# Enantioselective Synthesis of the Ester Side Chain of Homoharringtonine

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Details of the synthesis of the methyl ester of the side chain of homoharringtonine, a natural product with antileukemic properties, are reported below. The key tactical element involved a Michael addition between the known chiral imine **4** and 2-acetoxyacrylonitrile (**5**), furnishing the adduct (2*R*,1′*R*)-**6** with a high degree of regio- and stereoselectivity. This adduct was then converted into the target compound (*R*)-**2** by a linear sequence of ten chemical operations, in 6.0% overall yield.



## Introduction

*Cephalotaxus*, the only genus of the family Cephalotaxaceae (Coniferae), with eight species known so far, is mostly native of the southern provinces of China.[1] Conifers of the genus *Cephalotaxus* are evergreen trees, with yew-like leaves, or shrubs, growing in humid valleys or in forests. The presence of alkaloids in *Cephalotaxus* was first reported by Paudler, who isolated cephalotaxine (**1a**) in 1963.[2] Since the antitumor activity of several esters contained in *Cephalotaxus* was reported,[3] there has been a resurgence of interest in developing synthetic routes to these alkaloids. Research efforts have essentially focused on homoharringtonine (HHT, **1b**), since it is the main natural ester of cephalotaxine (**1a**) isolated from the leaves and stems of the plumyew *C. harringtonia*, and the most potent in this family of antitumor drugs (Figure 1).

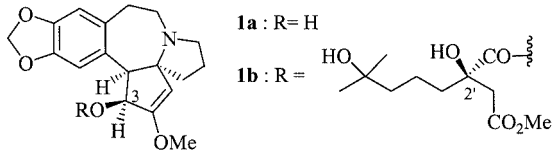


Figure 1. Structures of cephalotaxine (**1a**) and homoharringtonine (HHT, **1b**)

Several teams have investigated the mechanism by which HHT and related alkaloids exert their antineoplastic effects; all have concluded that these drugs block protein biosynthesis in the cell, through inhibition of the elongation phase of translation by prevention of substrate binding to the acceptor site on ribosomes.[4] HHT has been clinically tested in chronic myelogenous leukemia in late chronic phase, in myelodysplastic syndrome (MDS), and in MDS evolving to acute myeloid leukemia.[5] This drug is now used in China as the front-line chemotherapy for acute myeloid leukemia, particularly in acute promyelocytic leukemia. In the US, the efficiency of HHT in the treatment of chronic myeloid leukemia is being evaluated in a large-scale study.[6] In view of their wide range of antitumor activities, the structure-activity relationships among *Cephalotaxus* alkaloids are a matter of prime importance. In this respect, it has been established that cephalotaxine (**1a**), although much more abundant in *C. harringtonia* than HHT and related esters, is itself devoid of antileukemic activity. Therefore, the presence of a specific ester linkage branched at C-3 (relative to the cephalotaxine core) is a critical structural requirement for the antitumor potency of HHT and analogues. Furthermore, there is a marked influence of the structures of the side chains of *Cephalotaxus* alkaloids on their antineoplastic activity and toxicity; thus *epi*-HHT, which differs from HHT only in the configuration of the stereogenic center at C-2′, exhibited no significant antileukemic potency. As a result of 30 years or so of intensive research, several strategies for the elaboration of the side chain of HHT, or its cyclic equivalents, have been developed.[7] The problem with those approaches, however, turned out to be the difficulty of achieving stereoselectivity. Reported here is a highly stereoselective synthesis of the methyl ester of the side chain of HHT (**2**), in the natural (*R*) configuration, exploiting our general methodology for the enantioselective construction of quaternary carbon centers.[8]

## Results and Discussion

A key aspect of this work was to find a concise solution to the problem of synthesizing the cornerstone keto ester

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(*R*)-**3**. We envisaged stereoselective elaboration of **3** through asymmetric Michael addition of the known chiral imine **4**[9] to a two-carbon electrophilic alkene (or its equivalent), precursor of the acetate appendage of this keto ester. It was our original hope that nitroethylene or phenyl vinyl sulfone might play the role of a two-carbon Michael acceptor in the condensation with imine **4**. However, the addition of nitroethylene to chiral imines having proved to be non-regioselective,[10] this electrophilic alkene was not suited to the task. Since addition of chiral imines to phenyl vinyl sulfone gave the desired adducts with high degrees of regio- and stereoselectivity,[11] condensation of imine **4** with this electrophile might offer an alternative access to subgoal **3**. However, the sensitive imine **4** was found to be unstable under the conditions required for these Michael condensations (24 hours at 80 °C).[12] Consequently, the strategy ultimately adopted for the introduction of the acetate side chain of **3** was the elaboration of adduct **6**, through Michael condensation between imine **4** and the three-carbon acceptor 2-acetoxyacrylonitrile (**5**),[13] followed by the transformation of the α-acetoxypropionitrile appendage of adduct **6** into an acetate moiety. The capto-dative electrophilic alkene **5** has previously been utilized by Barton[14] and Scheffold[15] as a two-carbon equivalent building block in the Michael-type trapping of radical species. The conversion of Michael adduct **6** into the methyl ester of the HHT side chain (**2**) would require three essential chemical operations: the transformation of the α-acetoxypropionitrile appendage into an acetate moiety (**A**), the regioselective oxidative cleavage of the cyclohexane ring at the less substituted α-side of the carbonyl function (**B**), and the introduction of two geminate methyl groups to complete the carbinol terminus (**C**) (Figure 2).

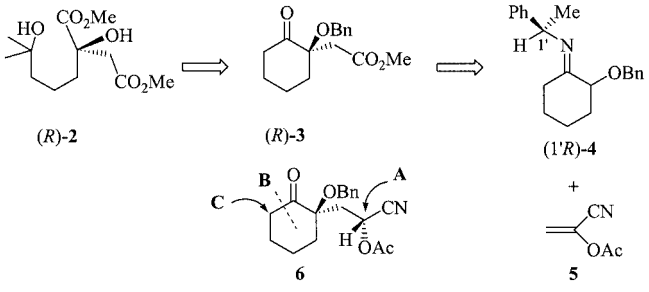
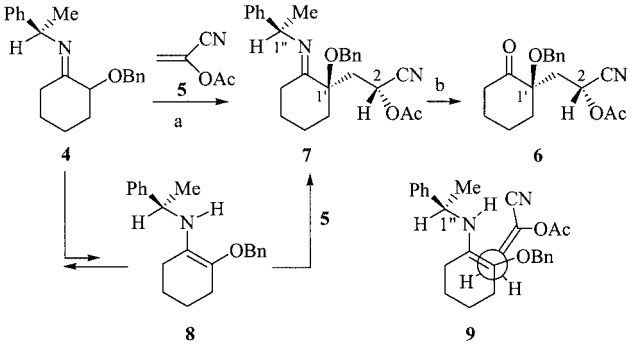



Figure 2. Retrosynthetic analysis of diester (*R*)-**2** (**A**, **B**, **C**: see text)

The first stage of the synthesis required the preparation of Michael adduct **6**. For that purpose, *racemic* 2-benzyloxycyclohexanone was condensed with (*R*)-1-phenylethylamine (> 98% *ee*) in the presence of an activated catalyst at room temperature and the resulting crude chiral imine **4**[9] was subjected to a Michael reaction with 2-acetoxyacrylonitrile (**5**), affording the adduct (2*R*,1′*R*,1′′*R*)-**7**, *which turned out to be stereochemically homogeneous by* $^1H$ *and* $^{13}C$ *spectroscopy.*[8m] Hydrolysis of crude imine **7** next afforded cyclohexanone (2*R*,1′*R*)-**6** (72% overall yield, calculated from starting 2-benzyloxycyclohexanone). The de and *ee* in **6** were both > 95% as evidenced by $^1H$ NMR spectroscopy with addition of $Eu(fod)_3$ and $Eu(hfc)_3$ as shift reagents. The relative configuration of the two stereogenic centers in ketone **6** was assigned by NMR spectroscopy including NOESY experiments at the level of the bicyclic derivatives **10** and **16**, and the absolute configuration was definitively secured by correlation of **6** with our goal (*R*)-**2**. The remarkable complete stereocontrol over the two newly created stereogenic centers in adduct **7** can be interpreted by evoking for the addition the compact approach **9**, involving a *synclinal* arrangement of the two partners: electrophile **5** and, as nucleophilic species, the more substituted secondary enamine **8**, which is in tautomeric equilibrium with imine **4**.[8a,16] According to this model, the alkylation process takes place preferentially on the less hindered π-face of the enamine **8** (*anti* to the bulky phenyl group), portrayed in its energetically preferred conformation minimizing the $A^{1,3}$-type strain (C1′′−H bond more or less eclipsing the cyclohexene ring). This accounts for the absolute configuration at C-1′ in the resulting adduct **7**. Control over the stereogenic center at C-2 in **7** originates from a concerted transfer of the NH proton of enamine **8** to the α-vinylic center of electrophile **5**,[17] the nitrile end of this acceptor facing the nitrogen atom of the enamine ("*endo* arrangement")[8a,17,18] (Scheme 1).



