.53 (m, 8 H), 2.39 (s, 3 H), 2.79 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.2, 24.6, 27.4, 29.0, 34.4, 43.8, 43.9, 41.3, 46.6, 49.2, 50.5, 58.5, 77.3, 212.6. − IR (KBr): ṽ [cm^{-1}] = 2970, 1765, 1175, 960. − MS (70 eV); *m/z* (%): 223 (7) [M$^+$], 190 (19), 139 (43), 124 (26), 110 (47). − $C_{14}H_{25}NO$ (223.2): calcd. C 75.28, H 11.28, N: 6.27; found C 74.98, H 10.96, N 6.04.

Synthesis of (−)-Isoretronecanol

(4*S*,2′*S*)-4-(1′-Methylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (22a): Sodium tetrahydroborate (300 mg, 7.9 mmol, 1.3 equiv.) was added slowly to a solution of **3a** (1.97 g, 6.1 mmol, 1 equiv.) in methanol (120 mL) at 0 °C. After stirring the solution for 1 h at room temperature, a sodium hydroxide solution (20%, 50 mL) was added. The reaction mixture was then neutralized with a solution of hydrochloric acid (2 N) and extracted with Et_2O (3 × 50 mL). The solution was dried with magnesium sulfate, concentrated and the residue purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant; 0.84 g (89%) of menthol was recovered. Yield: 830 mg (81%). − R_f = 0.17 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −54.4 (*c* = 1.06, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.30−1.97 (m, 4 H), 2.19 (s, 3 H), 2.07−2.23 (m, 2 H), 2.29 (dd, *J* = 16.9, 4.8 Hz, 1 H), 2.47 (dd, *J* = 16.9, 7.9 Hz, 1 H), 2.69 (m, 1 H), 2.89 (m, 1 H), 3.98 (dd, *J* = 14.2, 6.3 Hz, 1 H), 4.36 (dd, *J* = 14.2, 8.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.0, 26.4, 32.1, 36.8, 40.7, 57.0, 67.2, 71.5, 177.6. − IR (KBr): ṽ [cm^{-1}] = 2920, 1760, 1440, 1165. − MS (70 eV); *m/z* (%): 169 (11) [M$^+$], 168 (31), 125 (24), 84 (100). − $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.55, H 9.21, N 8.06.

(4*S*,2′*S*)-4-(1′-*tert*-Butylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (22d): Sodium tetrahydroborate (275 mg, 7.2 mmol, 1.3 equiv.) was added slowly to a solution of **3a** (2.02 g, 5.54 mmol, 1 equiv.) in methanol (120 mL) at 0 °C. After stirring the solution for 1 h at room temperature, a sodium hydroxide solution (20%, 50 mL) was added. The reaction mixture was then neutralized with a solution of hydrochloric acid (2 N) and extracted with Et_2O (3 × 50 mL). The solution was dried with magnesium sulfate, concentrated and the residue purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant; 0.84 g (82%) menthol was recovered. Yield: 937 mg (80%). − R_f = 0.21 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −51.2 (*c* = 1.08, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.19 (s, 9 H), 1.32−1.95 (m, 4 H), 2.04−2.17 (m, 2 H), 2.33 (dd, *J* = 14.8, 4.3 Hz, 1 H), 2.51 (dd, *J* = 14.8, 8.2 Hz, 1 H), 2.68 (m, 1 H), 2.91 (m, 1 H), 3.96 (dd, *J* = 14.4, 6.1 Hz, 1 H), 4.36 (dd, *J* = 14.4, 8.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.1, 26.1, 27.5, 32.4, 36.9, 53.8, 57.3, 67.1, 71.3, 177.4. − IR (KBr): ṽ [cm^{-1}] = 2925, 1750, 1400, 1155. − MS (70 eV); *m*/*z* (%): 211 (14) [M^+], 196 (62), 167 (32), 153 (10), 126 (100). − $C_{12}H_{21}NO_2$ (211.3): calcd. C 68.21, H 10.02, N 6.63; found C 68.01, H 9.78, N 6.39.

