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An alkaloid-mediated desymmetrization of *meso*-anhydrides via a nucleophilic ring opening with benzyl alcohol and its application in the synthesis of highly enantiomerically enriched β-amino acids

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Dedicated to Professor H. Schwarz on the occasion of his 60th birthday

Abstract—The cinchona alkaloid-mediated opening of prochiral cyclic anhydrides in the presence of benzyl alcohol leading to optically active hemiesters is described. Structurally diverse anhydrides are converted into their corresponding benzyl monoesters with either enantiomer being obtained with up to 99% e.e. by using quinine or quinidine as the directing additive. A simple aqueous work-up protocol permits the isolation of the products in analytically pure form and the recovery of the alkaloids almost quantitatively. These hemiesters can be converted to *N*-protected β-amino esters by means of Curtius degradation of the corresponding acyl azides. Subsequent cleavage of both protecting groups by a single reaction step leads to the free β-amino acids in excellent yields. The efficiency of this procedure is demonstrated by the short asymmetric synthesis of the fungicide *cis*-pentacin delivering the amino acid with >99.7% enantiomeric excess.

1. Introduction

The asymmetric opening of a *meso*-anhydride by a nucleophile is an efficient and versatile strategy to establish multiple stereogenic centers in a target molecule,[1] since the resulting functional groups can selectively be manipulated in further reaction steps. Therefore valuable building blocks for the synthesis of natural products or biologically active substances can be prepared in only one symmetry breaking operation starting from easily accessible substrates. Impressive examples of this include Carreira's sequence to prepare the cyclopentyl core of the axinellamines[2] and Kraft's total synthesis of a new and powerful oxamacrolide-musk odorant.[3] The interest in the development of selective methods has increased considerably within the last 5 years and along with reliable concepts using alcohols[4] or amines,[5] new approaches for the ring opening with carbon-based nucleophiles have recently been introduced by Rovis[6] and Fu.[7] With respect to the stereochemistry determining step, the existing methods can be divided into two categories: First, anhydride openings employing a *chiral* nucleophile, and second, procedures using an *achiral* nucleophile in combination with a chiral Lewis acid catalyst or a metal-free chiral mediator: Whereas the first gives diastereomers, the second only gives enantiomeric products (Fig. 1).

As chiral mediators cinchona alkaloids showed very high enantioselectivities,[8] and excellent procedures for asymmetric methanolyses of anhydrides have been developed.[9] Recently, we reported on a simple and highly enantioselective stoichiometric process, which allowed the preparation of a wide variety of structurally highly diverse mono methylesters in their pure form.[9c,d] The mediator, which is used in stoichiometric quantities, can easily be recovered from the aqueous phase by acid extraction and reused without loss of selectivity. Both ester enantiomers are available in excellent yields with up to 99% e.e. using either quinine or quinidine as the directing additive. Comparable results were subsequently obtained by Deng et al.,[9e] who applied substoi-

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chiometric quantities[10] of Sharpless's biscinchona alkaloid derivatives $(DHQ)_2AQN$ and $(DHQD)_2AQN$.[11,12] The mechanism of the alkaloid-mediated methanolysis has not yet been fully elucidated. So far two general models are discussed,[13] although neither provides a clear explanation for the cause in the distinction between the enantiotopic carbonyl groups. On the one hand, a nucleophilic catalyst is suggested in which the alkaloid attacks the anhydride with the quinuclidine nitrogen atom at one of the carbonyl groups.[8c,9d] This mechanism is similar to the one accepted for the amine-catalyzed kinetic resolution of secondary alcohols by acylation.[14] However on the other hand, the alkaloid could serve as chiral base for the methanol molecule.[8a] This proposal corresponds to the one suggested by Wynberg for the asymmetric addition of thiols to enones.[15] Evidence has been found for both models. However the kinetic isotope effect ($k_{MeOH}/k_{MeOD}=2.3$) observed by Oda et al.[8a] supports the latter, while Carloni's detection of an anhydride-quinidine adduct by mass spectroscopy[16] indicates the formation of an acylammonium-type intermediate.[17]