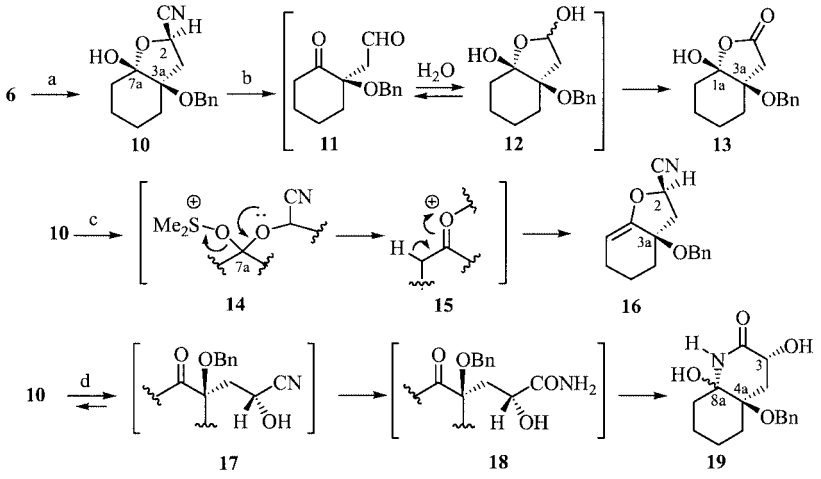

Scheme 1. Synthesis of Michael adduct **6**; reagents and conditions: (a) neat, room temperature; (b) 20% AcOH/THF, 1:1 (72%); tautomeric equilibrium between imine **4** and enamine **8** and synclinal approach of enamine **8** to Michael acceptor **5** (**9**)

Regeneration of the masked aldehyde function at C-2 in **6** was examined first. This requires a deacetylation step, followed by dehydrocyanation of the resulting cyanohydrin. While basic treatment of **6** invariably furnished undefined compounds, the bicyclic hemiacetal (2*R*,3a*R*,7a*S*)-**10** was formed in 77% yield when the reaction was conducted under acidic conditions. However, all efforts at generating aldehyde **11** through dehydrocyanation of **10**, a process which would in fact implicate the open form of this hemiacetal, were fruitless. In contrast, sequential treatment of **10** with NaOMe and $NaO_2Cl$[19] gave the sensitive bicyclic lactone (1a*S*,3a*R*)-**13**, albeit in modest yield (ca. 35%). Formation of compound **13** clearly involves the transient aldehyde **11**, in equilibrium − through the addition of a molecule of water − with the bis-hemiacetal **12**, the in situ oxidation of the latter ultimately furnishing lactone **13**. Incidentally, another interesting observation was made when compound

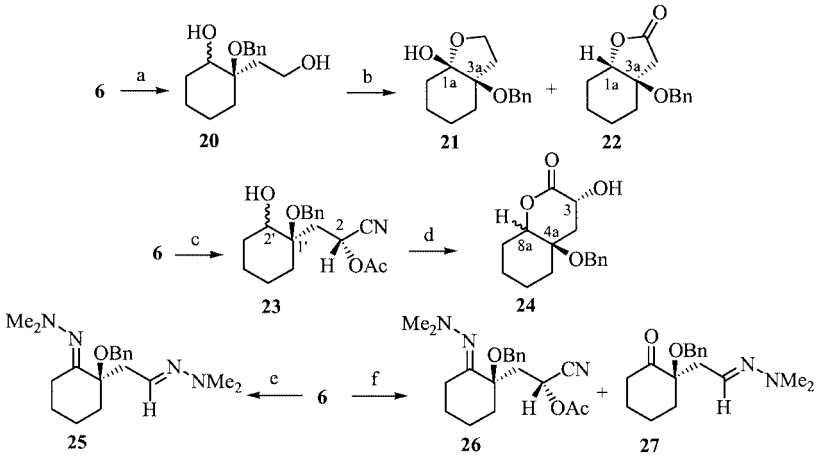
  

**10** was subjected to the Swern reagent: the olefinic derivative (2*R*,3a*R*)-**16** was isolated in 55% yield. This apparently unprecedented dehydration process can be interpreted by assuming the original formation at C-7a of a dimethylalkoxysulfonium ion[20] **14**, which collapses to olefin **16**, a fragmentation assisted by the neighboring oxygen atom and which probably implicates the intermediary oxonium ion **15**. An alternative route for the conversion of **10** into **16** was also investigated, with employment of Burgess' inner salt ($Et_3N^+SO_2N^-COOMe$)[21] as a dehydration agent (60% yield). The transformation of cyanohydrins into the corresponding aldehydes has also been accomplished by treatment with silver nitrate in the presence of ammonium hydroxide at room temperature.[22] Under such conditions, however, the hemiacetal **10** was converted in 68% yield into the bicyclic lactams **19**. Such a result can be explained in terms of the cyanohydrin **17**, in equilibrium with hemiacetal **10**, being primarily hydrolyzed into the α-hydroxy amide **18**, precursor of the bicyclic derivatives **19** (Scheme 2).

In order to circumvent the above troublesome hemiacetalization side-reactions, the masking of the carbonyl group of adduct **6** as a secondary alcohol function was investigated next. When, however, compound **6** was treated with $NaBH_4$ in EtOH, an overreduction of the molecule took place, furnishing diols **20** with a moderate yield (37%). Oxidation of these derivatives with $H_5IO_6$ in the presence of a catalytic amount of $CrO_3$[23] then produced a mixture of hemiacetal **21** and lactone **22** in 64% yield. In contrast, the utilization of $Zn(BH_4)_2$ as a reducing agent was more satisfying, giving the desired alcohols **23** in 90% yield. Acidic cleavage of **23** was next attempted, but concomitant hydrolysis of the nitrile end occurred during this reaction, furnishing lactones **24** (71% yield). At this juncture, it was deemed necessary to select a different carbonyl protecting



Scheme 2. Attempts at regeneration of the masked aldehyde function at C-2 in **6**: hemiacetalization side-reactions; reagents and conditions: (a) 1 M HCl, THF, 50 °C (77%); (b) i. MeONa, MeOH, 0 °C; ii. $NaO_2Cl$, *t*BuOH, $H_2O$, $NaH_2PO_4$, 2-methyl-2-butene, room temperature (35% − 2 steps); (c) i. $(COCl)_2$, $Me_2SO$, $CH_2Cl_2$; ii. $Et_3N$ (55%) or Burgess' salt, toluene, 50 °C (60%); (d) $AgNO_3$, $NH_4OH$, $Et_2O$, room temperature (68%)



Scheme 3. Tentative approaches to protection of the carbonyl group of **6**; reagents and conditions: (a) $NaBH_4$, EtOH, room temperature (37%); (b) $H_5IO_6$, cat. $CrO_3$, $CH_3CN$, $H_2O$, 0 °C (64%, 1.5:1 mixture); (c) $Zn(BH_4)_2$, $Et_2O$, 0 °C; (d) 1 M HCl, THF, 50 °C (64%, 2 steps); (e) 4 equiv. of 1,1-dimethylhydrazine, EtOH, mol. sieves, reflux (34%); (f) 1.1 equiv. of 1,1-dimethylhydrazine, EtOH, mol. sieves, reflux (58%, 1:1 mixture)

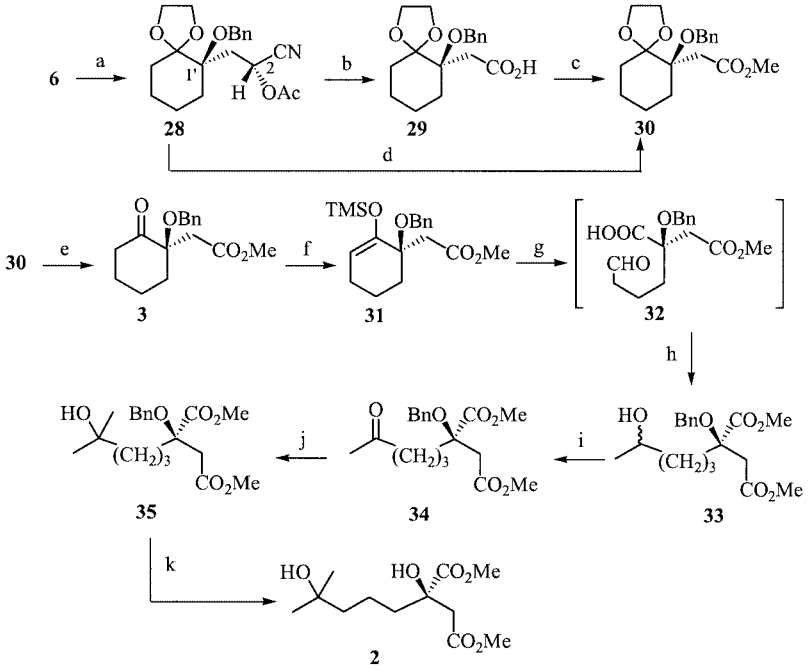
group. Derivatization of **6** as a 1,1-dimethylhydrazone was first undertaken. Treatment of adduct **6** with an excess of 1,1-dimethylhydrazine resulted in the formation of bis-hydrazone **25**. However, since we have demonstrated that the two hydrazones **26** and **27** were formed in approximately equal amounts when the two reagents were used in a stoichiometric ratio, this methodology was abandoned (Scheme 3).

The protecting group that was finally adopted in order to achieve our original objective was the 1,3-dioxolane group, which was easily introduced by condensation of the adduct **6** with $TMSOCH_2-CH_2OTMS$ in the presence of TMSOTf, furnishing acetal **28** (80% yield).[24] Transformation of the protected cyanohydrin moiety of **28** into a methoxycarbonyl group now proceeded straightforwardly, either by basic treatment (LiOH) followed by the in situ oxidation ($NaO_2Cl$) of the intermediary aldehyde and esterification ($CH_2N_2$) of the resulting acid **29** (75% yield), or more directly by treatment of **28** with $MnO_2$ in MeOH in the presence of NaCN (61% yield).[15,25] Unmasking of the ketal group of ester **30** was then investigated. While treatment of **30** under mildly acidic hydrolytic conditions to produce ketone **3** was to some avail, under more drastic conditions side-reactions competed with removal of the ketal group, ruining the structure. Finally, after extensive experimentation, it was discovered that treatment of ketal **30** with cerium(III) chloride heptahydrate in the presence of NaI in MeCN at reflux[26] delivered the cornerstone ketone (*R*)-**3** in 85% yield.