(4*S*,8*S*)-1-(Hydroxymethyl)hexahydropyrrolizin-3-one (23): A solution of the lactone **22a** (800 mg, 4.72 mmol, 1 equiv.), lithium perchlorate (250 mg, 2.4 mmol, 0.5 equiv.) and dicyanonaphthalene (90 mg, 0.5 mmol, 0.1 equiv.) in acetonitrile (100 mL) was saturated with oxygen (bubbling of pure oxygen during 20 min). After irradiation with visible light for 90 min, the solution was treated for 3 h with a sodium hydroxide solution (20%, 50 mL) and extracted with Et_2O (3 × 50 mL). The ethereal solution was dried with magnesium sulfate and concentrated. The residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). Yield: 616 mg (84%). − R_f = 0.22 (ethyl acetate/petroleum ether, 2:1). − $[\alpha]_D^{21}$ = −69.6 (*c* = 1.02, EtOH). − ^{1}H NMR ($CDCl_3$): δ = 1.39−1.57 (m, 1 H), 1.92−2.14 (m, 3 H), 2.29−2.61 (m, 3 H), 3.08 (ddd, *J* = 12.3, 8.2−4.2 Hz, 1 H), 3.48 (dt, *J* = 12.3, 7.3 Hz, 1 H), 3.55−3.72 (m, 2 H), 4.07 (dd, *J* = 11.9, 6.9 Hz, 1 H), 4.18 (dd, *J* = 11.9, 5.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 26.9, 31.2, 38.0, 42.6, 43.2, 65.3, 65.9, 173.8. − IR (film): ṽ = 3520, 2970, 1710, 1280, 950. − MS (70 eV); *m*/*z* (%): 155 (46) [M^+], 138 (25), 124 (17), 97 (100). − $C_8H_{13}NO_2$ (155.2): calcd. C 61.91, H 8.44, N 9.03; found C 61.72, H 8.15, N 8.81.

(4*S*,8*S*)-1-(Hydroxymethyl)hexahydropyrrolizin-3-one (23): Trifluoroacetic acid (1.71 g, 4.26 mmol, 3.5 equiv.) was added to a solution of **22d** (902 mg, 4.26 mmol, 1 equiv.) in dichloromethane (20 mL). The solution was heated at reflux for 10 h, then cooled at 0 °C and treated with a 10% sodium hydroxide solution (10 mL). After stirring for 3 h, the solution was extracted with Et_2O (3 × 50 mL). The ethereal solution was dried with magnesium sulfate and concentrated. The residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). Yield: 516 mg (78%).

(−)-Isoretronecanol (−)-24: Lithium tetrahydroaluminate (355 mg, 9.35 mmol, 2.5 equiv.) was added to a solution of **23** (580 mg, 3.74 mmol, 1 equiv.) in tetrahydrofuran (40 mL). The solution was heated at reflux for 10 h. After cooling, water (390 μL), a sodium hydroxide solution (15%, 390 μL) and water (1.15 mL) were added successively. The solution was extracted with Et_2O (3 × 25 mL) and the organic phase was dried with magnesium sulfate and concentrated. The oily residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). An *ee* > 98% was determined by GC on a chiral column (CP-Cyclodextrin-B-236-M-19) from Chrompack. Yield: 454 mg (86%). − R_f = 0.21 (ethyl acetate/petroleum ether, 2:1). − $[\alpha]_D^{21}$ = −76.4 (*c* = 1.14, EtOH). − ^{1}H NMR ($CDCl_3$): δ = 1.54−2.22 (m, 6 H), 2.36−2.69 (m, 4 H), 3.01−3.16 (m, 1 H, H3), 3.21−3.42 (ddd, *J* = 7.2, 6.9, 6.8 Hz, 1 H), 3.63−3.73 (m, 2 H), 4.31 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 26.0, 26.5, 27.3, 44.4, 54.0, 55.6, 62.6, 66.1. − IR (KBr): ṽ [cm^{-1}] = 3380, 2970, 1460, 1110, 1040, 950. − MS (70 eV); *m*/*z* (%): 141 (19) [M^+], 124 (17), 110 (80), 83 (100). − $C_8H_{15}NO$ (141.2): calcd. C 68.04, H 10.71, N 9.92; found C 67.77, H 10.96, N 9.81.

