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Chemical Differentiation of Enantiotopic Groups: Diastereoselective Opening of a Prochiral Dilactone

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Abstract: Prochiral dilactone **1** has been synthesized and subjected to diastereoselective nucleophilic opening. The structural features of chiral, enantiomerically pure nucleophiles have been optimized regarding their capability to perform prochiral recognition at dilactone **1**. 3-Ketoglutaric mono acid products **2** of dilactone opening, which are versatile building blocks for natural product synthesis, have been obtained in diastereomeric ratios up to 84:16 and were enriched by subsequent crystallization to 97.5:2.5. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Differentiation of enantiotopic groups is an attractive option in the field of asymmetric synthesis.[1] There are outstanding examples such as the Hajos-Wiechert reaction[2] or the asymmetric Sharpless epoxidation of prochiral divinyl carbinols,[3] but the field is dominated by enzymatic reactions. This is particularly true for carboxylic substrates. Enantioselective hydrolysis of prochiral diesters to chiral ester acids or hydroxy esters using hydrolases has become a routine method,[4] and since Klibanov did his pioneering work on the activity of lipases in organic media,[5] many workers have described successful selective acylations of enantiotopic hydroxy groups.[6] In very recent reports C. H. Heathcock and D. Seebach announced nonenzymatical but highly stereoselective conversions of prochiral anhydrides into their corresponding mono esters[7,8].

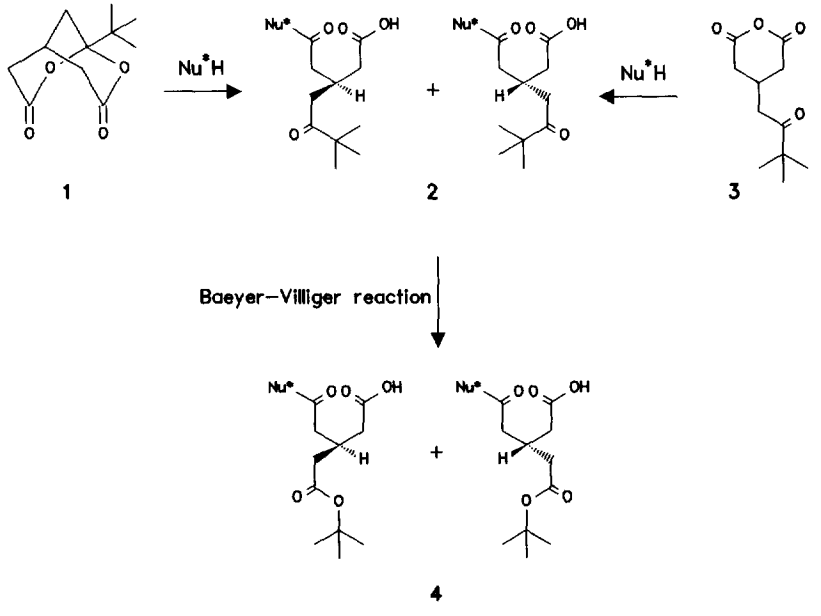
Studying these and other publications on this topic, the attentive reader can not fail to notice one thing: chemical differentiation of enantiotopic groups makes comparatively great demands on substrate structure as do enzymatic methods, which are so often cited in this context. We decided to make a virtue out of this necessity. By choosing the rigid dilactone **1**, we made a particularly well prepared prochiral system the basis of our research. In the following

we report on the optimization of diastereoselective opening of dilactone 1 by using properly chosen chiral, enantiomerically pure nucleophiles. Ring-opening products are 3-ketoglutaric mono acids 2 which, after derivatization and crystallization, have been isolated in high diastereomeric purity.

Opening of dilactone 1 is an instructive example of nucleophilic attack directed by the concave-convex principle,[9] but above all, this reaction followed by regioselective Baeyer-Villiger oxidation of the 3-ketoglutaric mono acids 2, obtained initially, will provide very interesting products: triacetic acid methane derivatives 4 of defined absolute configuration. The three functional groups of these compounds, although of rough structural similarity, should allow a multitude of chemoselective transformations. Furthermore there should be access to both enantiomers of 4: by making use of the nucleophile's enantiomer in the opening reaction or by subsequent stereoselective manipulations of the dilactone opening products. Configurative as well as constitutive flexibility make 3-ketoglutaric mono acids 2 attractive and versatile building blocks for natural product synthesis.

RESULTS AND DISCUSSION

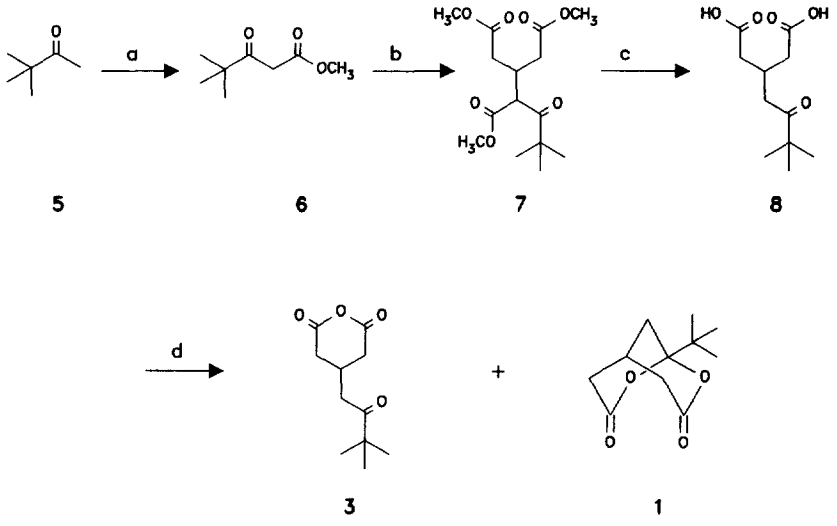
Nucleophilic opening of prochiral dilactone 1 to a mixture of diastereomeric keto mono acids and a potential subsequent Baeyer-Villiger reaction are shown in scheme 1.



Scheme 1. Dilactone opening and potential consecutive oxidation

Of course, 3-ketoglutaric mono acids **2** could equally be prepared by nucleophilic opening of the suitably substituted glutaric anhydride **3**. However, to our knowledge, examples of a stereoselective course are not yet known.[10] We have tested asymmetric opening of anhydride **3** with several chiral nucleophiles, and as expected, the results were discouraging.[11]

tert-Butyl dilactone **1** has been prepared in accordance with the literature instructions given for the methyl derivative[12] (Scheme 2).



a) $(CH_3O)_2CO$, NaH, dioxane, 85°C, 5 h, 72%; b) dimethyl glutaconate (**9**), $NaOCH_3$, MeOH, room temp., 33 h, 57%; c) conc. HCl, reflux, 8 h; d) AcCl, reflux, 3 h.

Scheme 2. Synthesis of dilactone **1**

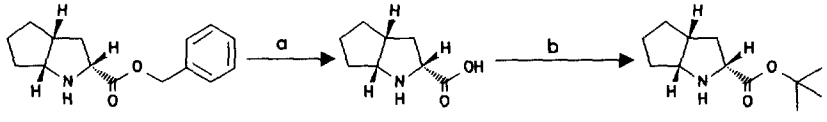
Under Michael conditions[13] methyl 4,4-dimethyl-3-oxo-pentanoate (**6**), obtained by carbomethoxylation[14] of pinacolone (**5**), was added to dimethyl glutaconate (**9**) to give keto triester **7** in 57% yield. Subsequent saponification/decarboxylation under acidic conditions provided keto dicarboxylic acid **8**. Finally, after dehydration, the constitutional isomeric keto-anhydride **3** and the desired dilactone **1** were obtained in 27% yield in a 2:1 ratio. The crystalline dilactone **1** could be isolated without any chromatographic step by simply washing out the dicarboxylic acid **8** followed by recrystallization. The low yield of dilactone is compensated by the possibility of recycling the starting materials very efficiently.

The tertiary butyl group in dilactone **1** should serve two purposes: first to improve discrimination of the enantiotopic lactone moieties and second to guarantee regioselectivity of the later Baeyer-Villiger reaction. Preliminary studies actually showed a clear superiority of *tert*-butyl dilactone **1** to its methyl analogue[12] in diastereoselective opening reactions.[11]

Furthermore the nucleophilicity of alcohols was found to be too low to efficiently open dilactone 1. In solvent tests toluene was found to be particularly useful as reaction medium.[11]

Based on these findings an optimization of the diastereoselective opening of dilactone 1 was done by a systematic variation of the nucleophile. Generally bifunctional nucleophiles were chosen which provide a proton acceptor group at a favourable distance to the nucleophilic centre. This setup is typical for the corresponding enzymes and it helps to synchronize nucleophilic attack with deprotonation of the nucleophilic centre, thus increasing reaction rates. The experimental results fulfilled this expectation. Two classes of nucleophiles have been explored:

Monocyclic and Bicyclic Proline Derivatives. Of all nucleophiles tested the bicyclic amino acid benzyl ester **10** (Scheme 3) showed the highest selectivity in opening dilactone 1. After 17 hours at room temperature a 84:16 ratio of the diastereomeric mono amides was obtained. To determine the diastereomeric ratios for the cases investigated, a set of analytical techniques comprising ^{1}H NMR spectroscopy and high-pressure liquid chromatography was established. (For details see Experimental.) Reference samples with diastereomeric ratios 1:1 were synthesized by independent methods for each dilactone opening product. Absolute configurations of surplus products have not been determined so far.



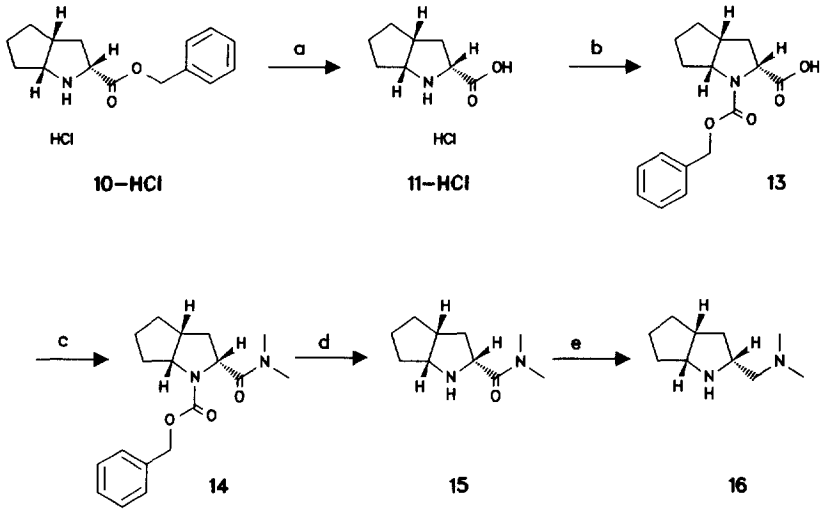
10 **11** **12**

a) H_2, Pd/C, MeOH, 89%; b) $(CH_3)_2C{=}CH_2$, H_2SO_4, dioxane, 43%.