The oxidative cleavage of the cyclohexane ring of **3** was then undertaken. For this purpose, this ketone was first converted into the silyl enol ether **31** (TMSCl, $Et_3N$, NaI),[27] which was ozonized ($O_3$ then $Me_2S$) into the sensitive aldehyde **32** (not characterized). Slow addition of two equivalents of MeMgBr to crude aldehyde **32** at −40 °C[28] and subsequent esterification with $CH_2N_2$ then afforded an equimolar mixture of epimeric alcohols **33** in 35% overall yield, calculated from ketone **3**. At this juncture, we stood ready to complete the synthesis of the methyl ester derivative of the HHT side chain. In the event, treatment of alcohols **33** with pyridinium chlorochromate gave ketone (*R*)-**34** (80% yield). Slow addition at −30 °C of one equivalent of MeMgBr to **34** produced carbinol (*R*)-**35** (in 42% yield), which was transformed by hydrogenolysis of the benzyloxy group ($H_2$, Pd/C, quantitative yield) into our target compound, (*R*)-methyl 3,7-dihydroxy-3-methoxycarbonyl-7-methyloctanoate (**2**), identical in all respects with the ester deriving from methanolysis of natural HHT[3] (Scheme 4).

## Conclusion

To conclude, a highly stereoselective synthesis of the methyl ester derivative of the HHT side chain **2** in the natural *R* configuration, has been completed, in 4.3% overall yield, from 2-benzyloxycyclohexanone by a linear sequence of twelve chemical operations (mean yield per step: 77%). The key tactical element of the strategy involved the




Scheme 4. Synthesis of the HHT dimethyl ester side chain (*R*)-**2** from **6**; reagents and conditions: (a) i. $TMSOCH_2CH_2OTMS$, TMSOTf cat., $CH_2Cl_2$, −78 °C to room temperature; ii. pyridine (80%); (b) i. LiOH, THF, room temperature; ii. $NaO_2Cl$, *t*BuOH, $H_2O$, $NaH_2PO_4$, 2-methyl-2-butene, room temperature (75%, 2 steps); (c) $CH_2N_2$, 0 °C to room temperature (100%); (d) $MnO_2$, NaCN, MeOH, room temperature (61%); (e) $CeCl_3{\cdot}7H_2O$, NaI cat., $CH_3CN$, reflux (85%); (f) TMSCl, NaI, $Et_3N$, $CH_3CN$, room temperature; (g) i. $O_3/O_2$, $CH_2Cl_2$, MeOH, −78 °C; ii. $Me_2S$, −78 °C to room temperature; (h) i. MeMgBr, THF, −40 °C; ii. $CH_2N_2$, 0 °C to room temperature (35%, 4 steps); (i) PCC, $CH_2Cl_2$, room temperature (80%); (j) MeMgBr, THF, −30 °C (42%); (k) $H_2$, Pd/C, MeOH, room temperature (100%)

Michael addition between chiral imine **4** and 2-acetoxyacrylonitrile (**5**), furnishing adduct **6** with a high degree of regio- and stereoselectivity (Scheme 1). Conversion of adduct **6** into the target compound **2** was achieved through three essential chemical steps: the transformation of the α-acetoxypropionitrile appendage into an acetate moiety (**6** → **3**), the regioselective oxidative cleavage of the cyclohexane ring at the less substituted α-side of the carbonyl function (**3** → **32**), and the introduction of two geminate methyl groups to complete the carbinol terminus (**32** → **35**). Studies directed towards the elaboration of sterically less hindered, cyclic forms of **2**, suitable for coupling with cephalotaxine (**1a**) to produce enantiopure HHT (**1b**), are currently under investigation.

## Experimental Section

**General Remarks:** All reactions not involving aqueous reagents were carried out under a nitrogen atmosphere in flame-dried glassware. Commercial reagents were used as purchased without further purification. Tetrahydrofuran (THF), toluene, and diethyl ether ($Et_2O$) were distilled from sodium/benzophenone ketyl, dichloromethane, dimethyl sulfoxide, and acetonitrile were distilled from calcium hydride, triethylamine ($Et_3N$) was distilled from potassium hydroxide, and ethanol and methanol were distilled from magnesium. Reactions were followed by TLC, carried out on Merck 60 F254 silica gel plates, which were viewed by UV irradiation at 254 nm and/or by staining with *p*-anisaldehyde. A Fischer 500 ozone generator was used for ozonolyses. Flash column chromatography was performed on Merck 230−400 mesh silica gel. Melting points were recorded on a Büchi apparatus and are uncorrected. Accurate mass spectra measurements were obtained on a Voyager-DE STR, Perspective Biosystem by MALDI-TOF or on a Micromass LCT by electrospray (+ESI) at the Institut de Chimie des Substances Naturelles (ICSN, CNRS, Gif sur Yvette, France). Optical rotations were recorded with a Polartronic E Schmidt+Haensch 2095 polarimeter in 1 dm cells (concentrations are indicated in g per 100 mL). Infrared spectra were recorded with a Bruker Vector 22 Fourier transform spectrometer. $^1$H NMR spectra were recorded at 300 K on AC 200 P or ARX 400 Bruker spectrometers, at 200 or 400 MHz, with $CHCl_3$ as the internal standard ($\delta_H$ = 7.26 ppm). $^{13}$C NMR spectra were recorded at 300 K on the same spectrometers, at 50 or 100 MHz, with the central peak of $CHCl_3$ as the internal standard ($\delta_C$ = 77.0 ppm). DEPT 135 and two-dimensional NMR experiments (COSY, HMQC and HMBC) were used for the assignments of signals in the $^1$H and $^{13}$C NMR spectra. Elemental analyses were performed on a Perkin−Elmer 2400-CHN analyzer at the Faculté de Pharmacie de Châtenay-Malabry.

**(2*R*,1′*R*,1′′*R*)-2-Acetoxy-3-[1′-benzyloxy-2′-(1′′-phenylethylimino)-cyclohexyl]propionitrile (7):** A mixture of powdered molecular sieves (5 Å, 9 g), basic aluminum oxide (Brockmann I, 2 g), and silica gel (Merck 230−400 mesh, 1 g) was flame-dried under vacuum for 10 minutes, cooled to room temperature, and suspended in anhydrous cyclohexane (15 mL). 2-Benzyloxycyclohexanone (7.5 g, 36.7 mmol) and (*R*)-(+)-phenylethylamine (5.2 mL, 40.4 mmol) were successively added to the suspension, and the resulting mixture was stirred at 20 °C under nitrogen for 4 hours. [The reaction was monitored by IR and $^1$H NMR, in $CDCl_3$ containing a pinch of $K_2CO_3$.] The catalyst was filtered off and washed with anhydrous THF (3 × 30 mL), and the solvent was removed under vacuum to give the crude imine **4**.[9] 2-Acetoxyacrylonitrile (**5**, 7.79 mL, 73.4 mmol) was added dropwise to this imine under nitrogen and the reaction mixture was stirred at room temperature for 36 hours. The excess of 2-acetoxyacrylonitrile was removed by low pressure distillation to give crude imine **7**. An aliquot of this imine **7** (oil) was taken up to record its spectroscopic data. IR (neat): $\tilde{\nu}$ = 2233, 1752, and 1658 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.5 Hz, 3 H, C$H_3$CH), 1.32−2.48 (m, 8 H, cyclohexyl $CH_2$), 1.98 (s, 3 H, $CH_3CO$), 2.45 (dd, *J* = 15.4, 6.2 Hz, 1 H, CC$H_A$H$_B$CH), 2.79 (dd, *J* = 15.4, 5.4 Hz, 1 H, CCH$_A$$H_B$CH), 4.00 (d, *J* = 11.7 Hz, 1 H, C$H_A$H$_B$O), 4.36 (d, *J* = 11.7 Hz, 1 H, CH$_A$$H_B$O), 4.74 (q, *J* = 6.5 Hz, 1 H, C*H*CH$_3$), 5.55 (dd, *J* = 6.2 and 5.4 Hz, 1 H, CHCN), 7.07−7.45 (m, 10 H, arom. CH) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 20.1 (*C*H$_3$CO), 20.6 (cyclohexyl $CH_2$), 25.3 (*C*H$_3$CH), 25.8 (cyclohexyl $CH_2$), 27.0 (cyclohexyl $CH_2$), 36.2 (cyclohexyl $CH_2$), 37.1 (C*C*H$_2$CH), 58.2 (*C*HCH$_3$), 58.4 (CH$_2$*C*HCN), 63.9 ($CH_2O$), 79.6 (C), 118.1 (CN), 126.4 (2 arom. CH), 126.6 (arom. CH), 126.7 (2 arom. CH), 127.2 (arom. CH), 128.1 (2 arom. CH), 128.3 (2 arom. CH), 138.0 (arom. C), 145.8 (arom. C), 168.8 (C=O or C=N), 169.7 (C=N or C=O) ppm.