As an extension of our work in this field, we demonstrated the use of the methanolysis procedure in the preparation of β-amino acids such as *cis*-pentacin hydrochloride,[18] γ-amino alcohols,[19] and vicinal diamines.[20] These applications were supplemented by the synthetic work of others.[2,16,21] Herein we report an improvement in the existing procedure by using benzyl alcohols as the nucleophile for the ring opening, which substantially extends the scope of potential chemical transformations. Furthermore, we demonstrate the usefulness of this new protocol in a highly efficient asymmetric synthesis of cispentacin, which is a potent fungicide that was independently isolated a decade ago by two Japanese groups from *Bacillus cereus* and *Streptomyces setonii*,[22] and (–)-2-aminocyclobutane-1-carboxylic acid, which has recently been used for the synthesis and structural investigation of a conformationally constrained β-dipeptide.[23]

2. Results and discussion

In our previous approach towards cispentacin, which involved the *meso*-anhydride opening with methanol as nucleophile, we observed epimerization of the amino ester during its saponification. Consequently, a mixture of diastereomeric products was obtained.[18] The problem was solved by an acidic hydrolysis, which yielded the hydrochloric salt of the fungicide. However, in this case an additional ion exchange chromatography was required to liberate the unprotected amino acid.[36b] In order to circumvent these difficulties we have now examined the use of other alcohols as nucleophiles in the quinidine-mediated anhydride opening, which lead to esters that can easily be cleaved under very mild conditions.

As demonstrated earlier, the steric properties of a nucleophile have a pronounced effect on the rate and selectivity of the anhydride opening. Thus, almost no reaction took place with more sterically hindered alcohols such as 2-propanol, even when they were used as solvent.[9d,19] Ethanol as the nucleophile exhibited a significantly lower reactivity and selectivity when compared to methanol.[8a] Accordingly, using anhydride **1** as the model substrate, the reaction time had to be increased from 60 to 108 h for achieving complete conversion when methanol was substituted by ethanol as the nucleophile (Table 1, entry 2). On the other hand, 2,2,2-trifluoroethanol showed a considerable reaction rate, but gave a product that was racemic (entry 3). This result was analogous to the findings by Oda, who found a significant decrease in e.e.[8a] It contrasted, however, the observations made by Deng in studies of the openings of monosubstituted succinic anhydrides. There, higher enantiomeric excesses were achieved when the fluorinated alcohol was used as the nucleophile.[9f] Since the irreversible Pd(0)-catalyzed transfer of allyl to weakly basic morpholine offers the possibility of a mild cleavage of allylic esters,[24] the synthesis of **5** with 97% e.e. (Table 1, entry 4) already fulfilled the initially demanded criteria. However, taking into account the potentially tedious product purification in an amino acid synthesis this sequence appeared unsatisfactory.[25] We therefore decided to focus our attention on the establishment of a benzyl ester functionality. The initial results proved promising. Thus, using benzyl alcohols as the nucleophile, hemiesters **7** and **8** were obtained in analytically pure form with 97% e.e. and in high yields (Table 1, entries 6–8). In contrast to the nucleophiles described so far, the required excess of the alcohol could not completely be removed in vacuo after terminating the reaction. Nevertheless, the preparative advantage of a simple workup without chromatographic product purification was maintained for most products. Thus, an acidic wash permitted the recovery of the alkaloid and a subsequent