Scheme 3. Bicyclic proline derivatives

By using *tert*-butyl ester **12** (Scheme 3) instead of benzyl ester **10**, an enlargement of the alkoxy group's passive spatial requirement was achieved, but prochiral recognition was not improved, the diastereomeric ratio in the dilactone opening product being 77:23. It may be supposed that both amino ester compounds preferentially reacted out of their sterically less demanding *s-trans*-conformations (see structures given in scheme 3) which are additionally the higher populated conformations in the ground state anyway.[15]

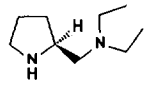
On the tightrope walk between nucleophilicity break down caused by steric overload on the one hand and the lack of selectivity on the other, diamines performed particularly well, and they were easily prepared on a multigram scale. The synthesis of bicyclic diamine **16** for instance, starting with (1*R*,3*R*,5*R*)-benzyl 2-azabicyclo[3.3.0]octane-3-carboxylate hydrochloride (**10**-HCl), followed well established proline chemistry[16] (Scheme 4).



a) H_2, Pd/C, MeOH, room temp., 24 h, 98%; b) ZCl, NaOH, H_2O, -8°C to 0°C, 2 h, 86%; c) N,N′-carbonyldiimidazole, THF, 0°C to room temp., 2 h, then $HN(CH_3)_2$ 40 wt-% in H_2O, THF, room temp., 67 h, 64%; d) H_2, Pd/C, MeOH, room temp., 17 h, 87%; e) LAH, THF, reflux, 24 h, 85%.

Scheme 4. Synthesis of (1*R*,3*R*,5*R*)-3-(dimethylaminomethyl)-2-azabicyclo[3.3.0]octane (16)

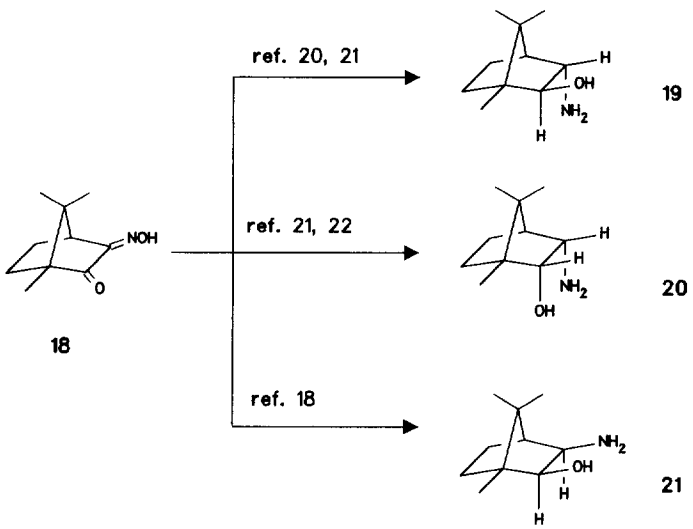
The diamine **16** opened dilactone 1 at a practically useful rate (42 hours at room temperature), as was expected, but with surprisingly low selectivity to provide a 58:42 mixture of diastereomers. However, by dropping the demand for maximum conformative rigidity, with pyrrolidine derivative 17[17] (Scheme 5) a powerful opening reagent was found which received excellent marks in both categories: Its nucleophilicity made dilactone opening complete within 48 hours at room temperature and its selectivity was remarkably high too. The diastereomeric ratio found for the opening product was 82:18. And the steric loadability of diamine 17 is certainly not exhausted yet. It is to be expected that a variation of the substituents on nitrogen will further improve the selectivity.



17

Scheme 5. Monocyclic proline derived nucleophile (*S*)-2-diethylaminomethylpyrrolidine (17)

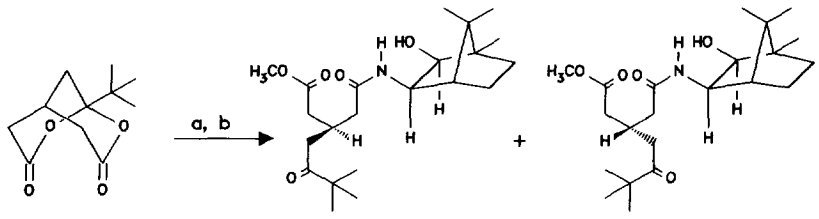
Camphor Derivatives. In choosing this system, we reasoned that, if the tendency of camphor derivatives to crystallize would be transferable to their dilactone derivatives, there should be the chance of additional diastereomeric enrichment. On top of that, configurationally well defined camphor derivatives are easily accessible and well documented in the literature. Among others we noticed amino alcohols **19**, **20**, and **21** which could all be synthesized in high optical purity out of a common precursor, the camphorquinone monooxime **18**[18,19] (Scheme 6).



Scheme 6. Synthesis of (1*R*,4*S*)-3-amino-2-hydroxybornane configurational isomers **19** - **21**

Amino alcohols **19**, **20**, and **21** all opened dilactone **1** to mixtures of diastereomeric mono amide mono acids exclusively. The corresponding mono ester mono acids were not found. It was quite instructive to compare the diastereomeric ratios of these amides (see brackets) to the configuration of the amino alcohols giving rise to them. As expected, selectivity enhancement by going from *trans*-amino alcohol **19** (62:38) to *cis,endo*-isomer **20** (72:28) was quite large.

A further increase was expected from *cis,exo*-amino alcohol **21** as a result of its inherent sterical hindrance caused by the 8-methyl group of the bornane skeleton. This effect, however, turned out to be comparatively low (78:22). Anyway, twofold crystallization of amide ester **22**, generated by successive dilactone opening with amino alcohol **21** followed by diazomethane treatment (Scheme 7), brought the diastereomeric enrichment up to the practically useful ratio of 97.5:2.5.



1 22

a) Aminoborneol 21, toluene, room temp., 60 h; b) diazomethane in $EtOH/Et_2O$, $CHCl_3$, room temp., 30 min.

Scheme 7. Dilactone opening with (1*R*,4*S*)-3-*exo*-amino-2-*exo*-hydroxybornane (21)

Conclusions. The asymmetric dilactone opening, presented here, is a clean reaction, which can be easily performed (stirring for several hours or days at ambient temperature) and worked up. In yields ranging from 73 to 99% it provides diastereomeric 3-ketoglutaric mono amides in ratios up to 84:16. Chiral opening reagents were synthesized either by starting from the chiral pool compounds (*S*)-proline and (1*R*,4*R*)-camphor or by making use of the industrial waste compound[23] (1*R*,3*R*,5*R*)-benzyl 2-azabicyclo[3.3.0]octane-3-carboxylate (10). All are available in both enantiomeric forms.

At this point, one may safely predict, that by making good use of the experience gained so far, one should be able to develop an even more successful nucleophile. As promising candidates configurationally well defined 2,3-diamino bornanes remain to be synthesized.

The investigations described here, used for the first time a dilactone as a synthetic equivalent of a ketoanhydride, which simultaneously disguises the keto group and enhances conformational rigidity.

Our efforts at this stage focused on variations in the nucleophile without any change in reaction conditions and optimum results were obtained with *cis,exo*-aminoborneol 21 which opened dilactone 1 with a respectable chemical enrichment of diastereomers. Subsequent two-fold crystallization resulted in a product of high optical purity, ready for use.

EXPERIMENTAL

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. An alcoholic-ethereal solution of diazomethane was prepared from the reaction of N-methyl-N-nitroso-*p*-toluenesulfonamide (Diazald®) with KOH and stored at -20°C. Sodium hydride was liberated out of a 60% suspension in mineral oil by triple washing

with petroleum ether and evaporation in high vacuum. Dioxane, tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane was freshly distilled from calcium hydride. Methanol was twice distilled from sodium and stored over 4Å molecular sieves.

All reactions were conducted under nitrogen (Linde 5.0), glassware was flame-dried under vacuum. Thin-layer chromatography (TLC) for analysis of reactions and fractions was performed with silica gel plates Merck 60 F_{254} or aluminium oxide plates Polygram® Alox N/UV_{254} of Macherey and Nagel; compound visualization was effected by either UV or by staining with a solution of 0.5 g *o*-vanillin in 100 mL of a 85:10:5 mixture of methanol, glacial acetic acid, and concentrated sulfuric acid or with a solution of 0.3 g ninhydrine in 100 mL *n*-butanol and 3 mL glacial acetic acid. Baker silica gel (30-60 μm particle size) was used for flash chromatography, eluent compositions are described as volume:volume ratios before mixing. Concentration refers to removal of volatile components under water aspirator pressure on a Büchi rotavapor evaporator at ≤40°C and, if not otherwise stated, to subsequent subjection to high vacuum. Kugelrohr bulb to bulb distillations were done with a Büchi GKR 50 apparatus; distillation vacua were measured with a McLeod manometer, they are reported uncorrected.

Melting points were determined on a Gallenkamp heating block and are reported uncorrected. UV spectra were measured in MeOH on a Beckman 3600 instrument. IR spectra were determined with a Perkin Elmer Model 580 or Model FT 1710 spectrometer. NMR spectra were recorded on a Bruker WP 200 or AM 300 spectrometer (measuring frequency and solvent in brackets). NMR spectra are reported in ppm on the δ scale relative to internal tetramethylsilane. ^{1}H NMR data are presented in the following manner: multiplicity (abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak), coupling constant(s) in hertz, number of protons, and, where significant, assignment. ^{13}C NMR spectra are proton-off-resonance-decoupled and tabulated with the mutiplicities in brackets.