**(2*R*,1′*R*)-2-Acetoxy-3-[1′-benzyloxy-2′-oxocyclohexyl]propionitrile (6):** The preceding crude imine **7** was hydrolyzed with an aqueous solution of acetic acid (20%, 25 mL) in THF (25 mL) for 4 hours at room temperature. Solvents were removed in vacuo. The residue was taken up in $Et_2O$ (75 mL) and aqueous HCl (1 M, 15 mL), and the aqueous layer was separated and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (3 × 25 mL) and with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 9:1) to give the Michael adduct **6** as a white solid (8.32 g, 72%); m.p. 62 °C. $[\alpha]_D^{20}$ = +75.1 (*c* = 2.13, EtOH). IR (neat): $\tilde{\nu}$ = 2251, 1756, 1721 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.51−1.64 (m, 4 H, cyclohexyl $CH_2$), 1.99 (s, 3 H, $CH_3CO$), 2.12 (m, 1 H, cyclohexyl C*H*H), 2.21 (dd, *J* = 15.7, 7.1 Hz, 1 H, CC$H_A$H$_B$CH), 2.27−2.40 (m, 2 H, cyclohexyl $CH_2$), 2.67 (dd, *J* = 15.7, 5.4 Hz, 1 H, CCH$_A$$H_B$CH), 2.77 (ddd, *J* = 12.8, 12.2, 4.9 Hz, 1 H, cyclohexyl C*H*H), 4.17 (d, *J* = 11.1 Hz, 1 H, C$H_A$H$_B$O), 4.53 (d, *J* = 11.1 Hz, 1 H, CH$_A$$H_B$O), 5.43 (dd, *J* = 7.1, 5.4 Hz, 1 H, CHCN), 7.28−7.44 (m, 5 H, arom. CH) ppm. NMR $^{13}$C (100 MHz, $CDCl_3$): δ = 20.2 (*C*H$_3$CO), 20.4 (cyclohexyl $CH_2$), 27.7 (cyclohexyl $CH_2$), 34.3 (C*C*H$_2$CH), 37.5 (cyclohexyl $CH_2$), 39.1 (cyclohexyl $CH_2$), 57.3 (CH$_2$*C*HCN), 65.4 ($CH_2O$), 81.3 (C), 117.1 (CN), 127.1 (2 arom. CH), 127.7 (arom. CH), 128.5 (2 arom. CH), 136.8 (arom. C), 169.0 ($CH_3CO$), 211.0 ($CH_2COC$) ppm. $C_{18}H_{21}NO_4$ (315.4): calcd. C 68.54, H 6.71, N 4.44; found C 68.66, H 6.81, N 4.36.

**(2*R*,3a*R*,7a*S*)-3a-Benzyloxy-7a-hydroxyoctahydrobenzofuran-2-carbonitrile (10):** Aqueous HCl (2 M, 40 mL) was added to a solution of Michael adduct **6** (2 g, 6.3 mmol) in THF (32 mL). The reaction mixture was stirred at 50 °C for 30 hours and concentrated in vacuo. The residue was taken up in water (10 mL) and EtOAc (50 mL), and the aqueous layer was separated and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 6:1) to give hemiacetal **10** as a white solid (1.33 g, 77%); m.p. 105 °C. $[\alpha]_D^{20}$ = +17.3 (*c* = 2.95, $CH_2Cl_2$). IR (neat): $\tilde{\nu}$ = 3543, 2235 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.31−1.74 (m, 5 H, cyclohexyl $CH_2$ and cyclohexyl C*H*H), 1.80 (m, 2 H, cyclohexyl $CH_2$), 2.01 (m, 1 H, cyclohexyl C*H*H), 2.39 (dd, *J* = 12.6, 8.6 Hz, 1 H, CC$H_A$H$_B$CH), 2.64 (dd, *J* = 12.6 and 5.2Hz, 1 H,

$CCH_AH_BCH$), 3.73 (br. s, 1 H, OH), 4.47 (d, $J$ = 10.6 Hz, 1 H, $CH_AH_BO$), 4.57 (d, $J$ = 10.6 Hz, 1 H, $CH_AH_BO$), 4.71 (dd, $J$ = 8.6, 5.2 Hz, 1 H, CHCN), 7.28−7.39 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.0 (cyclohexyl $CH_2$), 22.3 (cyclohexyl $CH_2$), 29.9 (cyclohexyl $CH_2$), 33.5 ($CCH_2CH$), 36.8 (cyclohexyl $CH_2$), 62.0 ($CH_2CHCN$), 66.1 ($CH_2O$), 81.3 (C), 105.0 (OCOH), 119.4 (CN), 127.9 (2 arom. CH), 128.4 (3 arom. CH), 137.3 (arom. C) ppm. $C_{16}H_{19}NO_3$ (273.4): calcd. C 70.31, H 7.01, N 5.12; found C 70.25, H 7.03, N 5.02.

**(1a*S*,3a*R*)-3a-Benzyloxy-7a-hydroxyhexahydrobenzofuran-2-one (13):** A solution of sodium methoxide (0.7 M, 0.6 mL, 0.34 mmol) in methanol was slowly added, under nitrogen and at 0 °C, to a solution of hemiacetal **10** (100 mg, 0.36 mmol) in dry methanol (3 mL) and dry chloroform (4 mL). The reaction mixture was stirred at 0 °C for 30 minutes, hydrolyzed with aqueous HCl (1 M, 0.3 mL), and extracted with $CH_2Cl_2$ (4 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the intermediary aldehyde **11** as a pale yellow oil. This oil was not characterized, due to its instability, and was used without further purification. 2-Methyl-2-butene (0.17 mL, 2.09 mmol) and aqueous sodium hydrogen phosphate (1 M, 0.45 mL, 0.45 mmol) were added successively to a solution of crude aldehyde **11** (90 mg) in *tert*-butyl alcohol (4 mL). Sodium chlorite (100 mg, 1.04 mmol) was added portionwise at 0 °C, and the reaction mixture was allowed to warm up and was stirred vigorously overnight at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography (cyclohexane/EtOAc, 1:1.5) to give lactone **13** as a white, sensitive solid (33 mg, 35%). IR (neat): $\tilde{\nu}$ = 3383 and 1769 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.09−1.95 (m, 5 H, cyclohexyl $CH_2$ and cyclohexyl C*H*H), 2.01−2.47 (m, 3 H, cyclohexyl $CH_2$ and cyclohexyl C*H*H), 2.68 (d, $J$ = 17.1 Hz, 1 H, $CCH_AH_BCO$), 2.85 (d, $J$ = 17.1 Hz, 1 H, $CCH_AH_BCO$), 4.38 (d, $J$ = 10.1 Hz, 1 H, $CH_AH_BO$), 4.50 (d, $J$ = 10.1 Hz, 1 H, $CH_AH_BO$), 4.71 (br. s, 1 H, OH), 7.18−7.42 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 21.6 (cyclohexyl $CH_2$), 22.0 (cyclohexyl $CH_2$), 29.4 (cyclohexyl $CH_2$), 34.9 (cyclohexyl $CH_2$), 36.9 ($CH_2CO$), 65.1 ($CH_2O$), 81.2 (C), 106.7 (OCOH), 127.7 (2 arom. CH), 128.2 (arom. CH), 129.0 (2 arom. CH), 136.9 (arom.C), 171.8 (CO) ppm.

**(2*R*,3a*R*)-3a-Benzyloxy-2,3,3a,4,5,6-hexahydrobenzofuran-2-carbonitrile (16). Swern Route:** Dry dimethyl sulfoxide (156 μL, 2.16 mmol) was added dropwise, under nitrogen and at −60 °C, to a solution of oxalyl chloride (128 μL, 1.44 mmol) in dry $CH_2Cl_2$ (2.6 mL). The reaction mixture was stirred at −60 °C for 10 minutes, and a solution of hemiacetal **10** (100 mg, 0.36 mmol) in dry $CH_2Cl_2$ (1 mL) was added. The reaction mixture was kept at −40 °C for 2.5 hours, dry triethylamine was added (0.49 mL, 3.6 mmol), and the resulting mixture was allowed to warm up and was stirred for 30 minutes at room temperature. The solvent was removed in vacuo and the residue was taken up with EtOAc (10 mL). The solution was filtered through Celite and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 6:1) to give enol ether **16** as a white solid (51 mg, 55%).

**Burgess' Salt Route:** A solution of hemiacetal **10** (150 mg, 0.55 mmol) in dry toluene (3 mL) was added under nitrogen to a suspension of Burgess' salt (133 mg, 0.59 mmol) in dry toluene (2 mL). The reaction mixture was stirred at 50 °C for two days and concentrated in vacuo. The residue was taken up in water (10 mL) and $CH_2Cl_2$ (25 mL), and the aqueous layer was separated and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 9:1) to give enol ether **16** as a white solid (84 mg, 60%); m.p. 107 °C. $[\alpha]_D$ = −30.4 ($c$ = 0.35, $CHCl_3$). MS: $m/z$ (MALDI-TOF) found 278.1166 [$MNa^+$], $C_{16}H_{17}NO_2$ (M, 255.4) requires 278.1157. IR (neat): $\tilde{\nu}$ = 2233 and 1705 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.34 (td, $J$ = 13.8, 3.5 Hz, 1 H, cyclohexyl C*H*H), 1.72 (m, 1 H, cyclohexyl C*H*H), 1.84 (m, 1 H, cyclohexyl C*H*H), 2.02−2.13 (m, 2 H, cyclohexyl C*H*H and $CCH_AH_BCH$), 2.23 (m, 1 H, cyclohexyl C*H*H), 2.51 (dt, $J$ = 13.8, 3.5 Hz, 1 H, cyclohexyl C*H*H), 2.85 (d, $J$ = 13.6 Hz, 1 H, $CCH_AH_BC$), 4.49 (d, $J$ = 10.3 Hz, 1 H, $CH_AH_BO$), 4.58 (d, $J$ = 10.3 Hz, 1 H, $CH_AH_BO$), 4.99 (d, $J$ = 8.2 Hz, 1 H, CHCN), 5.12 (t, $J$ = 3.8 Hz, 1 H, CH=C), 7.27−7.46 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 17.3 (cyclohexyl $CH_2$), 22.9 (cyclohexyl $CH_2$), 30.1 (cyclohexyl $CH_2$), 39.4 ($CCH_2CH$), 64.7 ($CH_2CHCN$), 66.3 ($CH_2O$), 77.5 (C), 99.8 (=CH), 118.3 (CN), 127.6 (2 arom. CH), 128.4 (3 arom. CH), 137.5 (arom. C), 154.1 ($C$=CH) ppm.