(4*S*,2′*R*)-4-(1′-Methylpyrrolidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (25): Sodium tetrahydroborate (248 mg, 6.5 mmol, 1.3 equiv.) was added slowly to a solution of **3a** (1.61 g, 5.0 mmol, 1 equiv.) in methanol (100 mL) at 0 °C. After stirring the solution for 1 h at room temperature, a solution of sodium hydroxide (20%, 50 mL) was added. The reaction mixture was then neutralized with a solution of hydrochloric acid (2 N) and extracted with Et_2O (3 × 50 mL). The solution was dried with magnesium sulfate, concentrated, and the residue was purified by chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant. Menthol (0.67 g, 68%) was recovered. Yield: 702 mg (83%). − R_f = 0.17 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −59.3 (*c* = 1.00, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.27−1.96 (m, 4 H), 2.18 (s, 3 H), 2.07−2.23 (m, 2 H), 2.21 (dd, *J* = 16.8, 4.5 Hz, 1 H), 2.38 (dd, *J* = 16.8, 7.7 Hz, 1 H), 2.66 (m, 1 H), 2.89 (m, 1 H), 3.92 (dd, *J* = 15.5, 5.9 Hz, 1 H), 4.19 (dd, *J* = 15.5, 7.6 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 22.1, 27.2, 30.1, 38.0, 40.9, 56.9, 67.2, 69.6, 177.7. − IR (KBr): ṽ [cm^{-1}] = 2930, 1745, 1410, 1155. − MS (70 eV); *m*/*z* (%): 169 (16) [M^+], 168 (42), 125 (12), 84 (100). − $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.45, H 9.21, N 8.01.

(1*S*,8*R*)-1-(Hydroxymethyl)hexahydropyrrolizin-3-one (26): A solution of the lactone **25** (660 mg, 3.9 mmol, 1 equiv.), lithium perchlorate (212 mg, 2.0 mmol, 0.5 equiv.), and dicyanonaphthalene (72 mg, 0.4 mmol, 0.1 equiv.) in acetonitrile (100 mL) was saturated with oxygen (bubbling of pure oxygen during 20 min). After irradiation with visible light, for 90 min, the solution was treated for 3 h with sodium a hydroxide solution (20%, 50 mL) and extracted with Et_2O (3 × 50 mL). The ethereal solution was dried with magnesium sulfate and concentrated. The residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). Yield: 490 mg (81%). − R_f = 0.19 (ethyl acetate/petroleum ether, 2:1). $[\alpha]_D^{21}$ = −13.2 (*c* = 0.96, EtOH). − ^{1}H NMR ($CDCl_3$): δ = 1.34−1.50 (m, 1 H), 1.96−2.19 (m, 3 H), 2.38−2.59 (m, 3 H), 3.05 (ddd, *J* = 11.6, 8.2, 3.9 Hz, 1 H), 3.54 (dt, *J* = 11.6, 7.6 Hz, 1 H), 3.65−3.74 (m, 2 H), 4.10 (dd, *J* = 11.0, 7.2 Hz, 1 H), 4.21 (dd, *J* = 11.0, 5.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 26.8, 31.3, 38.2, 41.4, 41.5, 65.0, 65.3, 174.1. − IR (film): ṽ [cm^{-1}] = 3540, 2970, 1725, 1270, 950. − MS (70 eV); *m*/*z* (%): 155 (41) [M^+], 138 (23), 124 (21), 97 (100). − $C_8H_{13}NO_2$ (155.2): calcd. C 61.91, H 8.44, N 9.03; found C 61.77, H 8.46, N 8.81.