The corresponding ^{1}H NMR signals of diastereomers in the derivatives of the dilactone opening products, investigated here, or their derivatives were often insufficiently resolved. Therefore more sophisticated NMR techniques were established to successfully quantify diastereomeric ratios by means of integration. One approach made use of the aromatic solvent induced shift (ASIS)[24] by C_6D_6 to alter absolute and relative chemical shifts of diastereomer protons compared to spectra recorded with $CDCl_3$. Alternatively, to improve resolution of overlapping peaks without changing chemical shifts, the respective free induction decays (FID's) were subjected to Lorentz-Gauß transformation[25] prior to Fourier transformation.

Mass spectra were obtained with a Finnigan MAT 312 mass spectrometer at an ionization potential of 70 eV. Fast Atom Bombardment (FAB) spectra were determined with a VG Autospec mass spectrometer using *m*-nitrobenzylic alcohol as matrix substance. High-resolution mass spectra (HRMS) were recorded on a VG Autospec mass spectrometer at an ionization potential of 70 eV. Elemental analyses were performed on a Heraeus CHN rapid analyser. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

High-pressure liquid chromatography (HPLC) on an analytical scale (10-100 μg) was done with the following set-up: Waters model U6K universal liquid chromatograph injector, Waters Model 6000A solvent delivery system, Waters Lambda-Max Model 481 LC spectrophotometer, and Shimadzu data processor Chromatopac C-R1B. The column used was a Merck LiChroCART 250-4 filled with LiChrosorb Si 60 (7μm average particle size, nonspherical). It was run at a flow rate of 1.0 mL/min. For each separation the eluent used (HPLC-quality solvents of Janssen or Merck, mixtures described as volume:volume ratios, degasified for 30 min by ultrasonic treatment immediately prior to use) and detection wavelength are given. Retention times t_R are followed by the percentage of the eluted diastereomers determined by peak height measuring.

Methyl 3-Carbomethoxymethyl-4-carbomethoxy-5-keto-6,6-dimethylheptanoate (7). A solution of sodium (5.93 g, 247 mmol) in methanol (100 mL) was continously added at a rate of 3 mL/min using a perfusion system to a stirred solution of dimethyl glutaconate (9) (81.8 g, 517 mmol) and methyl 4,4-dimethyl-3-oxo-pentanoate (6) (134.5 g, 850 mmol) at room temperature. The obtained orange coloured solution was cooled by means of an ice-salt cooling bath. Then under stirring ice-cooled diethyl ether (400 mL) and aqueous citric acid (400 mL) were added which adjusted pH to 6. The ether layer was separated and the aqueous layer extracted with another portion of diethyl ether (200 mL). The combined organic extracts were washed with saturated aqueous sodium carbonate (300 mL) and saturated aqueous sodium chloride (2 x 300 mL), then dried over $MgSO_4$, filtered and concentrated by rotary evaporation. Excess educts were removed by distillation through a Vigreux column at high vacuum (boiling range 51-56°C, 1.5 Torr). The residue was Kugelrohr distilled (bp 150-200°C, 1.5 Torr) to yield 93.4 g (295 mmol, 57%) of title compound 7 as a colourless, viscous oil: IR (film): $\tilde{\nu}$ = 2960, 1740, 1710, 1440, 1370, 1270, 1200, 1170, 1000 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 4.37 (d, ^3J = 7, 1 H, $CH_3O_2CCHCOC(CH_3)_3$), 3.67 (s, 9 H, CO_2CH_3), 3.05-2.35 (m, 5 H, CH_2CHCH_2), 1.18 (s, 9 H, $COC(CH_3)_3$); MS (20°C): *m/z* (%) = 316 (1) [M^+], 259 (21), 227 (69), 224 (12), 200 (14), 185 (27), 172 (28), 140 (28), 127 (67), 99 (45), 95 (21), 85 (20), 59 (59), 57 (100); HRMS ($C_{15}H_{24}O_7$): calcd. 316.1522; found 316.1521.

3-(2,2-Dimethyl-3-oxo-but-4-yl)-glutaric Anhydride (3) *and 1-tert-Butyl-2,8-dioxabicyclo-[3.3.1]nonane-3,7-dione* (1). Keto triester 7 (57.5 g, 182 mmol) was dissolved in concentrated hydrochloric acid (500 mL) and heated at reflux for 8 h. The light yellow reaction mixture was concentrated under water aspirator vacuum. The residue, a viscous yellow oil, was evaporated with CH_2Cl_2 (5 x 300 mL), then treated with acetyl chloride (150 mL) and heated at reflux for a period of 3 h. After being cooled to room temperature, the yellow solution was concentrated under water aspirator vacuum. Kugelrohr distillation of the residue (bp 170-250°C, 2 Torr) afforded a pale yellow, highly viscous oil, which was subjected to flash chromatography (methyl-*tert*-butyl ether MTBE/acetone 5:1) yielding 7.0 g (33 mmol, 18%) of anhydride **3** and 3.50 g (16.5 mmol, 9%) of dilactone **1**, each as a white crystalline solid. In a second experiment the desired dilactone 1 was isolated without chromatographic step by stirring the Kugelrohr distillate with aqueous sodium carbonate (50 mL) for 45 min and extraction with CH_2Cl_2 (3 x

200 mL). To avoid emulsion formation during extraction a nonsaturated solution of Na_2CO_3 was used, which was prepared by diluting a saturated solution with an equal volume of distilled water. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude dilactone, a viscous yellow oil, was recrystallized from MTBE/acetone yielding 9% of dilactone **1**. This proved to be stable under the alkaline conditions by a blank experiment. A sample of pure dilactone **1** (22.0 mg, 0.104 mmol) was recovered without loss of material: Anhydride **3** (mp 84°C): IR (KBr): $\tilde{\nu}$ = 2980, 1810, 1773, 1695, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.91 (dd, ^2J = 17.1, ^3J = 4.4, 2 H, $(CHHCO)_2O$), 2.72 (m, 1 H, methine H), 2.60 (d, ^3J = 6.5, 2 H, $CH_2COC(CH_3)_3$), 2.48 (dd, ^2J = 17.1, ^3J = 9.1, 2 H, $(CHHCO)_2O$), 1.15 (s, 9 H, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.8 (s), 166.1 (s), 44.0 (s), 40.2 (t), 35.2 (t), 26.0 (q), 24.3 (d); MS (100°C): *m/z* (%) = 212 (2) [M^+], 184 (13), 156 (29), 140 (11), 128 (55), 113 (17), 100 (100), 85 (31), 69 (43), 57 (100). Anal. calcd. for $C_{11}H_{16}O_4$ (212.2): C 62.25, H 7.60. Found C 62.23 H 7.46. Dilactone **1** (mp 163°C): IR (KBr): $\tilde{\nu}$ = 2980, 1757, 1280, 1070, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.88 (dd, ^2J = 18.6, ^3J = 6.8, 2 H, 4-, 6-H), 2.73 (m, 1 H, 5-H), 2.66 (d, ^2J = 18.6, 2 H, 4-, 6-H), 2.18 (d, ^3J = 3.1, 2 H, 9-H_2), 1.12 (s, 9 H, $COC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1 (s), 110.0 (s), 38.8 (s), 36.1 (t), 25.9 (t), 23.9 (q), 22.7 (d); MS (150°C): *m/z* (%) = 212 (1) [M^+], 184 (3), 168 (7), 157 (17), 142 (42), 128 (28), 113 (25), 100 (56), 85 (47), 69 (41), 57 (100). Anal. calcd. for $C_{11}H_{16}O_4$ (212.2): C 62.25, H 7.60. Found C 62.26 H 7.53.

(1R,3R,5R)-tert-Butyl 2-Azabicyclo[3.3.0]octane-3-carboxylate (**12**). This reaction was performed in a pressure vessel made of thick-walled glass, which was cooled to -78°C prior to filling with the educts as well as before opening after the reaction had been done. Dioxane (25 mL), concentrated sulfuric acid (2.5 mL), and isobutene (25 mL) were added to (1*R*, 3*R*,5*R*)-2-azabicyclo[3.3.0]octane-3-carboxylic acid **11**[23] (2.02 g, 13 mmol). Isobutene had been condensed at -78°C. The reactor was tightly sealed, then the reaction mixture was allowed to reach room temperature and stirred for 20 h. The dark brown content of the reactor was poured to an ice-cooled, vigorously stirred mixture of 1N NaOH (125 mL) and diethyl ether (200 mL). After 5 min of stirring, the pale yellow organic phase was separated. The aqueous phase was extracted with further portions of diethyl ether (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. *tert*-Butyl ester **12** was isolated by flash chromatography (MTBE) as a clear, colourless oil (bp 145°C/ 0.8 Torr) of fruit-like perfume in 1.19 g (5.62 mmol, 43%) yield: $[\alpha]_D^{20}$ = +42.5° (c = 1.0 in $CHCl_3$); IR (film): $\tilde{\nu}$ = 3352, 2940, 2864, 1728, 1456, 1392, 1368, 1328, 1288, 1240, 1220, 1156, 1044 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.63 (m, 1 H, 1-H), 3.49 (dd, ^3J = 9.5, ^3J = 6.5, 1 H, 3-H), 2.56 (m, 1 H, 5-H), 2.32 (ddd, ^2J = 12.5, ^3J = 8.5, ^3J = 6.5, 1 H, 4-H), 2.19 (s, br, 1 H, NH), 1.82-1.36 (m, 6 H, 6-, 7-, 8-H_2), 1.47 (s, 9 H, $C(CH_3)_3$), 1.34 (ddd, ^2J = 12.5, ^3J = 9.5, ^3J = 7.5, 1 H, 4-H). Assignment of signals and interpretation of coupling constants were confirmed by decoupling experiments. MS (FAB): *m/z* (%) = 423 (5) [$2M^+$+H], 212 (100) [M^++H], 156 (91), 110 (51).