**(3*S*,4a*R*,8a*R*)- and (3*S*,4a*R*,8a*S*)-4a-Benzyloxy-3,8a-dihydroxyoctahydroquinolin-2-ones (19):** An aqueous solution of silver nitrate (1 M, 0.18 mL, 0.18 mmol) and an aqueous ammonia solution (20%, 15 μL, 0.18 mmol) were successively added to a solution of hemiacetal **10** (50 mg, 0.18 mmol) in $Et_2O$ (1 mL). The reaction mixture was vigorously stirred at room temperature for 24 hours and hydrolyzed with water (1 mL). The aqueous layer was separated and extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 1:3) to give α-hydroxy lactams **19** as a colorless oil (36 mg, 68%, mixture of diastereomers at C-8a). IR (neat): $\tilde{\nu}$ = 3477 and 1657 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.48 (m, 4 H, cyclohexyl $CH_2$), 1.61 (m, 2 H, cyclohexyl $CH_2$), 1.80 (m, 1 H, cyclohexyl C*H*H), 1.96 (m, 1 H, cyclohexyl C*H*H), 2.36 (dd, $J$ = 19.6, 8.6 Hz, 1 H, $CH_AH_BCHOH$), 2.41 (dd, $J$ = 19.6, 6.8 Hz, 1 H, $CH_AH_BCHOH$), 3.79 (br. s, 1 H, OH), 4.29 (d, $J$ = 10.5 Hz, 1 H, $CH_AH_BO$), 4.36 (dd, $J$ = 8.6, 6.8 Hz, C*H*OH), 4.47 (d, $J$ = 10.5 Hz, 1 H, $CH_AH_BO$), 5.30 (br. s, 1 H, NH or OH), 6.85 (br. s, 1 H, NH or OH), 7.28−7.35 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.1 (cyclohexyl $CH_2$), 22.5 (cyclohexyl $CH_2$), 29.5 (cyclohexyl $CH_2$), 33.7 (cyclohexyl $CH_2$), 36.2 ($CCH_2CH$), 66.1 ($CH_2O$), 77.5 (CHOH), 81.9 (COBn), 104.5 (OCNH), 127.8 (3 arom. CH), 128.5 (2 arom. CH), 137.6 (arom. C), 176.6 (CO) ppm.

**(1*R*,2*R*)- and (1*S*,2*R*)-2-Benzyloxy-2-(2′-hydroxyethyl)cyclohexanols (20):** Sodium borohydride (48 mg, 1.26 mmol) was added portionwise to a solution of Michael adduct **6** (200 mg, 0.63 mmol) in ethanol (5 mL). The reaction mixture was stirred at room temperature for 3 hours. An aqueous solution of HCl (0.5 M, 4 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 3:1) to give the diols **20** as a white solid (58 mg, 37%, 3:1 mixture of diastereomers at C-1, ratio determined by $^1H$ NMR). MS: $m/z$ (ESI) found 273.1453 [$MNa^+$], $C_{15}H_{23}O_3$ (M, 250.4) requires 273.1467. IR (neat): $\tilde{\nu}$ = 3385 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, major diastereomer): δ = 1.23−1.34 (m, 2 H, cyclohexyl $CH_2$), 1.39−1.48 (m, 2 H, cyclohexyl $CH_2$), 1.64−1.83 (m, 4 H, $CH_AH_BCH_2OH$, cyclohexyl $CH_2$ and cyclohexyl C*H*H), 2.04 (m, 1 H, cyclohexyl C*H*H), 2.12 (ddd, $J$ = 15.5, 6.1, 3.3 Hz, 1 H, $CH_AH_BCH_2OH$), 2.40−3.20 (br. s, 2 H, OH), 3.53 (dd, $J$ = 9.9, 4.1 Hz, 1 H, C*H*OH), 3.64 (ddd, $J$ = 11.4, 6.9, 3.3 Hz, $CH_AH_BOH$), 3.82 (ddd, $J$ = 11.4, 6.1, 3.9 Hz, 1 H, $CH_AH_BOH$), 4.31 (d, $J$ = 10.7 Hz, 1 H, $CH_AH_BO$), 4.43 (d, $J$ = 10.7 Hz, 1 H, $CH_AH_BO$), 7.24−7.36 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$, major diastereomer): δ = 20.9 (cyclohexyl

$CH_2$), 23.9 (cyclohexyl $CH_2$), 30.6 (cyclohexyl $CH_2$), 32.6 (cyclohexyl $CH_2$), 39.2 ($CH_2CH_2OH$), 57.7 ($CH_2CH_2OH$), 62.4 ($CH_2O$), 74.4 (CHOH), 77.2 (C), 127.4 (2 arom. CH), 128.3 (3 arom. CH), 138.6 (arom. C) ppm.

**(3a*R*,1a*R*)-3a-Benzyloxyhexahydrobenzofuran-7a-ol (21) and (3a*R*,1a*S*)-3a-benzyloxyhexahydrobenzofuran-2-one (22):** A solution of periodic acid (130 mg, 0.57 mmol) and chromium trioxide (2 mg, 0.02 mmol) in $CH_3CN$ (1.3 mL) and water (0.1 mL) was added dropwise at 0 °C to a solution of diols **20** (58 mg, 0.23 mmol) in $CH_3CN$ (3 mL). The reaction mixture was stirred at 5 °C for 1 hour and quenched with aqueous $NaH_2PO_4$ (1 M, 4 mL). The aqueous layer was separated and extracted with EtOAc (10 mL). The combined organic layers were successively washed with brine (2 × 5 mL), a saturated aqueous solution of $NaHSO_3$ (5 mL), and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 2:1 to 1:1) to give an inseparable 1.5:1 mixture of hemiacetal **21** and lactone **22** as a white solid (36 mg, 64% combined yield). IR (neat): $\tilde{\nu}$ = 3526 and 1781 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): **21** (pertinent signals): δ = 3.46 (br. s, 1 H, OH), 3.91 (dd, *J* = 8.4, 1.3 Hz, 1 H, $CH_2CH_AH_BO$), 4.14 (ddd, *J* = 12.8, 8.4, 4.2 Hz, 1 H, $CH_2CH_AH_BO$), 4.40 (d, *J* = 11.1 Hz, 1 H, $CH_AH_BO$), 4.60 (d, *J* = 11.1 Hz, 1 H, $CH_AH_BO$) ppm; **22** (pertinent signals): δ = 2.35 (d, *J* = 16.6 Hz, 1 H, $CH_AH_BCO$), 2.85 (d, *J* = 16.6 Hz, 1 H, $CH_AH_BCO$), 4.10 (*J* = 12.3, 4.0 Hz, 1 H, CHOCO), 4.35 (d, *J* = 11.3 Hz, 1 H, $CH_AH_BO$), 4.45 (d, *J* = 11.3 Hz, 1 H, $CH_AH_BO$) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): **21** (pertinent signals): δ = 32.4 ($CH_2CH_2O$), 64.3 ($CH_2CH_2O$), 66.8 ($CH_2O$), 82.5 (C), 102.6 (HOCO) ppm; **22** (pertinent signals): δ = 39.2 ($CH_2CO$), 63.8 ($CH_2O$), 79.8 (C), 86.5 (CHOCO) 175.2 (CO) ppm.

**(2*R*,1′*R*,2′*R*)- and (2*R*,1′*R*,2′*S*)-2-Acetoxy-2-(1′-benzyloxy-2′-hydroxycyclohexyl)propionitriles (23):** Zinc borohydride (2 mL of a 0.17 M solution in $Et_2O$, 0.34 mmol), was added dropwise at 0 °C under nitrogen to a solution of Michael adduct **6** (500 mg, 1.58 mmol) in dry $Et_2O$ (5 mL). The reaction mixture was stirred at 0 °C for 30 minutes, hydrolyzed with water (5 mL) and aqueous HCl (1 M, 1 mL), and extracted with $Et_2O$ (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give **23** as a colorless oil (450 mg, 90% (crude), 3:1 mixture of diastereomers at C-2′, ratio determined by $^1H$ NMR). This crude material was used directly in the next step. These diastereomers could be separated by column chromatography (cyclohexane/EtOAc, 10:1). IR (neat): $\tilde{\nu}$ = 3521, 2246 and 1750 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, major diastereomer): δ = 1.28−1.53 (m, 3 H, cyclohexyl $CH_2$ and cyclohexyl CHH), 1.76 (m, 3 H, cyclohexyl $CH_2$ and cyclohexyl CHH), 1.96 (s, 3 H, $CH_3CO$), 2.04 (m, 1 H, cyclohexyl CHH), 2.19 (m, 2 H, cyclohexyl $CH_2$), 2.29 (dd, *J* = 15.4, 6.3 Hz, 1 H, $CCH_AH_BCH$), 2.47 (dd, *J* = 15.4, 6.3 Hz, 1 H, $CCH_AH_BCH$), 3.60 (m, 1 H, CHOH), 4.42 (d, *J* = 11.1 Hz, 1 H, $CH_AH_BO$), 4.50 (d, *J* = 11.1 Hz, 1 H, $CH_AH_BO$), 5.76 (t, *J* = 6.3 Hz, 1 H, CHCN), 7.26−7.38 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$, major diastereomer): δ = 20.2 ($CH_3CO$), 20.9 (cyclohexyl $CH_2$), 23.1 (cyclohexyl $CH_2$), 30.6 (cyclohexyl $CH_2$), 31.7 (cyclohexyl $CH_2$), 38.1 ($CCH_2CH$), 58.4 (CHCN), 62.8 ($CH_2O$), 73.9 (CHOH), 76.5 (C), 117.8 (CN), 127.1 (2 arom. CH), 127.6 (arom. CH), 128.5 (2 arom. CH), 138.1 (arom. C), 168.9 (CO) ppm. $C_{18}H_{23}NO_4$ (317.4), calcd. C 68.12, H 7.30, N 4.41; found C 67.72, H 7.12, N 4.37.