Laburnine (+)-28: Lithium tetrahydroaluminate (280 mg, 7.38 mmol, 2.5 equiv.) was added to a solution of **26** (463 mg, 2.98 mmol, 1 equiv.) in tetrahydrofuran (40 mL). The solution was heated at reflux for 10 h. After cooling, water (310 μL), a 15% sodium hydroxide solution (310 μL) and water (910 μL) were successively added. The solution was extracted with Et_2O (3 × 25 mL) and the organic phase was dried with magnesium sulfate and concentrated. The oily residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). An *ee* > 98% was determined by GC on a chiral column (CP-Cyclodextrin-B-236-M-19)

from Chrompack. Yield: 328 mg (78%). − M.p. 115 °C (chloro hydrate, AcOEt/MeOH). − R_f = 0.16 (ethyl acetate/petroleum ether, 2:1). − $[\alpha]_D^{21}$ = +14.0 (c = 1.20, EtOH). − ^{1}H NMR ($CDCl_3$): δ = 1.52−2.10 (m, 7 H), 2.53−2.70 (m, 2 H), 3.08 (dt, J = 10.8, 6.3 Hz, 1 H), 3.18−3.30 (m, 1 H), 3.26 (ddd, J = 9.6, 7.2, 3.9 Hz, 1 H), 3.41 (q, J = 7.3 Hz, 1 H), 3.58−3.66 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 25.7, 30.2, 32.0, 48.4, 54.3, 56.8, 65.3, 67.6. − IR (KBr): ṽ [cm^{-1}] = 3340, 2970, 1450, 1280, 950. − MS (70 eV); *m/z* (%): 141 (17) [M^+], 124 (45), 110 (57), 83 (100). − $C_8H_{15}NO$ (141.2): calcd. C 68.04, H 10.71, N 9.92; found C 67.77, H 10.96, N 9.81.

(4*S*,2′*S*)-4-(1′-Methylpiperidin-2′-yl)-4,5-dihydrofuran-2(3*H*)-one (29): Sodium tetrahydroborate (285 mg, 7.5 mmol, 1.3 equiv.) was added slowly to a solution of **3k** (1.95 g, 5.8 mmol, 1 equiv.) in methanol (120 mL) at 0 °C. After stirring of the solution for 1 h at room temperature, a sodium hydroxide solution (20%, 50 mL) was added. Then, the reaction mixture was neutralized with a solution of hydrochloric acid (2 N) and extracted with Et_2O (3 × 50 mL). The solution was dried with magnesium sulfate, concentrated and the residue was chromatographed on silica gel by using petroleum ether/ethyl acetate (2:1) as eluant; 0.78 g (86%) of menthol was recovered. Yield: 834 mg (83%). − R_f = 0.23 (ethyl acetate/petroleum ether, 1:2). − $[\alpha]_D^{21}$ = −62.8 (c = 1.06, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.22−1.97 (m, 6 H), 2.16 (s, 3 H), 2.05−2.21 (m, 2 H), 2.29 (dd, J = 16.7, 4.3 Hz, 1 H), 2.47 (dd, J = 16.7, 8.0 Hz, 1 H), 2.62 (m, 1 H), 2.92 (m, 1 H), 3.96 (dd, J = 14.7, 6.1 Hz, 1 H), 4.32 (dd, J = 14.7, 8.1 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 21.3, 22.0, 26.4, 32.0, 36.9, 41.2, 54.3, 62.3, 71.1, 177.3. − IR (KBr): ṽ [cm^{-1}] = 2645, 1755, 1420, 1150. − MS (70 eV); *m/z* (%): 183 (34) [M^+], 182 (100), 139 (23), 125 (13), 98 (33). − $C_{10}H_{17}NO_2$ (183.2): calcd. C 65.54, H 9.35, N 7.64; found C 65.22, H 9.04, N 7.36.