(1R,3R,5R)-2-(Benzyloxycarbonyl)-2-azabicyclo[3.3.0]octane-3-carboxylic Acid N,N-Dimethylamide (**14**). (1*R*,3*R*,5*R*)-2-(Benzyloxycarbonyl)-2-azabicyclo[3.3.0]octane-3-carboxylic acid **13**[23]

(18.4 g, 63.6 mmol) was dissolved in THF (40 mL) and added to N,N´-carbonyldimidazole (11.3 g, 70 mmol) in THF (140 mL) at 0-5°C. After 2 h stirring at room temperature a 40 wt-% solution of dimethylamine in water (8.8 mL) was added. Stirring was continued for 67 h, then THF and excess dimethylamine were evaporated. The remaining viscous yellow oil was dissolved in ethyl acetate (100 mL) and washed with 1N HCl (5 x 40 mL), then with diluted aqueous sodium hydrogencarbonate (3 x 100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to yield 12.9 g (40.8 mmol, 64%) of analytically pure amide **14** as a white solid (mp 87°C): UV (CH_3OH): λ = 213, 250, 256, 263, 267 nm; IR (KBr): $\tilde{\nu}$ = 3095, 3065, 3040, 2950, 2880, 1703, 1648, 1499, 1470, 1456, 1417, 1353, 1338, 1303, 1290, 1222, 1205, 1139, 1060, 1018, 960, 897, 768, 735, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.44-7.28 (m, 5 H, phenyl protons), 5.14 (AB-q, ^2J = 12.5, 0.6 x 2 H, $PhCH_2OCO$), 5.05 (AB-q, ^2J = 12.5, 0.4 x 2 H, $PhCH_2OCO$), 4.73 (dd, ^3J = 9, ^3J = 6, 0.6 x 1 H, 3-H), 4.63 (dd, ^3J = 9, ^3J = 7, 0.4 x 1 H, 3-H), 4.31 (m, 1 H, 1-H), 3.08 (s, 0.3 x 6 H, $N(CH_3)_2$), 2.99 (s, 0.3 x 6 H, $N(CH_3)_2$), 2.84 (s, 0.2 x 6 H, $N(CH_3)_2$), 2.82 (s, 0.2 x 6 H, $N(CH_3)_2$), 2.71 (m, 1 H, 5-H), 2.4 (m, 1 H, 4-H), 2.23-1.4 (m, 7 H, 4-H, 6-, 7-, 8-H_2). Hindered rotation around the N-CO bonds of carbamate and amide causes signal splitting in a ratio 3:2 for $PhCH_2OCO$, 3-H, and $N(CH_3)_2$ as well as an additional 1:1 splitting of the $N(CH_3)_2$ signal. MS (90°C): *m/z* (%) = 315 (1) [M^+-H], 245 (4), 244 (21), 201 (5), 200 (31), 181 (81), 110 (3), 91 (100); HRMS ($C_{18}H_{24}N_2O_3$): calcd. 316.1787; found 317.1786. Anal. calcd. for $C_{18}H_{24}N_2O_3$ (316.4): C 68.33, H 7.65, N 8.85. Found C 68.46, H 7.58, N 8.80.

(1R,3R,5R)-2-Azabicyclo[3.3.0]octane-3-carboxylic Acid N,N-Dimethylamide (**15**). (1*R*,3*R*,5*R*)-2-(Benzyloxycarbonyl)-2-azabicyclo[3.3.0]octane-3-carboxylic acid N,N-dimethylamide (**14**) (1.05 g, 3.32 mmol) was dissolved in methanol (20 mL). In the presence of palladium on charcoal (10% Pd) (177 mg) hydrogenation was performed employing 0.04 bar excess hydrogen pressure for 17 h at room temperature. The catalyst was filtered off (CAUTION! Risk of spontaneous ignition) and thoroughly washed with methanol. The combined filtrates were concentrated on the rotary evaporator to yield 0.585 g (≥ 90% purity by ^1H NMR, 87%) of the deprotected amide (**15**) as a colourless oil, which crystallized by cooling (mp 40°C): IR ($CHCl_3$): $\tilde{\nu}$ = 3292, 3000, 2952, 2864, 1644, 1500, 1448, 1392, 1348, 1256, 1224, 1156, 1116, 1092, 1056, 976, 880, 856 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.76 (dd, ^3J = 10, ^3J = 6.5, 1 H, 3-H), 3.62 (m, 1 H, 1-H), 3.02 (s, 0.5 x 6 H, $N(CH_3)_2$), 2.97 (s, 0.5 x 6 H, $N(CH_3)_2$), 2.59 (m, 1 H, 5-H), 2.30 (m, br, 2 H, 4-H, NH), 1.86-1.34 (m, 6 H, 6-, 7-, 8-H_2), 1.22 (ddd, ^2J = 12.5, ^3J = 10, ^3J = 7.5, 1 H, 4-H). Hindered rotation around the N-CO bond causes 1:1 splitting of the $N(CH_3)_2$ singlet. Assignment of signals and interpretation of coupling constants were confirmed by decoupling and NOE experiments. MS (20°C): *m/z* (%) = 182 (2) [M^+], 167 (2), 93 (12), 124 (3), 137 (3), 111 (10), 110 (100), 67 (42). Anal. calcd. for $C_{10}H_{18}N_2O$ (182.3): C 65.90 , H 9.95, N 15.37. Found C 65.12, H 10.01, N 14.82. A sixty-fold scale-up of the experiment yielded 81% of amide **15**. In this case removal of the CO_2, formed during the reaction, was necessary. It was done by periodical evaporation of the gas phase using a water aspirator pump. Crude amino amide **15** was used for the subsequent reduction step without further purification.

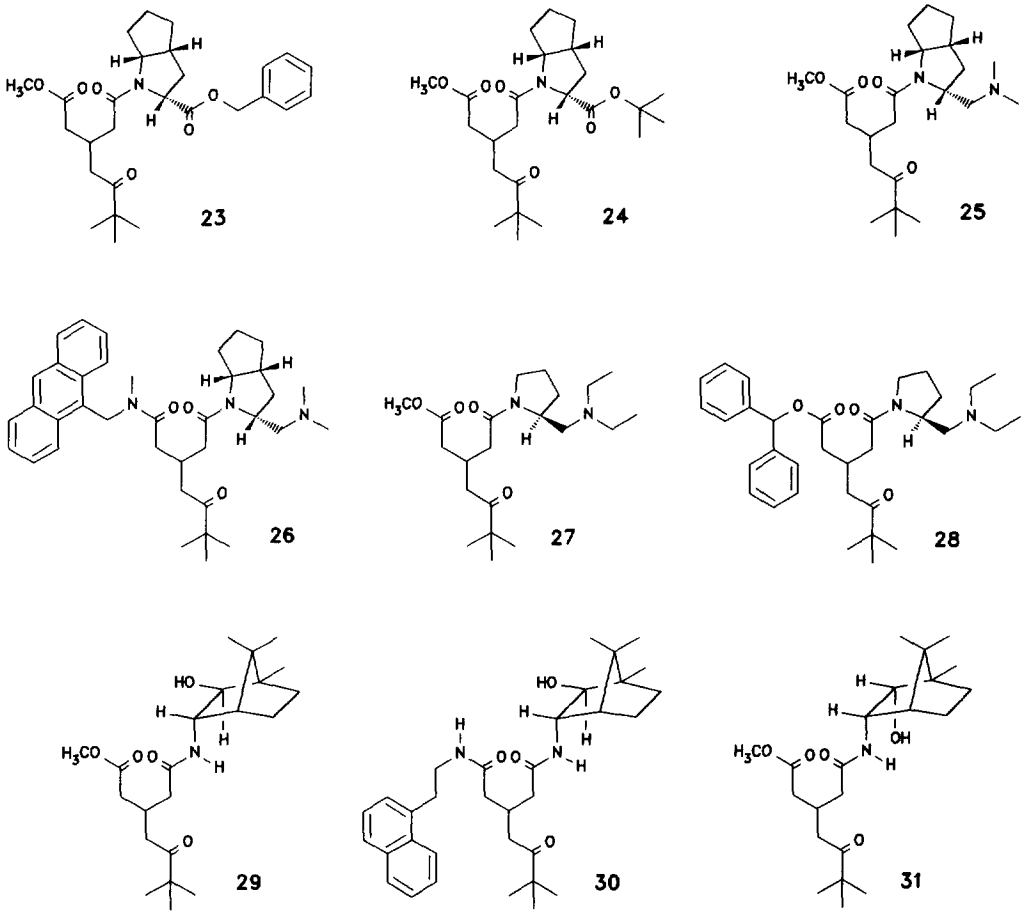
(1R,3R,5R)-3-(N,N-Dimethylaminomethyl)-2-azabicyclo[3.3.0]octane (**16**). (1*R*,3*R*,5*R*)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid N,N-dimethylamide (**15**) (9.11 g, ≥ 90% purity by ^{1}H NMR) dissolved in THF (25 mL) was dropwise added over 25 min to lithium aluminium hydride (5.69 g, 150 mmol) in THF (60 mL) at 0°C. The reaction mixture was heated at reflux for 24 h. After cooling to 0°C distilled water (11 mL), 15 wt-% aqueous NaOH (11 mL), and again distilled water (34 mL) were added in this order and in small portions. After gas evolution had ceased, the reaction mixture was heated at reflux for another hour. The supernatant was decanted from the white precipitate and the latter boiled out with a 14:1 (v/v) mixture of dichloromethane and methanol (3 x 75 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated on the rotary evaporator. Subsequent column chromatography was performed using neutral aluminium oxide (Alumina N-Super I of ICN Biomedicals) desactivated by adding 7 wt-% of distilled water as the stationary phase and methanol as the mobile phase. Thus, 6.44 g (38.3 mmol, 85%) of diamine **16** were obtained as yellowish brown oil (bp 150°C/ 1 Torr): $[\alpha]_D^{20}$ = + 14.3° (c = 1.0 in $CHCl_3$); IR (film): $\tilde{\nu}$ = 3306, 2944, 2859, 2817, 2765, 2720, 1456, 1408, 1369, 1325, 1290, 1269, 1241, 1182, 1158, 1124, 1100, 1043, 1028, 981, 852 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.62 (m, 1 H, 1-H), 3.05 (X-portion of an ABX-spin system, additionally splitted to a dd, ^3J = 10.5, ^3J = 5, 1 H, 3-H), 2.53 (m, 1 H, 5-H), 2.31 (AB-portion of an ABX-spin system, ^2J = 12, 2 H, $CH_2N(CH_3)_2$), 2.23 (s, 6 H, $N(CH_3)_2$), 2.06 (m, br, 2 H, 4-H, NH), 1.83-1.32 (m, 6 H, 6-, 7-, 8-H_2), 0.88 (ddd, ^2J = 12, ^3J = 10.5, ^3J = 8.5, 1 H, 4-H). Assignment of signals and interpretation of coupling constants were confirmed by decoupling experiments. MS (20°C): *m/z* (%) = 168 (4) [M$^+$], 123 (4), 111 (11), 110 (100), 109 (8), 93 (15), 67 (43); HRMS ($C_{10}H_{20}N_2$): calcd. 168.1626; found 168.1622.