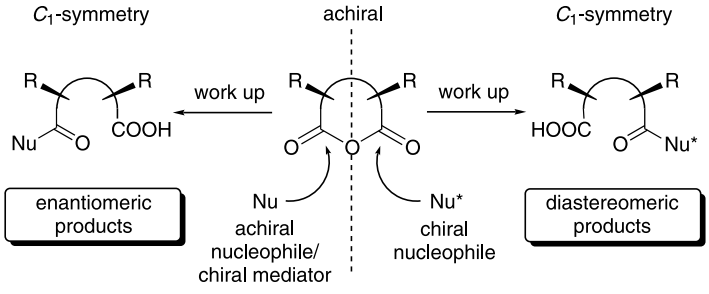
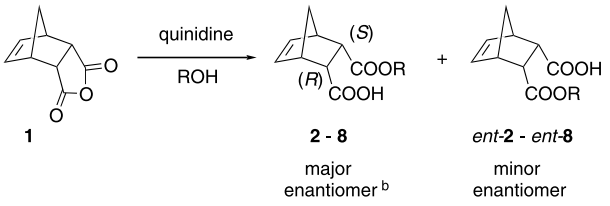


Figure 1. Stereoselective desymmetrization of *meso*-anhydrides by nucleophilic ring opening.

Table 1. Quinidine-mediated opening of anhydride **1** using different alcohols[a]



Entry	Alcohol	Hemiester	E.e. (%)[c]	Yield (%)
1	Methanol	**2**	99	99
2	Ethanol	**3**	89	97[d]
3	2,2,2-Trifluoro-ethanol	**4**	Rac.	96
4	Allyl alcohol	**5**	97	97
5	Propargyl alcohol	**6**	79	97
6	Benzyl alcohol	**7**	97	92
7	Benzyl alcohol	*ent*-**7**[e]	96	93
8	*p*-Anisyl alcohol	**8**	97	93

[a] All reactions were performed at −55°C for 60 h using 1.1 equiv. of quinidine and 3.0 equiv. of alcohol in a toluene/CCl_4 mixture (1:1), 0.2 M solution related to anhydride.

[b] For determination of the absolute configuration, see text and Ref. 9d.

[c] Determined by GC-analysis of the corresponding lactone using a chiral stationary phase.

[d] Complete conversion was only achieved after 108 h.

[e] Quinine was used as chiral mediator.

mild basic extraction removed the remaining benzyl alcohol. Furthermore, benzyl hemiester **7** nicely crystallized from ether, allowing the enantiomeric excess to be increased from a single recrystallization to >99% in only a few hours. Diastereomeric quinine, which can be considered as a pseudo-enantiomer of quinidine, generated *ent*-**7** with 96% e.e. The opening with *p*-anisyl alcohol ocurred analogously and gave the product with 97% e.e. in 93% yield (Table 1, entry 8).

The ease of the benzyl ester deprotection by simple hydrogenation performed after derivatization reactions broadens the applicability of the alkaloid-mediated anhydride opening favourably and encouraged us to evaluate the scope of the benzyl alcoholysis. These results are summarized in Table 2.

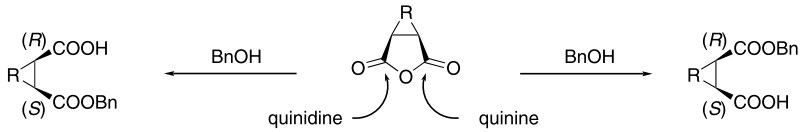
Under the conditions optimized in our primary investigation,[9c] a large variety of bicyclic and tricyclic anhydrides were opened with benzyl alcohol to give products in high yields and with impressive enantioselectivities (up to 99% e.e.). In general, quinidine-mediated ring openings furnished monoesters with slightly higher enantiomeric excesses in comparison to the quinine reactions. To our surprise, the difference in enantioselectivity observed in the products was rather low using benzyl alcohol as a nucleophile. For example, both benzyl ester enantiomers derived from oxanorbornene anhydride **25** were formed in a highly enantioselective manner (entry 9). In contrast, the corresponding methanolysis gave products with 18% e.e. difference.[9d] Also the yields of **26** and *ent*-**26** were significantly higher than those of products which were obtained from the opening of the same starting material with methanol. This is due to a lower water solubility of the benzyl hemiesters, which results in a reduced loss of product during the aqueous workup. Since such oxatricyclic molecules are known to react with basic reagents,[26] the second extraction procedure was omitted and the products purified by chromatography (entries 9 and 10). The cleavage of the oxygen bridge offers an access to carba-sugar derivatives,[26a] and investigations for the development of asymmetric syntheses involving the alkaloid-mediated anhydride opening are currently in progress.