(1*S*,9*S*)-1-(Hydroxymethyl)hexahydroindolizin-3-one (30): A solution of the lactone **29** (857 mg, 4.68 mmol, 1 equiv.), lithium perchlorate (240 mg, 2.3 mmol, 0.5 equiv.), and dicyanonaphthalene (80 mg, 0.4 mmol, 0.1 equiv.) in acetonitrile (100 mL) was saturated with oxygen (bubbling of pure oxygen during 20 min). After irradiation with visible light for 90 min, the solution was treated for 3 h with a sodium hydroxide solution (20%, 50 mL) and extracted with Et_2O (3 × 50 mL). The ethereal solution was dried with magnesium sulfate and concentrated. The residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). Yield: 663 mg (83%). − R_f = 0.22 (ethyl acetate/petroleum ether, 1:1). $[\alpha]_D^{21}$ = −73.6 (c = 1.02, EtOH). − ^{1}H NMR ($CDCl_3$): δ = 1.31−1.59 (m, 3 H), 1.90−2.13 (m, 3 H), 2.31−2.63 (m, 3 H), 3.08 (ddd, J = 14.2, 8.0, 3.9 Hz, 1 H), 3.48 (dd, J = 14.2, 7.3−5.2 Hz, 1 H), 3.56−3.74 (m, 1 H), 4.07 (m, 2 H), 4.18 (dd, J = 13.8, 6.2 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 23.1, 27.2, 31.4, 38.7, 42.4, 42.8, 62.8, 66.3, 173.9. − IR (film): ṽ [cm^{-1}] = 3525, 2980, 1720, 1295, 965. − MS (70 eV); *m/z* (%): 169 (36) [M^+], 152 (28), 138 (21), 111 (100). − $C_9H_{15}NO_2$ (169.2): calcd. C 63.88, H 8.93, N 8.28; found C 63.58, H 8.72, N 8.01.

(1*S*,9*S*)-1-(Hydroxymethyl)octahydroindolizidine (31): Lithium tetrahydroaluminate (355 mg, 9.34 mmol, 2.5 equiv.) was added to a solution of **30** (632 mg, 3.73 mmol, 1 equiv.), in tetrahydrofuran (40 mL). The solution was heated at reflux of THF for 10 h. After cooling, water (390 μL), a sodium hydroxide solution (15%, 390 μL) and water (1.15 mL) were added successively. The solution was extracted with Et_2O (3 × 25 mL) and the organic phase was dried with magnesium sulfate and concentrated. The oily residue was purified by chromatography on a short column (3 cm) of silica gel and eluted with a mixture of dichloromethane and methanol (20:1). Yield: 506 mg (88%). − R_f = 0.21 (ethyl acetate/petroleum ether, 2:1). − $[\alpha]_D^{21}$ = −82.1 (c = 1.00, EtOH). − ^{1}H NMR ($CDCl_3$): δ = 0.94−2.29 (m, 8 H), 2.36−2.69 (m, 4 H), 3.01−3.16 (m, 1 H), 3.21−3.42 (ddd, J = 7.3, 6.9, 4.3 Hz, 1 H), 3.58−3.68 (m, 2 H), 4.51 (s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 24.3, 25.2, 25.4, 30.4, 46.1, 53.1, 53.4, 64.6, 67.4. − IR (KBr): ṽ [cm^{-1}] = 3330, 2950, 1280, 950. − MS (70 eV); *m/z* (%): 155 (19) [M^+], 154 (33), 124 (100), 97 (45). − $C_9H_{17}NO$ (155.2): calcd. C 69.63, H 11.04, N 9.02; found C 69.77, H 10.96, N 8.81.

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