General Procedure for the Opening of Dilactone **1** *with Chiral, Enantiomerically Pure Nucleophiles (GP 1).* Crystalline opening reagents **19**, **20**, or **21** (0.4 mmol) were weighed into the reaction vessel together with crystalline dilactone **1** (42.4 mg, 0.2 mmol), then toluene (3 mL) was added. Liquid opening reagents as **10**, **12**, **16**, or **17** (0.4 mmol) were dissolved in toluene (2 mL) under nitrogen and added to dilactone **1** (42.4 mg, 0.2 mmol), partially dissolved in toluene (1 mL). In each case suspended dilactone **1** was completely dissolved during the reaction. This was performed by stirring at room temperature (20-25°C) until TLC control (acetone/CH_2Cl_2 2:1) indicated complete conversion of dilactone starting material. Then the solvent was removed on the rotary evaporator and under high vacuum. Optional work-up was done as follows. The concentrated reaction mixture was dissolved in CH_2Cl_2 (15 mL) and washed with 1N HCl (2 x 10 mL). The combined aqueous layers were backwashed with CH_2Cl_2 (10 mL). Then the combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude dilactone opening products so obtained, which are mono acids of the type **2** (scheme 1), were characterized and analysed regarding the proportion of diastereomers after an appropriate derivatization (see below).

General Procedure for the Conversion of the Mono Amide Mono Acid Dilactone Opening Products to their Methyl Ester Derivatives (GP 2). Ethereal-ethanolic diazomethane was added

dropwise to the crude dilactone opening product, dissolved in CH_2Cl_2 (2 mL), until the yellow colour of the latter just persisted. After 30 min of stirring at room temperature, the reaction mixture was concentrated on the rotary evaporator and under high vacuum.

Determination of Diastereomeric Ratios of the Dilactone Opening Products. This was done by analysing ^1H NMR spectra of the routinely prepared methyl ester derivatives (GP 2). If, even exploiting techniques such as ASIS and Lorentz-Gauß transformation, results remained unsatisfactory, dilactone opening products were converted to UV-detectable compounds and investigated by HPLC. All derivatives prepared from dilactone opening products are presented in scheme 8, except amide ester **22**, which is depicted in scheme 7.



Scheme 8. Synthesized derivatives of dilactone opening products

Opening of Dilactone 1 *with (1R,3R,5R)-Benzyl 2-Azabicyclo[3.3.0]octane-3-carboxylate* (**10**). According to GP 1, dilactone **1** (42.4 mg, 0.2 mmol) was opened using (1*R*,3*R*,5*R*)-benzyl 2-azabicyclo[3.3.0]octane-3-carboxylate (**10**) (98.1 mg, 0.4 mmol) within 17 h at room temperature. After work-up the dilactone opening product (91.0 mg) was obtained as a yellow oil.

Amide Ester **23**. The product (91.0 mg) obtained by opening dilactone **1** with (1*R*,3*R*,5*R*)-benzyl 2-azabicyclo[3.3.0]octane-3-carboxylate (**10**) was treated with diazomethane following GP 2 to yield 92.0 mg (0.195 mmol, 97% referring to initial dilactone 1) of analytically pure amide ester **23** (84:16 mixture of diastereomers) as a yellow oil. The ratio of diastereomers in **23** was determined by ^{1}H NMR analysis on the basis of the *tert*-butyl ketone singlets at δ = 1.018, δ = 1.003, δ = 0.995, and δ = 0.980. Assignment of diastereomer and amide conformer signals was done consulting the ^{1}H NMR spectrum of the reference 1:1 mixture of diastereomers (see below): UV (CH_3OH): λ = 210, 257 nm; IR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2872, 1732, 1700, 1636, 1436, 1368, 1264, 1172, 1024 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6): δ = 7.34-7.02 (m, 5 H phenyl protons), 5.04 (m, 2 H, CO_2CH_2Ph), 4.73-3.79 (m, 2 H, 1-, 3-H of the 2-azabicyclo[3.3.0]octane system), 3.33 and 3.31 (2 x s, 3 H, CO_2CH_3 diastereomers), 3.26-1.08 (m, 16 H), 1.018 (s, 0.84 (diastereomer) x 0.75 (amide conformer) x 9 H, $COC(CH_3)_3$), 1.003 (s, 0.16 (diastereomer) x 0.75 (amide conformer) x 9 H, $COC(CH_3)_3$), 0.995 (s, 0.16 (diastereomer) x 0.25 (amide conformer) x 9 H, $COC(CH_3)_3$), 0.980 (s, 0.84 (diastereomer) x 0.25 (amide conformer) x 9 H, $COC(CH_3)_3$); MS (100°C): *m/z* (%) = 472 (1) [M$^+$+H], 471 (2) [M$^+$], 456 (1), 440 (4), 415 (9), 414 (34), 386 (3), 336 (10), 287 (3), 274 (2), 227 (16), 209 (3), 167 (5), 153 (5), 124 (12), 123 (6), 111 (11), 110 (100), 109 (5), 97 (6), 91 (37), 82 (5), 71 (5), 67 (10), 57 (17), 56 (6); HRMS ($C_{27}H_{37}NO_6$): calcd. 471.2621; found 471.2624.

Opening of Dilactone 1 *with (1R,3R,5R)-tert-Butyl 2-Azabicyclo[3.3.0]octane-3-carboxylate* (**12**). According to GP 1, dilactone 1 (42.4 mg, 0.2 mmol) was opened using (1*R*,3*R*,5*R*)-*tert*-butyl 2-azabicyclo[3.3.0]octane-3-carboxylate (**12**) (84.5 mg, 0.4 mmol) within 17 h at room temperature. The reaction mixture was concentrated to a pale yellow oil that was directly inserted in the next step, the working up procedure of GP 1 was omitted.

Amide Ester **24**. The crude product obtained by opening dilactone 1 with (1*R*,3*R*,5*R*)-*tert*-butyl 2-azabicyclo[3.3.0]octane-3-carboxylate (**12**) was treated with diazomethane following GP 2. Purification by flash chromatography (EtOAc/petroleum ether 1:2) gave 73.1 mg (0.167 mmol, 83% referring to initial dilactone **1**) of amide ester **24** (77:23 mixture of diastereomers) as a colourless viscous oil. The ratio of diastereomers in **24** was determined by ^{1}H NMR analysis on the basis of the *tert*-butyl ketone singlets at δ = 1.025, δ = 1.010, δ = 0.999, and δ = 0.984. Assignment of diastereomer and amide conformer signals was done consulting the ^{1}H NMR spectrum of the reference 1:1 mixture of diastereomers (see below): IR ($CHCl_3$): $\tilde{\nu}$ = 2968, 2872, 1732, 1700, 1636, 1436, 1368, 1156, 1104 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6): δ = 4.62-3.78 (m, 2 H, 1-, 3-H of the 2-azabicyclo[3.3.0]octane system), 3.325 and 3.315 (2 x s, 3 H, CO_2CH_3, diastereomers), 3.26-1.08 (m, 16 H), 1.41 (s, 0.75 x 9 H, $CO_2C(CH_3)_3$, amide conformer), 1.36 (s, 0.25 x 9 H, $CO_2C(CH_3)_3$, amide conformer), 1.025 (s, 0.77 (diastereomer) x 0.75 (amide conformer)

x 9 H, $COC(CH_3)_3$), 1.010 (s, 0.23 (diastereomer) x 0.75 (amide conformer) x 9 H, $COC(CH_3)_3$), 0.999 (s, 0.23 (diastereomer) x 0.25 (amide conformer) x 9 H, $COC(CH_3)_3$), 0.984 (s, 0.77 (diastereomer) x 0.25 (amide conformer) x 9 H, $COC(CH_3)_3$); MS (100°C): *m/z* (%) = 437 (1) [M⁺], 406 (2), 380 (11), 350 (7), 336 (35), 324 (21), 227 (34), 110 (100), 57 (13); HRMS ($C_{24}H_{39}NO_6$): calcd. 437.2777; found 437.2750.

Opening of Dilactone 1 *with (1R,3R,5R)-3-(Dimethylaminomethyl)-2-azabicyclo[3.3.0]-octane* (**16**). According to GP 1, dilactone **1** (42.4 mg, 0.2 mmol) was opened completely using (1*R*,3*R*,5*R*)-3-(dimethylaminomethyl)-2-azabicyclo[3.3.0]octane (**16**) (67.3 mg, 0.4 mmol) within 42 h at room temperature as verified by TLC. For derivative preparation, however, an alternative protocol was established using an excess of dilactone **1** as detailed below: (1*R*,3*R*,5*R*)-3-(Dimethylaminomethyl)-2-azabicyclo[3.3.0]octane (**16**) (52.2 mg, 0.31 mmol) was dissolved in toluene (3 mL) under nitrogen and added to a solution of dilactone **1** (127 mg, 0.6 mmol). The reaction mixture was stirred for 9 d at room temperature, then only traces of diamine **16** could be detected by TLC. The reaction mixture was concentrated on the rotary evaporator and under high vacuum to yield a pale yellow foam that was used without further purification.

Amide Ester **25**. 18.2 wt-% of the crude product obtained by opening excess dilactone **1** with (1*R*,3*R*,5*R*)-3-(dimethylaminomethyl)-2-azabicyclo[3.3.0]octane (**16**) were treated with diazomethane following GP 2. Purification by flash chromatography ($CHCl_3$/CH_3OH 5:1) gave 16.2 mg (0.041 mmol, 73% referring to initial diamine **16**) of amide ester **25** as a yellow oil. Determination of the diastereomeric ratio by ^1H NMR analysis of **25** failed: IR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2868, 2828, 2776, 1728, 1700, 1628, 1460, 1420, 1368, 1236, 1164 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 4.24 (m, 2 H), 3.65 (s, 3 H, CO_2CH_3), 2.93-0.75 (m, 18 H), 2.32 (s, 6 H, $N(CH_3)_2$), 1.12 (s, 9 H, $COC(CH_3)_3$); MS (80°C): *m/z* (%) = 394 (26) [M⁺], 379 (23), 363 (36), 336 (19), 227 (24), 201 (20), 167 (23), 149 (44), 124 (77), 110 (100); HRMS ($C_{22}H_{38}N_2O_4$): calcd. 394.2832; found 394.2841.