The enantiomeric excesses of the benzyl esters were determined by GC analysis of the appropriate lactones, which were obtained by selective reduction of the ester group with $LiBEt_3H$ followed by acid-catalyzed lactonization.[4a] Since we had already established the absolute configurations of the methanolysis products, the retention times of the lactones derived from these methyl esters permitted a direct assignment also for the benzyl analogues. In all cases the stereochemical outcome of the desymmetrization was uniform: the quinidine-mediated ring opening of anhydrides generated the ester function at the carbonyl group indicated in the scheme of Table 2. For the anhydrides containing unsubstituted all-carbon backbones, this is the *pro-S*-carbonyl group; due to the reversal of the CIP-priorities it is the *pro-R*-carbonyl group of anhydrides **9**, **25** and **27**. In the same manner quinine always exhibited the opposite selectivity. Due to this stereoselection rule being strictly valid for a wide range of substrates,[9d,18a] the absolute configurations of other alcoholysis products become highly predictable.

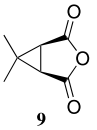
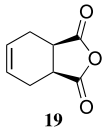
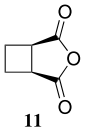
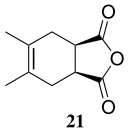
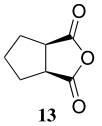
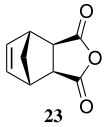
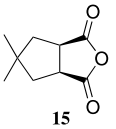
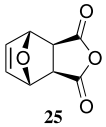
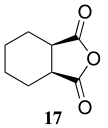
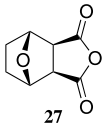
In the methanolysis reaction, the highest enantiomeric excesses were achieved with a solvent system consisting of a 1:1 mixture of toluene and CCl_4. However, combinations of solvents without the potentially harmful halogenated solvent[27] were also applicable and gave products with high e.e.[4c,19] We now find that with benzyl alcohol acting as a nucleophile, the anhydride openings occured with almost the same enantioselectivities and yields in pure toluene, with the only difference being that the quinine-mediated alcoholyses required higher concentrations. The largest difference in enantioselectivity between reactions performed in mixtures of toluene/CCl_4 (Table 3, entry 2) and pure toluene (Table 2, entry 1) was Δe.e. = 3% for ester *ent*-**10**. In some cases, avoiding the use of CCl_4 led to an even slightly higher enantiomeric excess (Table 3, entries 3 and 5).

Next, we selected representative benzyl monoesters to demonstrate that they are valuable intermediates for the synthesis of highly enantiomerically enriched β-

Table 2. Quinidine- and quinine-mediated opening of various meso-anhydrides with benzyl alcohol[a]



(*S*)-benzyl hemiester **B** [b] anhydride **A** (*R*)-benzyl hemiester *ent*-**B** [b]

Entry	Anhydride	Quinidine-Mediated			Quinine-Mediated			Entry	Anhydride	Quinidine-Mediated			Quinine-Mediated		
		Hemi-ester	E.e. [%][c]	Yield [%]	Hemi-ester	E.e. [%][c]	Yield [%]			Hemi-ester	E.e. [%][c]	Yield [%]	Hemi-ester	E.e. [%][c]	Yield [%]
1	 **9**	**10**	92	95	*ent*-**10**	88	94	6	 **19**	**20**	94	84	*ent*-**20**	95	84
2	 **11**	**12**	93	90	*ent*-**12**	90	85	7	 **21**	**22**	98	88	*ent*-**22**	97	87
3	 **13**	**14**	97	93	*ent*-**14**	95	89	8	 **23**	**24**	96	95	*ent*-**24**	92	81
4	 **15**	**16**	97	78[d]	*ent*-**16**	95	83[d]	9	 **25**	**26**	99	84[d]	*ent*-**26**	94	77[d]
5	 **17**	**18**	95	88	*ent*-**18**	93	84	10	 **27**	**28**	96	79[d]	*ent*-**28**	90	85[d]