**(3*S*,4a*R*,8a*R*)- and (3*R*,4a*R*,8a*R*)-4a-Benzyloxy-3-hydroxyoctahydrochromen-2-ones (24):** An aqueous solution of HCl (1 M, 15.2 mL) was added at room temperature to a solution of crude **23** (450 mg, 1.42 mmol) in THF (7 mL). The reaction mixture was stirred at 50 °C for 50 hours and the solvent was removed in vacuo. The residue was taken up in water (5 mL) and EtOAc (20 mL), and the aqueous layer was separated and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 2:1) to give α-hydroxy lactones **24** as a white solid (280 mg, 71%, 3:1 mixture of diastereomers at C-8a, ratio determined by $^1H$ NMR). These diastereomers could be separated by column chromatography (cyclohexane/EtOAc, 3:1). MS: *m*/*z* (ESI) found 299.1251 [$MNa^+$], $C_{16}H_{20}O_4$ (M, 276.4) requires 299.1259. IR (neat): $\tilde{\nu}$ = 3249 and 1733 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$, major diastereomer): δ = 1.27 (m, 1 H, cyclohexyl CHH), 1.36 (m, 1 H, cyclohexyl CHH), 1.52 (m, 2 H, cyclohexyl $CH_2$), 1.76 (t, *J* = 12.5 Hz, 1 H, $CH_AH_BCHOH$), 1.85 (m, 2 H, cyclohexyl $CH_2$), 2.10 (ddd, *J* = 16.7, 12.1, 3.9 Hz, 1 H, cyclohexyl CHH), 2.22 (dd, *J* = 15.1, 1.6 Hz, 1 H, cyclohexyl CHH), 2.74 (dd, *J* = 12.5, 7.1 Hz, 1 H, $CH_AH_BCHOH$), 3.03 (br. s, 1 H, OH), 4.21 (dd, *J* = 12.1, 4.3 Hz, 1 H, CHOCO), 4.36 (dd, *J* = 12.5, 7.1 Hz, CHOH), 4.42 (d, *J* = 11.2 Hz, 1 H, $CH_AH_BO$), 4.52 (d, *J* = 11.2 Hz, 1 H, $CH_AH_BO$), 7.28−7.38 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$, major diastereomer): δ = 19.7 (cyclohexyl $CH_2$), 23.7 (cyclohexyl $CH_2$), 26.1 (cyclohexyl $CH_2$), 30.9 (cyclohexyl $CH_2$), 35.7 ($CCH_2CH$), 62.3 ($CH_2O$), 65.4 (CHOH), 73.4 (C), 85.9 (CHOCO), 126.9 (2 arom. CH), 127.5 (arom. CH), 128.4 (2 arom. CH), 137.7 (arom. C), 173.9 (CO) ppm.

**(2*R*)-*N*-{2-Benzyloxy-2-[2′-(dimethylhydrazono)ethylcyclohexanone]}-*N*′,*N*′-dimethylhydrazone (25):** 1,1-Dimethylhydrazine (0.29 mL, 3.8 mmol) was added to a solution of Michael adduct **6** (300 mg, 0.95 mmol) in dry ethanol (3 mL). The reaction mixture was heated at reflux under nitrogen in the presence of anhydrous powdered molecular sieves for 12 hours. The reaction mixture was filtered through Celite and concentrated in vacuo, and the residue was purified by column chromatography (cyclohexane/EtOAc/$Et_3N$, 40:7:1) to give bis-hydrazone **25** as a pale yellow oil (105 mg, 34%). MS: *m*/*z* (ESI) found 353.2301 [$MNa^+$], $C_{19}H_{30}N_4O$ (M, 330.6) requires 353.2317. IR (neat): $\tilde{\nu}$ = 1607 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.38−1.56 (m, 3 H, cyclohexyl CHH and cyclohexyl $CH_2$), 1.83−1.90 (m, 1 H, cyclohexyl CHH), 1.95 (m, 1 H, cyclohexyl CHH), 2.05 (td, *J* = 13.4, 5.3 Hz, 1 H, cyclohexyl CHH), 2.12−2.20 (m, 1 H, cyclohexyl CHH), 2.47 (s, 6 H, $CH_3$), 2.68 (dd, *J* = 14.8, 5.8 Hz, $CH_AH_BCH{=}N$), 2.71 (s, 6 H, $CH_3$), 2.98 (dd, *J* = 14.8, 5.8 Hz, $CH_AH_BCH{=}N$), 3.11 (m, 1 H, cyclohexyl CHH), 4.20 (d, *J* = 11.5 Hz, 1 H, $CH_AH_BO$), 4.49 (d, *J* = 11.5 Hz, 1 H, $CH_AH_BO$), 6.77 (t, *J* = 5.8 Hz, 1 H, CH=N), 7.26−7.34 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 20.7 (cyclohexyl $CH_2$), 25.9 (cyclohexyl $CH_2$), 26.3 (cyclohexyl $CH_2$), 37.0 ($CH_2CH{=}N$), 37.9 (cyclohexyl $CH_2$), 43.4 (2 $CH_3$), 47.8 (2 $CH_3$), 63.9 ($CH_2O$), 78.9 (C), 127.3 (2 arom. CH), 128.3 (3 arom. CH), 136.9 (arom. C), 139.1 (CH=N), 167.7 (C=N) ppm.

**(2*R*,1′*R*)-2-Acetoxy-3-(1′-benzyloxy-1′′,4′′-dioxaspiro[4.5]-decyl)propionitrile (28):** A solution of Michael adduct **6** (3.2 g, 10.1 mmol) in dry $CH_2Cl_2$ (13 mL) was added dropwise, under nitrogen and at −78 °C, to a solution of trimethylsilyl triflate (0.51 mL, 3 mmol) and 1,2-bis(trimethylsilyloxy)ethane (4.8 mL, 20.3 mmol) in dry $CH_2Cl_2$ (13 mL). The reaction mixture was allowed to warm up, was stirred for 6 hours at room temperature, and was quenched with dry pyridine (2 mL). A saturated aqueous solution of sodium hydrogen carbonate (25 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The oily residue was taken up in hot ethanol (20 mL) and recrystallized

at −20 °C to give ketal **28** as a white solid (2.91 g, 80%); m.p. 138 °C. $[\alpha]_D^{20}$ = +106.0 (*c* = 2.15, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2250 and 1743 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.41−1.73 (m, 4 H, cyclohexyl $CH_2$), 1.88 (m, 1 H, cyclohexyl C*H*H), 1.95−1.98 (m, 4 H, cyclohexyl C*H*H and $CH_3CO$), 2.16 (dd, *J* = 15.9, 5.2 Hz, 1 H, $CH_AH_BCHCN$), 2.65 (dd, *J* = 15.9, 5.2 Hz, 1 H, $CH_AH_BCHCN$), 4.01 (m, 3 H, $OCH_2CHHO$), 4.18 (m, 1 H, $OCH_2CHHO$), 4.49 (d, *J* = 11.4 Hz, $CH_AH_BO$), 4.55 (d, *J* = 11.4 Hz, 1 H, $CH_AH_BO$), 5.72 (t, *J* = 5.2 Hz, 1 H, CHCN), 7.27−7.34 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 20.1 ($CH_3CO$), 20.4 (cyclohexyl $CH_2$), 22.5 (cyclohexyl $CH_2$), 29.8 (cyclohexyl $CH_2$), 32.2 (cyclohexyl $CH_2$), 34.8 ($CH_2CHCN$), 58.1 (*C*HCN), 63.7 ($CH_2O$), 64.1 ($OCH_2CH_2O$), 64.4 ($OCH_2CH_2O$), 78.6 (C), 110.3 (OCO), 118.3 (CN), 126.8 (2 arom. CH), 127.2 (arom. CH), 128.3 (2 arom. CH), 138.4 (arom. C), 168.9 (CO) ppm. $C_{20}H_{25}NO_5$ (M, 359.5), calcd. C 66.83, H 7.01, N 3.89; found C 66.89, H 7.14, N 3.92.

**(*R*)-2-(1′-Benzyloxy-1′′,4′′-dioxaspiro[4.5]decyl)ethanoic Acid (29):** An aqueous solution of LiOH (1 M, 31.6 mL, 31.6 mmol) was added dropwise to a solution of ketal **28** (5.68 g, 15.8 mmol) in THF (100 mL). The reaction mixture was vigorously stirred at room temperature for 1 hour and the solvent was removed in vacuo. The residue was taken up in water (50 mL) and EtOAc (75 mL), and the aqueous layer was separated and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo to give an intermediary aldehyde as a pale yellow oil, which was used without further purification in the next step.