Diamide **26**. To guarantee complete conversion of the mono amide mono acid even in the presence of the diacid, resulting from dilactone hydrolysis over the extended reaction time, an excess of coupling reagent was used. Thus, 81.8 wt-% of the crude product obtained by opening excess dilactone **1** with (1*R*,3*R*,5*R*)-3-(dimethylaminomethyl)-2-azabicyclo[3.3.0]octane (**16**) and N,N′-carbonyldiimidazole (159 mg, 0.98 mmol) were weighed into the reaction vessel under nitrogen. CH_2Cl_2 (5 mL) was added and the resulting pale yellow clear solution stirred for 2 h at room temperature, then 9-(methylaminomethyl)-anthracene (435 mg, 1.97 mmol) was added. Stirring was continued for 3 d at room temperature. Then the reactor content was transferred into a separatory funnel by means of CH_2Cl_2 (10 mL). Stepwise washing was done with saturated aqueous solutions of $NaHCO_3$ (2 x 15 mL, combined and backwashed once with CH_2Cl_2 (10 mL)) and NaCl (20 mL). After drying ($MgSO_4$) and filtration the organic phase was concentrated on the rotary evaporator and in high vacuum. The crude product was purified by repeated flash chromatography (1. gradient elution CH_3OH/$CHCl_3$ 1:3 ... CH_3OH, 2. EtOAc/Et_3N 100:1) to yield

81.7 mg (0.140 mmol, 55%) of diamide **26** (58:42 mixture of diastereomers) as a yellow solid (mp 52°C). The ratio of diastereomers in **26** was determined by HPLC (eluent: CH_2Cl_2/CH_3OH 10:1 + 0.001 vol% Et_3N, detection wavelength 254 nm). The diastereomers were eluted at retention times t_R = 16.73 min (42%) and t_R = 16.88 min (58%): UV (CH_3OH): λ = 254, 347, 365, 385 nm; IR ($CHCl_3$): $\tilde{\nu}$ = 3086, 3056, 2996, 2964, 2868, 2828, 2776, 1700, 1628, 1448, 1408, 1244, 888 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.55-7.40 (m, 9 H, aromatic protons), 5.65 (m, 2 H, $ArCH_2$), 4.24 (m, 2 H), 3.23-0.75 (m, 18 H), 2.67 and 2.66 (2 x s, 3 H, $CONCH_3$), 2.26 (s, 6 H, $N(CH_3)_2$), 1.14 (s, 9 H, $COC(CH_3)_3$; MS (190°C): *m/z* (%) = 585 (1) [M^++ 2 H], 584 (4) [M^++ H], 583 (9) [M^+], 417 (6), 416 (19), 415 (1), 238 (3), 193 (2), 192 (17), 191 (100), 190 (3), 189 (4), 151 (2), 111 (3), 110 (5), 109 (2), 97 (4), 95 (5); HRMS ($C_{37}H_{49}N_3O_3$): calcd. 583.3774; found 583.3796. Anal. calcd. for $C_{37}H_{49}N_3O_3$ (583.8): C 73.84, H 8.54, N 6.98. Found C 73.39, H 8.36, N 6.79.

Opening of Dilactone **1** *with (S)-Diethylaminomethylpyrrolidine* (**17**). According to GP 1, dilactone **1** (42.4 mg, 0.2 mmol) was opened using (*S*)-diethylaminomethylpyrrolidine (**17**) (63 mg, 0.4 mmol) within 48 h at room temperature. The reaction mixture was concentrated to a brown oil, which was treated with aqueous $NaHCO_3$ (10 mL). After adjusting pH to 4 by addition of citric acid, extraction was performed using CH_2Cl_2 (5 x 30 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated to give 58.3 mg of the dilactone opening product as a brown oil.

Amide Ester **27**. A 21.4 mg portion of the product obtained by opening dilactone **1** with (*S*)-diethylaminomethylpyrrolidine (**17**) was treated with diazomethane following GP 2 to yield 21.0 mg (0.055 mmol, 75% referring to initial dilactone **1**) of analytically pure amide ester **27**. Determination of the diastereomeric ratio by ^1H NMR analysis of **27** failed: IR ($CHCl_3$): $\tilde{\nu}$ = 2972, 2936, 2872, 2816, 1728, 1700, 1628, 1436, 1368, 1160, 1092 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 4.50-3.90 (m, 1 H, 2-H of the pyrrolidine system), 3.8-3.27 (m, 2 H), 3.65 (s, 3 H, CO_2CH_3), 2.87-2.15 (m, 13 H), 2.1-1.75 (m, 4 H), 1.2-0.94 (m, 6 H, $N(CH_2CH_3)_2$), 1.12 (s, 9 H, $COC(CH_3)_3$); MS (50°C): *m/z* (%) = 382 (1) [M^+], 351 (1), 325 (1), 236 (2), 227 (3), 211 (2), 206 (5), 201 (16), 173 (8), 169 (7), 127 (15), 111 (10), 110 (11), 97 (14), 95 (13), 86 (100), 71 (32); HRMS ($C_{21}H_{38}N_2O_4$): calcd. 382.2832; found 382.2823.

Amide Ester **28**. A 28.0 mg portion of the product obtained by opening dilactone **1** with (*S*)-diethylaminomethylpyrrolidine (**17**) (see above) was dissolved in toluene/$CHCl_3$ 3:2 (v/v) (5 mL), added to a solution of diphenyldiazomethane (44.1 mg, 0.227 mmol) in toluene (1 mL) and heated at reflux for 24 h. The violet colour of the reaction mixture changed to a dirty yellow. After removal of the solvents in vacuum, the reaction mixture was dissolved in EtOAc and silica gel was impregnated with it. Column chromatography was performed using basic aluminium oxide (Alumina B-Super I of ICN Biomedicals) desactivated by adding 7 wt-% of distilled water as the stationary phase and a gradient EtOAc/petroleum ether 1:5 ... EtOAc as the mobile phase. 19.8 mg (0.037 mmol, 38% referring to initial dilactone **1**) of amide ester **28** (82:18 mixture of diastereomers) were obtained as a yellow oil. The ratio of diastereomers in **28** could be determined

by ^1H NMR analysis on the basis of the *tert*-butyl ketone singlets at δ = 0.958 and δ = 0.954: UV (CH_3OH): λ = 210, 252, 257 nm; IR ($CHCl_3$): ν̃ = 3094, 3064, 2972, 2932, 2872, 2816, 1732, 1700, 1628, 1496, 1424, 1368, 1136, 1104, 996 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 7.39-7.28 (m, 4 H, phenyl protons), 7.14-6.94 (m, 7 H, phenyl protons and Ph_2CH), 4.26 (m, 1 H, 2-H of the pyrrolidine system), 3.16 (m, 1 H), 3.03-1.75 (m, 14 H), 1.57-1.23 (m, 4 H), 1.05-0.81 (m, 6 H, $N(CH_2CH_3)_2$), 0.958 (s, 0.82 x 9 H, $COC(CH_3)_3$), 0.954 (s, 0.18 x 9 H, $COC(CH_3)_3$); MS (120°C): *m/z* (%) = 536 (2) [M^+ + 2 H], 535 (2) [M^+ + H], 534 (2) [M^+], 505 (1), 461 (2), 449 (2), 417 (1), 372 (1), 351 (1), 308 (2), 295 (2), 280 (2), 236 (2), 216 (2), 201 (3), 184 (15), 183 (10), 182 (27), 167 (15), 165 (8), 152 (7), 135 (5), 107 (8), 106 (10), 105 (100), 97 (5), 87 (65), 77 (71); HRMS ($C_{33}H_{46}N_2O_4$): calcd. 534.3458; found 534.3472.

Opening of Dilactone **1** *with (1R,4S)-3-endo-Amino-2-exo-hydroxybornane* (**19**). According to GP 1, dilactone **1** (42.4 mg, 0.2 mmol) was opened using (1*R*,4*S*)-3-*endo*-amino-2-*exo*-hydroxybornane (**19**) (67.7 mg, 0.4 mmol) within 3 d at room temperature. After work-up the dilactone opening product (63.0 mg) was obtained as a pale yellow oil.

Amide Ester **29**. One third (21.0 mg) of the product obtained by opening dilactone **1** with (1*R*,4*S*)-3-*endo*-amino-2-*exo*-hydroxybornane (**19**) was treated with diazomethane following GP 2 to yield 21.0 mg (0.053 mmol, 80% referring to initial dilactone **1**) of analytically pure amide ester **29** as a yellow oil. Determination of the diastereomeric ratio by ^1H NMR analysis of **29** failed: IR ($CHCl_3$): ν̃ = 3441, 3420, 2957, 2880, 1730, 1703, 1651, 1505, 1479, 1439, 1369, 1164, 1082, 1011 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 6.03 (m, br, 1 H, CONH); 4.17 (s, br, 1 H, OH), 4.06 (m, 1 H, 3-H of the bornane system), 3.36 (m, 1 H, 2-H of the bornane system), 3.31 (2 x s, 3 H, CO_2CH_3), 2.93 (m, 1 H), 2.76-2.14 (m, 6 H), 1.65-0.71 (m, 5 H, 4-H, 5-, 6-H_2 of the bornane system), 1.27 (s, 3 H, CCH_3), 0.98 (s, 9 H, $COC(CH_3)_3$), 1.07 (s, 3 H, CCH_3), 0.77 (s, 3 H, CCH_3); MS (120°C): *m/z* (%) = 396 (4) [M^++H], 395 (4) [M^+], 381 (5), 380 (1), 370 (14), 369 (56), 368 (100), 367 (5), 355 (12), 355 (12), 354 (53), 353 (22), 352 (90), 346 (14), 339 (20), 338 (35), 227 (69), 209 (25), 168 (21), 167 (29), 153 (27), 152 (23), 135 (38), 123 (22), 109 (32), 107 (26), 95 (47); HRMS ($C_{22}H_{37}NO_5$): calcd. 395.2672; found 395.2656.

Diamide **30**. Two thirds (42.0 mg) of the above-mentioned product obtained by opening dilactone **1** with (1*R*,4*S*)-3-*endo*-amino-2-*exo*-hydroxybornane (**19**) were dissolved in CH_2Cl_2 (1.25 mL) under nitrogen and added to a solution of N,N′-carbonyldiimidazole (19.9 mg, 0.123 mmol) in CH_2Cl_2 (0.75 mL) accompanied by a gentle effervescence. After 1 h of stirring at room temperature 2-(1-naphthyl)-ethylamine (21.1 mg, 0.123 mmol), dissolved in CH_2Cl_2 (1 mL) under nitrogen, were added. Stirring was continued for 18 h at room temperature. Then the reaction mixture was transferred into a separatory funnel using CH_2Cl_2 (10 mL). It was washed with 1N HCl, then with saturated aqueous $NaHCO_3$ finally with saturated aqueous NaCl (10 mL each). After drying ($MgSO_4$) and filtration the organic phase was concentrated to yield 32.1 mg (0.06 mmol, 45% referring to initial dilactone **1**) of analytically pure amide ester **30** (62:38 mixture of diastereomers) as a white solid (mp 72°C). The ratio of diastereomers in **30** could be

determined by ^1H NMR analysis on the basis of the *tert*-butyl ketone singlets at δ = 1.03 and δ = 0.99: UV (CH_3OH): λ = 223, 270, 280, 292 nm; IR ($CHCl_3$): ν̃ = 3439, 3320, 2970, 2935, 2875, 1699, 1657, 1596, 1515, 1479, 1460, 1448, 1397, 1368, 1266, 1106, 1010, 896 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 8.25-7.21 (m, 9 H, naphthyl protons, 2 x CONH), 4.67-4.19 (m, 2 H, 3-H of the bornane system, OH), 3.7-2.26 (m, 12 H), 1.98-0.85 (m, 5 H), 1.32 and 1.30 (2 x s, 3 H, CCH_3), 1.07 (s, 3 H, CCH_3), 1.03 (s, 0.38 x 9 H, $COC(CH_3)_3$), 0.99 (s, 0.62 x 9 H, $COC(CH_3)_3$), 0.78 (2 x s, 3 H, CCH_3); MS (20°C): *m/z* (%) = 535 (1) [M^+ + H], 507 (4), 491 (4), 366 (9), 346 (6), 212 (6), 201 (3), 168 (14), 167 (11), 156 (17), 155 (53), 154 (10), 153 (19), 152 (10), 141 (11), 135 (11), 111 (11), 109 (12), 95 (17), 93 (11); HRMS ($C_{33}H_{46}N_2O_4$): calcd. 534.3458; found 534.3458.

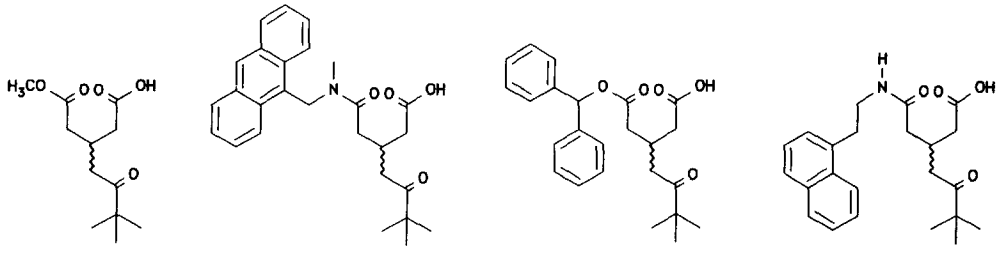
Opening of Dilactone 1 *with (1R,4S)-3-endo-Amino-2-endo-hydroxybornane* (**20**). According to GP 1, dilactone 1 (42.4 mg, 0.2 mmol) was opened using (1*R*,4*S*)-3-*endo*-amino-2-*endo*-hydroxybornane (**20**) (67.7 mg, 0.4 mmol) within 3 d at room temperature. After work-up the dilactone opening product (70.0 mg) was obtained as colourless crystals.

Amide Ester **31**. The product (70.0 mg) obtained by opening dilactone **1** with (1*R*,4*S*)-3-*endo*-amino-2-*endo*-hydroxybornane (**20**) was treated with diazomethane following GP 2 to yield 70.0 mg (0.177 mmol, 88% referring to initial dilactone **1**) of analytically pure amide ester **31** (72:28 mixture of diastereomers) as an off-white solid (mp 110°C). The ratio of diastereomers in **31** was determined by ^1H NMR analysis on the basis of the *tert*-butyl ketone singlets at δ = 1.00 and δ = 0.99: IR (KBr): ν̃ = 3385, 3346, 2956, 2875, 1742, 1704, 1635, 1519, 1478, 1439, 1368, 1307, 1167, 1146, 1096, 1068, 996, 879 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 6.27 (m, br, 1 H, CONH), 4.40 (m, 1 H, 3-H of the bornane systeme), 3.76 (m, 1 H, 2-H), 3.33 (s, 3 H, CO_2CH_3), 3.00 (m, 1 H), 2.88-1.96 (m, 8 H), 1.62-0.9 (m, 4 H, 5-, 6-H_2 of the bornane system), 1.00 (s, 0.72 x 9 H, $COC(CH_3)_3$), 0.99 (s, 0.28 x 9 H, $COC(CH_3)_3$), 0.84 (s, 3 H, CCH_3), 0.81 (s, 3 H, CCH_3), 0.76 (s, 3 H, CCH_3); MS (220°C): *m/z* (%) = 396 (3) [M^++H], 395 (3) [M^+], 380 (5), 368 (23), 367 (91), 353 (22), 352 (100), 337 (46), 283 (24), 209 (21), 168 (21), 167 (35), 153 (37), 140 (36), 135 (69), 123 (26), 109 (37), 107 (32), 95 (58); HRMS ($C_{22}H_{37}NO_5$): calcd. 395.2672; found 395.2676.

Opening of Dilactone 1 *with (1R,4S)-3-exo-Amino-2-exo-hydroxybornane* (**21**). Besides following GP 1, this reaction was perfomed also on a gram scale as detailed below: Dilactone **1** (785 mg, 3.699 mmol) and (1*R*,4*S*)-3-*exo*-amino-2-*exo*-hydroxybornane (**21**) (1.252 g, 7.397 mmol) were weighed into the reaction vessel and placed under nitrogen. Toluene (20 mL) was added and the resulting cloudy solution was stirred at room temperature. After 36 h the reaction mixture was clear, TLC control (acetone/CH_2Cl_2 2:1) indicated almost complete conversion of dilactone **1**. After a total reaction time of 60 h the solvent was removed under reduced pressure. The remaining white solid was dissolved in $CHCl_3$ (50 mL) and washed with 1N HCl (3 x 25 mL). The combined aqueous phases were backwashed once with $CHCl_3$ (20 mL). The combined organic extracts were washed with saturated aqueous NaCl (20 mL), dried over $MgSO_4$, filtered and concentrated to yield 1.401 g of the dilactone opening product as a white solid.

Amide Ester **22**. An ethereal-ethanolic solution of diazomethane was added dropwise to the product (1.401 g) obtained by opening dilactone **1** with (1*R*,4*S*)-3-*exo*-amino-2-*exo*-hydroxybornane (**21**) dissolved in $CHCl_3$ (20 mL) until its yellow colour persisted. The mixture was stirred for 30 min at room temperature, then it was concentrated to yield 1.452 g (3.667 mmol, 99% referring to initial dilactone **1**) of analytically pure amide ester **22** (78:22 mixture of diastereomers) as colourless crystals (mp 109°C). The ratio of diastereomers in **22** was determined by ^1H NMR analysis on the basis of the *tert*-butyl ketone singlets at δ = 1.00 and δ = 0.99: IR ($CHCl_3$): $\tilde{\nu}$ = 3428, 3400, 2982, 2956, 2929, 2872, 1728, 1700, 1652, 1508, 1476, 1436, 1368, 1264, 1092, 1072 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ = 6.52 (m, 1 H, CONH), 3.94 (m, 1 H, 3-H of the bornane system), 3.71 (m, 1 H, 2-H of the bornane system), 3.44 (m, br, 1 H, OH), 3.34 (s, 3 H, CO_2CH_3), 2.99 (m, 1 H), 2.79-2.15 (m, 6 H), 1.88-0.60 (m, 5 H, 4-H, 5-, 6-H_2 of the bornane system), 1.22 (s, 3 H, CCH_3), 1.00 (s, 0.78 x 9 H, $COC(CH_3)_3$), 0.99 (s, 0.22 x 9 H, $COC(CH_3)_3$), 0.98 (s, 3 H, CCH_3), 0.72 (s, 3 H, CCH_3); MS (120°C): *m/z* (%) = 396 (6) [M^++H], 395 (5) [M^+], 368 (84), 354 (32), 353 (97), 338 (38), 320 (34), 227 (67), 209 (37), 168 (32), 167 (43), 153 (46), 152 (42), 149 (32), 140 (55), 136 (76), 123 (39), 121 (30), 109 (77), 107 (62); HRMS ($C_{22}H_{37}NO_5$): calcd. 395.2672; found 395.2666. Twofold recrystallization of amide ester **22** (78:22 mixture of diastereomers) (100 mg) from acetonitrile at -18°C resulted in 11.6 mg of a highly enriched diastereomeric mixture (97.5:2.5 by ^1H NMR analysis).

Synthesis of Reference Compounds. To ensure correct assignment of chromatographic and proton resonance peaks, references for the derivatized products of dilactone opening, which had been obtained under chiral conditions (as depicted in scheme 1), were independently prepared from the racemic mono acids **32**, **33**, **34**, or **35**, represented in scheme 9.



32 **33** **34** **35**

Scheme 9. Racemic mono acids obtained by opening of dilactone **1** under achiral conditions

Racemic mono acids **32**, **33**, **34**, and **35** were obtained by opening dilactone **1** with the appropriate alcohols or amines, i.e. under achiral conditions. Subsequent coupling with chiral amines **10**, **12**, **16**, **17**, **19**, **20**, or **21**, mediated by N,N´-carbonyldiimidazole, gave the desired reference probes for compounds **23**, **24**, **26**, **28**, **30**, **31**, and **22** with diastereomeric ratios 1:1. These reference samples proved particularly useful in cases where hindered rotation around

N-CO amide bonds caused additional signal splitting in the ^1H NMR spectra, thus seriously hampering signal assignment to the diastereomers. Reproduction of physical and chromatographic data of the reference compounds is omitted since they showed no significant deviation from their asymmetrically prepared counterparts.