2-Methyl-2-butene (9.5 mL, 91.6 mmol) and an aqueous solution of sodium hydrogen phosphate (1 M, 19.7 mL, 19.7 mmol) were added successively to the solution of crude aldehyde (4.59 g) in *tert*-butyl alcohol (63 mL). Sodium chlorite (5.1 g, 45.8 mmol) was added portionwise at 0 °C, and the reaction mixture was then vigorously stirred at room temperature for 24 hours. The solvent was removed in vacuo. The residue was taken up in water (75 mL) and $CH_2Cl_2$ (125 mL), and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give carboxylic acid **29** as a colorless oil. This material was used without further purification in the next step. IR (neat): $\tilde{\nu}$ = 3500−2500 and 1702 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.39−2.17 (m, 8 H, cyclohexyl $CH_2$), 2.63 (d, *J* = 15.9 Hz, 1 H, $CH_AH_BCO_2H$), 2.94 (d, *J* = 15.9 Hz, 1 H, $CH_AH_BCO_2H$), 4.00 (br. s, 4 H, $OCH_2CH_2O$), 4.58 (s, 2 H, $CH_2O$), 7.26−7.39 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 20.3 (cyclohexyl $CH_2$), 22.7 (cyclohexyl $CH_2$), 30.4 (cyclohexyl $CH_2$), 32.4 (cyclohexyl $CH_2$), 37.2 ($CH_2CO_2H$), 64.3 ($OCH_2CH_2O$), 64.6 ($CH_2O$), 65.0 ($OCH_2CH_2O$), 79.8 (C), 110.8 (OCO), 127.6 (2 arom. CH), 128.2 (3 arom. CH), 138.2 (arom. C), 174.4 ($CO_2H$).

**Methyl (*R*)-2-(1′-Benzyloxy-1′′,4′′-dioxaspiro[4.5]decyl)acetate (30). From Protected Cyanohydrin 28:** Activated manganese dioxide (24 g, 0.28 mol), and sodium cyanide (3.4 g, 69.5 mmol) were added to a solution of **28** (5 g, 13.9 mmol) in absolute methanol (200 mL). The resulting suspension was stirred for 3 days at room temperature, and $Et_2O$ (400 mL) was then added, causing the precipitation of the excess of sodium cyanide. The reaction mixture was filtered through Celite. The filter pad was washed with $Et_2O$ (3 × 100 mL) and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 20:1) to give methyl ester **30** as a colorless oil (2.7 g, 61%).

**From Carboxylic Acid 29:** A solution of diazomethane in $Et_2O$ (0.5 M, 50 mL) was added at 0 °C to the solution of crude carboxylic acid **29** (3 g, 9.8 mmol) in dry $Et_2O$ (50 mL). The resulting mixture was stirred at room temperature for 4 hours and the excess of diazomethane was destroyed by addition of acetic acid. The reaction mixture was taken up in $Et_2O$ (50 mL) and the resulting organic layer was washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give methyl ester **30** as a colorless oil (3.1 g, 75%, 3 steps from **28**). IR (neat): $\tilde{\nu}$ = 1733 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 1.27−1.61 (m, 5 H, cyclohexyl $CH_2$ and cyclohexyl C*H*H), 1.67−1.88 (m, 2 H, cyclohexyl $CH_2$), 1.96−2.12 (m, 1 H, cyclohexyl C*H*H), 2.52 (d, *J* = 13.7 Hz, 1 H, $CH_AH_BCO_2CH_3$), 2.73 (d, *J* = 13.7 Hz, 1 H, $CH_AH_BCO_2CH_3$), 3.55 (s, 3 H, $CO_2CH_3$), 3.75−3.98 (m, 4 H, $OCH_2CH_2O$), 4.54 (d, *J* = 11.3 Hz, 1 H, $CH_AH_BO$), 4.64 (d, *J* = 11.3 Hz, 1 H, $CH_AH_BO$), 7.11−7.38 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 20.2 (cyclohexyl $CH_2$), 22.9 (cyclohexyl $CH_2$), 30.5 (cyclohexyl $CH_2$), 32.6 (cyclohexyl $CH_2$), 35.8 ($CH_2CO_2CH_3$), 51.3 ($CO_2CH_3$), 64.1 ($OCH_2CH_2O$), 64.5 ($OCH_2CH_2O$), 65.2 ($CH_2O$), 79.9 (C), 110.9 (OCO), 126.9 (arom. CH), 127.3 (2 arom. CH), 128.1 (2 arom. CH), 139.4 (arom. C), 171.6 ($CO_2CH_3$) ppm.

**Methyl (*R*)-(1′-Benzyloxy-2-oxocyclohexyl)acetate (3):** Sodium iodide (0.53 g, 3.4 mmol) and cerium trichloride heptahydrate (7.95 g, 14.3 mmol) were successively added to a solution of ketal **30** (3.8 g, 11.9 mmol) in acetonitrile (120 mL). The reaction mixture was stirred at reflux overnight and partitioned between a 0.5 M aqueous solution of HCl (150 mL) and EtOAc (150 mL). The aqueous layer was separated and extracted with EtOAc (3 × 75 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 60 mL) and a 0.4 M aqueous solution of sodium thiosulfate (2 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 20:1) to give keto ester **3** as a colorless oil (2.8 g, 85%). MS: *m*/*z* (ESI) found 299.1252 [$MNa^+$], $C_{16}H_{20}O_4$ (M, 276.4) requires 299.1259. $[\alpha]_D^{20}$ = +131.4 (*c* = 0.73, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1735 and 1715 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.44−2.08 (m, 5 H, cyclohexyl $CH_2$ and cyclohexyl C*H*H), 2.16−2.44 (m, 2 H, cyclohexyl $CH_2$), 2.49−2.74 (m, 2 H, cyclohexyl C*H*H and $CH_AH_BCO_2CH_3$), 2.92 (d, *J* = 14.9 Hz, 1 H, $CH_AH_BCO_2CH_3$), 3.57 (s, 3 H, $CO_2CH_3$), 4.02 (d, *J* = 10.8 Hz, 1 H, $CH_AH_BO$), 4.57 (d, *J* = 10.8 Hz, 1 H, $CH_AH_BO$), 7.15−7.38 (m, 5 H, arom. CH) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): δ = 20.3 (cyclohexyl $CH_2$), 27.6 (cyclohexyl $CH_2$), 36.7 ($CH_2CO_2CH_3$), 38.2 (cyclohexyl $CH_2$), 39.1 (cyclohexyl $CH_2$), 51.5 ($CO_2CH_3$), 65.7 ($CH_2O$), 81.2 (C), 127.4 (2 arom. CH), 127.5 (arom. CH), 128.3 (2 arom. CH), 137.7 (arom. C), 170.8 ($CO_2CH_3$), 210.4 (CO) ppm.

**Methyl (*R*)-[1′-Benzyloxy-2-(trimethylsilanoxy)cyclohex-2-enyl]-acetate (31):** Dry triethylamine (1.12 mL, 8.1 mmol), trimethylsilyl chloride (0.86 mL, 7 mmol), and a solution of anhydrous sodium iodide (940 mg, 6.3 mmol) in dry acetonitrile (20 mL) were added successively to a solution of keto ester **3** (1.86 g, 6.7 mmol) in dry acetonitrile (20 mL). The reaction mixture was stirred under nitrogen at room temperature for 20 hours and taken up in dry $Et_2O$ (40 mL). The resulting organic solution was washed with a cold aqueous solution of potassium carbonate (1%, 20 mL), dried ($K_2CO_3$), and concentrated in vacuo to give silyl enol ether **31** as a colorless oil. This material was used without further purification in the next step. IR (neat): $\tilde{\nu}$ = 1737, 1655 and 841 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): δ = 0.11 [s, 9 H, $Si(CH_3)_3$], 1.40−2.06 (m, 6 H, cyclohexyl $CH_2$), 2.61 (d, *J* = 13.9 Hz, 1 H, $CH_AH_BCO_2CH_3$), 2.78 (d, *J* = 13.9 Hz, 1 H, $CH_AH_BCO_2CH_3$), 3.56 (s, 3 H, $CO_2CH_3$), 4.39 (d, *J* = 11.5 Hz, 1 H, $CH_AH_BO$), 4.49 (d, *J* = 11.5 Hz, 1 H, $CH_AH_BO$), 4.91 (t, *J* = 3.9 Hz, 1 H, CH=),

7.06−7.31 (m, 5 H, arom. CH) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 0.1 [$Si(CH_3)_3$], 19.0 (cyclohexyl $CH_2$), 24.2 (cyclohexyl $CH_2$), 33.5 (cyclohexyl $CH_2$), 40.9 ($CH_2CO_2CH_3$), 51.2 ($CO_2CH_3$), 65.7 ($CH_2O$), 76.1 (C), 107.0 (CH=C), 126.3 (arom. CH), 127.3 (2 arom. CH), 128.0 (2 arom. CH), 139.8 (arom. C), 149.0 (CH=C), 171.3 ($CO_2CH_3$) ppm.

**Dimethyl (2*R*,6*R*)- and (2*R*,6*S*)-2-Benzyloxy-6-hydroxyheptane-1,2-dicarboxylate (33):** Oxygen containing ca. 5% (v/v) ozone was bubbled through a sinter glass at −78 °C into a solution of silyl enol ether **31** (2 g, 5.7 mmol) in methanol (20 mL) and $CH_2Cl_2$ (60 mL) in the presence of a pinch of sodium hydrogen carbonate. The gas flow was stopped when TLC analysis of the mixture showed the total conversion of the starting material. Ozone in excess was flushed out with an oxygen flow, and dimethyl sulfide (2.45 mL, 40.7 mmol) was added at −78 °C. The reaction mixture was allowed to warm up and was stirred at room temperature for 5 hours. The solvents were removed in vacuo, the residue was taken up in EtOAc (120 mL), and the resulting organic solution was washed with brine (3 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give a sensitive aldehyde **32** as a yellow oil (not characterized), which was used without further purification.