Mono Ester Racemate **32**. Sodium methoxide in methanol was prepared from sodium (46.0 mg, 2 mmol) and methanol (4 mL). 1 mL of this solution was added to dilactone **1** (106.1 mg, 0.5 mmol), dissolved in methanol (2 mL). The reaction mixture was stirred for 5 min at room temperature. Then the solvent was removed on the rotary evaporator to give a white solid that was dissolved in distilled water (15 mL). After acidification from pH 7 to pH 4 by means of 1N HCl, extraction was done with CH_2Cl_2 (4 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to give 102.6 mg (0.42 mmol, 84%) of analytically pure amide ester racemate **32** as a yellow oil: IR ($CHCl_3$): $\tilde{\nu}$ = 3512, 3300-2500, 2968, 2908, 2872, 1732, 1708, 1604, 1476, 1436, 1368, 1164 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, CO_2CH_3), 2.91-2.63 (m, 3 H), 2.55-2.41 (m, 4 H), 1.14 (s, 9 H, $COC(CH_3)_3$); MS (20°C): *m/z* (%) = 213 (6) [M^+-OCH_3], 188 (9), 187 (100), 169 (9), 159 (19), 155 (9), 153 (10), 128 (5), 127 (36), 113 (23), 99 (5), 95 (7), 85 (5), 74 (6), 59 (6), 57 (46), 55 (7); HRMS ($C_{11}H_{17}O_4$): calcd. 213.1127; found 213.1125.

Mono Amide Racemate **33**. Dilactone **1** (42.4 mg, 0.2 mmol) and 9-(methylaminomethyl)-anthracene (48.7 mg, 0.22 mmol) were weighed into the reaction vessel, dissolved in THF (10 mL) and stirred for 23 d at room temperature under exclusion of light. Then the reaction mixture was concentrated to a yellow foam, which was dissolved in CH_2Cl_2 (20 mL) and washed with 1N HCl (3 x 20 mL) and saturated aqueous NaCl (20 mL). After drying over $MgSO_4$, filtration and concentration 81.1 mg (0.187 mmol, 93%) of analytically pure mono amide racemate **33** were obtained as yellow crystals (mp 152°C): UV (CH_3OH): λ = 254, 347, 365, 385 nm; IR (KBr): $\tilde{\nu}$ = 3420, 3080, 3050, 2968, 2930, 2910, 2870, 1728, 1703, 1630, 1600, 1525, 1478, 1449, 1407, 1367, 1245, 1160, 1062, 992, 891, 737 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ = 12.13 (s, br, 1 H, CO_2H), 8.66 (m, 1 H), 8.45 (m, 2 H), 8.14 (m, 2 H), 7.56 (m, 4 H), 5.60 (AB-q, ^2J = 14.5, 2 H, CH_2N), 2.75-2.18 (m, 7 H), 2.57 (s, 3 H, NCH_3), 1.05 (s, 9 H, $COC(CH_3)_3$); MS (150°C): *m/z* (%) = 433 (26) [M^+], 220 (38), 206 (29), 191 (57), 178 (28), 149 (35), 110 (70), 91 (100), 71 (76); HRMS ($C_{27}H_{31}NO_4$): calcd. 433.2253; found 433.2225.

Mono Ester Racemate **34**. At -10°C a solution of diphenylcarbinol (276.4 mg, 1.5 mmol) in THF (4.5 mL) was added dropwise to sodium hydride (24.0 mg, 1 mmol) accompanied by gas evolution. The temperature was maintained for 15 min, then the cooling bath was removed and stirring was continued for another hour. The alcoholate solution thus prepared was added dropwise to a solution of dilactone **1** (106.1 mg, 0.5 mmol) in THF (3.5 mL) at 0°C. Stirring was continued for 30 min at 0°C, then the cooling bath was removed. After another hour of stirring, the solvent was evaporated under reduced pressure. Distilled water (15 mL), which had been acidified with 1N HCl to pH 2, was added to the remaining pale yellow, viscous oil, and extrac-

tion was performed using CH_2Cl_2 (4 x 20 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (EtOAc/petroleum ether 1:1) gave 93.2 mg (0.235 mmol, 47%) of mono ester racemate **34** as a pale yellow oil: UV (CH_3OH) = λ = 210, 254 nm; IR ($CHCl_3$): $\tilde{\nu}$ = 3528, 3500-3000, 3088, 3064, 3032, 2968, 2936, 2908, 2872, 1732, 1708, 1600, 1496, 1452, 1396, 1372, 1248, 1156, 1096, 1080, 980 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2): δ = 7.44-7.20 (s, 10 H, phenyl protons), 6.83 (s, 1 H, C*H*Ph_2), 2.79 (m, 1 H), 2.58 (m, 4 H), 2.43 (m, 2 H), 1.04 (s, 9 H, $COC(CH_3)_3$); MS (140°C): *m/z* (%) = 397 (1) [M^++ H], 348 (23), 289 (13), 265 (20), 210 (71), 195 (32), 181 (25), 167 (100), 166 (30), 165 (52), 152 (25), 115 (21), 91 (37); HRMS was not feasible, compound **34** was judged to be pure from its ^1H NMR spectrum.

Mono Amide Racemate **35**. A solution of 2-naphthylethylamine (89.0 mg, 0.52 mmol) in THF (1 mL) was added to dilactone **1** (99.8 mg, 0.47 mmol) in THF (7 mL). After stirring for 14 h at room temperature, the solvent was removed in vacuum. The residue was dissolved in CH_2Cl_2 (10 mL), washed with 1 N HCl (10 mL) then with saturated aqueous NaCl (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated on the rotary evaporator and in high vacuum to yield 153.4 mg (0.4 mmol, 85%) of analytically pure mono amide racemate **35** as a white solid: IR (KBr): $\tilde{\nu}$ = 3400, 3340, 1700, 1620, 1560 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.12-7.27 (m, 7 H, aromatic protons), 6.18 (m, br, 1 H, CONH), 3.63 (m, 2 H), 3.28 (m, 2 H), 2.80-2.21 (m, 7 H), 1.10 (s, 9 H, $COC(CH_3)_3$); MS (50°C): *m/z* (%) = 383 (2) [M^+], 366 (5), 327 (5), 167 (5), 155 (21), 154 (100), 141 (17), 115 (11), 105 (6), 86 (13), 84 (20), 70 (11), 61 (18), 57 (64); HRMS ($C_{23}H_{29}NO_4$): calcd. 383.2097; found 383.2097.

General Procedure for the Coupling of Racemic Mono Acids **32**, **33**, **34**, *and* **35** *with Chiral, Enantiomerically Pure Amines*. The racemic mono acid (0.1 mmol) was dissolved in CH_2Cl_2 (1.5 mL) under nitrogen and added to N,N´-carbonyldiimidazole (18 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL). Imidazolide formation was found to be complete after 1.5-3 h of stirring at room temperature by TLC control (actone/CH_2Cl_2 2:1). Then a solution of the chiral, enantiomerically pure amine (0.11 mmol) in CH_2Cl_2 (1.5 mL) was added. The reaction mixture was stirred at room temperature until TLC control indicated total conversion of the imidazolide intermediate, which took times from 12 h to 9 d. The working up procedure was the same as described for diamide **30**.

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REFERENCES AND NOTES

1. Maier, M. Group Selective Reactions. In *Organic Synthesis Highlights II*, Waldmann, H. Ed.; VCH: Weinheim, 1995; pp. 203-222.
2. Agami, C. *Bull. Soc. Chim. Fr.* **1988**, 499-507.
3. Jäger, V.; Schröter, D.; Koppenhoefer, B. *Tetrahedron* **1991**, *47*, 2195-2210; Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9-17.
4. Ohno, M.; Otsuka, M. Chiral Synthons by Ester Hydrolysis Catalyzed by Pig Liver Esterase. In *Organic Reactions*, vol. 37, Kende, A. S. Ed.; John Wiley and Sons, Inc.: New York, 1989; pp. 1-55.
5. Klibanov, A. M. *Chemtech* **1986**, 354-359.
6. See *inter alia* Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414-9418.
7. Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142-146.
8. Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem.* **1995**, *107*, 2605-2606; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2395-2396.
9. Winterfeldt, E. *Prinzipien und Methoden der stereoselektiven Synthese;* Friedr. Vieweg & Sohn: Braunschweig 1988; p. 1.
10. For opening of the thioketal derivative of a 3-ketoglutaric acid anhydride by a chiral amine with low diastereoselectivity see Kurth, M. J.; Milco, L. A.; Miller, R. B. *Tetrahedron* **1992**, *48*, 1407-1416.
11. Hoyer, W. *Studien zur chemischen Differenzierung enantiotoper Gruppen*, Universität Hannover 1990.
12. Winterfeldt, E. *Angew. Chem.* **1967**, *79*, 148; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 172.
13. Van Tamelen, E. E.; Placeway, C.; Schiemenz, G. P.; Wright, I. G. *J. Am. Chem. Soc.* **1969**, *91*, 7359-7371.
14. Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485-492.
15. Nakanishi, H.; Fujita, H.; Yamamoto, O. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 214-218.
16. Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721-727.
17. Alker, D.; Doyle, K. J.; Harwood, L. M.; McGregor, A. *Tetrahedron: Asymmetry* **1990**, *1*, 877-880.
18. Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299-1308.
19. M'Boungou-M'Passi, A.; Hénin, F.; Muzart, J.; Pète, J.-P. *Bull. Soc. Chim. Fr.* **1993**, 214-217.
20. Daniel, A.; Pavia, A. A. *Bull. Soc. Chim. Fr.* **1971**, 1060-1074.
21. Chittenden, R. A.; Cooper, G. H. *J. Chem. Soc. (C)* **1970**, 49-54.
22. Pauling, H. *Helv. Chim. Acta* **1975**, *58*, 1781-1798.
23. Stingl, K.; Martens, J. *Liebigs Ann. Chem.* **1994**, 243-250.
24. Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH: Weinheim, 1990, p. 334.
25. Günther, H. *NMR-Spektroskopie*; Thieme: Stuttgart, 1992; pp. 239-240.

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