Methylmagnesium bromide (11.5 mL of a 1 M solution in di-*n*-butyl ether, 11.5 mmol) was added dropwise (30 minutes), under nitrogen and at −40 °C, to a solution of the crude aldehyde **32** (1.62 g) in dry THF (40 mL). The reaction mixture was stirred at −40 °C for a further 10 minutes and was then hydrolyzed by successive addition of a saturated aqueous solution of ammonium chloride (4 mL) and water (6 mL). Solvents were removed in vacuo, the residue was acidified with an aqueous solution of HCl (0.1 M, 75 mL), and the aqueous layer was extracted with EtOAc (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give an hydroxy acid as a yellow oil (not characterized). This material was used without further purification in the next step.

A solution of diazomethane in $Et_2O$ (0.5 M, 20 mL) was added at 0 °C to a solution of the crude hydroxy acid (1.8 g) in dry $Et_2O$ (70 mL). The resulting mixture was stirred at room temperature for 2 hours and the excess of diazomethane was destroyed with acetic acid. The reaction mixture was taken up in EtOAc (60 mL), and the resulting organic layer was washed with brine (3 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 9:1 to 1.5:1) to give dimethyl esters **33** as a colorless oil (687 mg, 35%, 4 steps from γ-keto ester **3**, 1:1 mixture of diastereomers at C-7). MS: *m*/*z* (MALDI-TOF) found 361.1641 [$MNa^+$], $C_{18}H_{26}O_6$ (M, 338.5) requires 361.1627. IR (neat): $\tilde{\nu}$ = 3447 and 1733 $cm^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.1 Hz, 3 H, $CH_3$CHOH) and 1.09 (d, *J* = 6.1 Hz, 3 H, $CH_3$CHOH), 1.23−1.67 (m, 4 H, $CH_2CH_2CH_2C$ and $CH_2CH_2CH_2C$), 1.75−2.00 (m, 2 H, $CH_2CH_2CH_2C$), 2.87 (m, 2 H, $CH_2CO_2CH_3$), 3.57 (s, 3 H, $CO_2CH_3$), 3.69 (s, 3 H, $CO_2CH_3$), 4.41 and 4.43 (2 d, *J* = 10.9 Hz, 1 H, $CH_AH_BO$), 4.44 (m, 1 H, CHOH), 4.50 and 4.52 (2 d, *J* = 10.9 Hz, 1 H, $CH_AH_BO$), 7.11−7.36 (m, 5 H, arom. CH) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 19.4 and 19.5 ($CH_2CH_2CH_2C$), 23.4 ($CH_3$CHOH), 35.1 ($CH_2CH_2CH_2C$), 38.9 and 39.0 ($CH_2CH_2CH_2C$), 39.5 and 39.8 ($CH_2CO_2CH_3$), 51.8 ($CO_2CH_3$), 52.2 ($CO_2CH_3$), 66.5 ($CH_2O$), 67.4 and 67.5 (CHOH), 80.9 and 81,0 (C), 127.5 (2 arom. CH), 128.2 (3 arom. CH), 138.1 (arom. C), 170.2 and 170.3 ($CO_2CH_3$), 172.9 ($CO_2CH_3$) ppm.

**Dimethyl (*R*)-2-Benzyloxy-6-oxoheptane-1,2-dicarboxylate (34):** A solution of alcohol **33** (530 mg, 1.57 mmol) in dry $CH_2Cl_2$ (10 mL) was added to a suspension of pyridinium chlorochromate (736 mg, 2.67 mmol) in dry $CH_2Cl_2$ (15 mL). The reaction mixture was vigorously stirred overnight at room temperature, taken up in $Et_2O$, and filtered through a short pad of silica gel. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (cyclohexane/EtOAc, 4:1) to give ketone **34** as a colorless oil (420 mg, 80%). MS: *m*/*z* (MALDI-TOF) found 359.1457 [$MNa^+$], $C_{18}H_{24}O_6$ (M, 336.4) requires 359.1471. IR (neat): $\tilde{\nu}$ = 1733 and 1714 $cm^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.62 (quint., *J* = 7.3 Hz, 2 H, $CH_2CH_2CH_2C$), 1.92 (t, *J* = 7.3 Hz, 2 H, $CH_2CH_2CH_2C$), 2.09 (s, 3 H, $CH_3CO$), 2.42 (t, *J* = 7.3 Hz, 2 H, $CH_2CH_2CH_2C$), 2.94 (s, 2 H, $CH_2CO_2CH_3$), 3.64 (s, 3 H, $CO_2CH_3$), 3.76 (s, 3 H, $CO_2CH_3$), 4.53 (s, 2 H, $CH_2O$), 7.14−7.38 (m, 5 H, arom. CH) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 17.4 ($CH_2CH_2CH_2C$), 29.7 ($CH_3CO$), 34.4 ($CH_2CH_2CH_2C$), 39.7 ($CH_2CO_2CH_3$), 43.0 ($CH_2CH_2CH_2C$), 51.6 ($CO_2CH_3$), 52.1 ($CO_2CH_3$), 66.4 ($CH_2O$), 80.6 (C), 127.4 (arom. CH), 127.5 (2 arom. CH), 128.1 (2 arom. CH), 138.0 (arom. C), 170.0 ($CO_2CH_3$), 172.6 ($CO_2CH_3$), 207.9 (CO) ppm.

**Dimethyl (*R*)-2-Benzyloxy-6-hydroxy-6-methylheptane-1,2-dicarboxylate (35):** Methylmagnesium bromide (1.25 mL of a 1 M solution in di-*n*-butyl ether, 1.25 mmol) was added dropwise (15 min), under nitrogen and at −30 °C, to a solution of ketone **34** (420 mg, 1.25 mmol) in dry THF (14 mL). The reaction mixture was stirred at −30 °C for 90 minutes, hydrolyzed successively with a saturated aqueous solution of ammonium chloride (2 mL) and water (2 mL), and taken up in $Et_2O$ (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (cyclohexane/EtOAc, 9:1 to 1.5:1) to give the tertiary alcohol **35** as a colorless oil (183 mg, 42%). MS: *m*/*z* (MALDI-TOF) found 375.1795 [$MNa^+$], $C_{19}H_{28}O_6$ (M, 352.5) requires 375.1784. IR (neat): $\tilde{\nu}$ = 3522 and 1733 $cm^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.17 [s, 6 H, $(CH_3)_2$COH], 1.31−1.51 (m, 4 H, $CH_2CH_2CH_2C$ and $CH_2CH_2CH_2C$), 1.55 (br. s, 1 H, OH), 1.93 (m, 2 H, $CH_2CH_2CH_2C$), 2.94 (m, 2 H, $CH_2CO_2CH_3$), 3.64 (s, 3 H, $CO_2CH_3$), 3.76 (s, 3 H, $CO_2CH_3$), 4.48 (d, *J* = 11.0 Hz, 1 H, $CH_AH_BO$), 4.56 (d, *J* = 11.0 Hz, 1 H, $CH_AH_BO$), 7.17−7.38 (m, 5 H, arom. CH) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 18.0 ($CH_2CH_2CH_2C$), 29.1 [$(CH_3)_2$COH], 35.7 ($CH_2CH_2CH_2C$), 39.8 ($CH_2CO_2CH_3$), 43.6 ($CH_2CH_2CH_2C$), 51.6 ($CH_2CO_2CH_3$), 52.1 ($CH_2CO_2CH_3$), 66.4 ($CH_2O$), 70.5 [$(CH_3)_2$COH], 80.9 (C), 127.3 (arom. CH), 127.4 (2 arom. CH), 128.1 (2 arom. CH), 138.1 (arom. C), 170.1 ($CO_2CH_3$), 172.8 ($CO_2CH_3$) ppm.

**Dimethyl (*R*)-2,6-Dihydroxy-6-methylheptane-1,2-dicarboxylate (2):** Palladium on charcoal (10%, 67 mg) was added to a solution of tertiary alcohol **35** (183 mg, 0.52 mmol) in methanol (36 mL). The suspension was vigorously stirred under hydrogen (1 bar) at room temperature for 2 hours and then filtered through Celite. The filter pad was washed several times with methanol, and the filtrate was concentrated in vacuo. The resulting solid was recrystallized from pentane at 0 °C to give diol **2** as a colorless solid (140 mg, 100%); m.p. 34 °C (ref.[3] m.p. 34−35 °C). $[\alpha]_D^{20}$ = −14.0 (*c* = 0.71, $CHCl_3$) {ref.[3] $[\alpha]_D^{20}$ = −18.0 (*c* = 0.71, $CHCl_3$)}. IR (neat): $\tilde{\nu}$ = 3501 and 1733 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.19 [s, 7 H, $(CH_3)_2$COH and OH], 1.24 (m, 1 H, $CH_2CHHCH_2C$), 1.41−1.57 (m, 3 H, $CH_2CH_2CH_2C$ and $CH_2CHHCH_2C$), 1.71 (m, 2 H, $CH_2CH_2CH_2C$), 2.70 (d, *J* = 16.3 Hz, 1 H, $CH_AH_B$ $CO_2CH_3$), 2.92 (d, *J* = 16.3 Hz, 1 H, $CH_AH_B$ $CO_2CH_3$), 3.67 (s, 3 H, $CO_2CH_3$), 3.72 (br. s, OH), 3.80 (s, 3 H, $CO_2CH_3$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 18.0 ($CH_2CH_2CH_2C$), 29.0 [$CH_3C(OH)CH_3$], 29.2

[$CH_3C(OH)CH_3$], 39.5 ($CH_2CH_2CH_2C$), 43.3 ($CH_2CO_2CH_3$), 43.5 ($CH_2CH_2CH_2C$), 51.7 ($CO_2CH_3$), 52.8 ($CO_2CH_3$), 70.6 [$(CH_3)_2COH$], 75.2 (C), 171.2 ($CO_2CH_3$), 175.5 ($CO_2CH_3$) ppm. $C_{12}H_{22}O_6$ (262.3): calcd. C 54.94, H 8.45; found C 54.97, H 8.55.

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