[a] All reactions were performed at −55°C for 60 h using 1.1 equiv. of alkaloid and 3.0 equiv. of benzyl alcohol in a toluene/CCl_4-mixture (1:1); for quinidine: 0.2 M with respect to the anhydride, for quinine: 0.05 M.

[b] For anhydrides containing unsubstituted all-carbon backbones (see text).

[c] Determined by GC-analysis of the corresponding lactones using a chiral stationary phase.

[d] After chromatographic purification (see experimental section).

Table 3. Opening of *meso*-anhydrides in toluene as solvent[a]

Entry	Anhydride	Quinidine-mediated			Quinine-mediated		
		Hemiester	E.e. (%)[b]	Yield (%)	Hemiester	E.e. (%)[b]	Yield (%)
1	**1**	**7**	96	84	*ent*-**7**	95	90
2	**9**	**10**	90	93	*ent*-**10**	85	86
3	**11**	**12**	95	94	*ent*-**12**	90	90
4	**13**	**14**	95	94	*ent*-**14**	94	90
5	**17**	**18**	96	85	*ent*-**18**	93	86

[a] All reactions were performed at −55°C for 60 h using 1.1 equiv. of alkaloid and 3.0 equiv. of benzyl alcohol; for quinidine: in a 0.2 M solution related to anhydride, for quinine: 0.1 M.

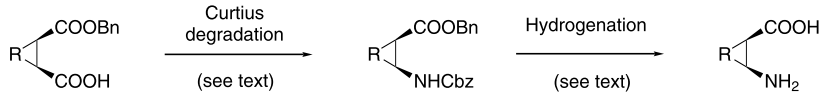
[b] Determined by GC-analysis of the corresponding lactones using a chiral stationary phase.

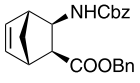
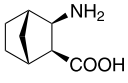
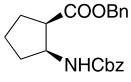
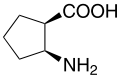
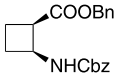
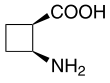
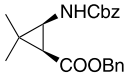
amino acids.[28] The increasing interest in such cyclic β-amino acids[29] results on the one hand from the fact that many of these compounds show antibiotic, antifungal, cytotoxic or other important biological properties in free form or as part of peptidic products.[25,29,30] On the other hand Gellman's reports on oligopeptidic *trans*-2-aminocycloalkane carboxylic acid chains, which can fold into stable helical structures,[31] raised the demand of efficient synthetic routes to β-amino acid derivatives. Furthermore, cyclic β-amino acids are of considerable significance in synthetic organic chemistry for the preparation of pharmacologically active heterocyclic products.[29,32] For the synthesis of *N*-Cbz protected β-amino acid benzyl esters, the corresponding dicarboxylic monoesters were activated by treatment with ethyl chloroformate and triethylamine. Addition of an aqueous solution of sodium azide afforded crude acyl azides, which were dissolved in benzene and subjected to thermal rearrangement. After removal of the solvent, addition of the benzyl alcohol to a methylene chloride solution of the resulting isocyanates in the presence of triethylamine gave the desired amino ester derivatives without purification of any of the intermediates.[18] Finally, the ester and the carbamate protecting groups were removed in a single step by a simple hydrogenation, delivering the free β-amino acids in excellent yields (Table 4).

The Pd/C-catalyzed deprotection step, which was performed at 1 atm hydrogen, required a reaction time of 1–2 h until complete conversion occurred (monitored by TLC). While carbon–carbon double bonds in substrates with a cyclohexene backbone do not react under these conditions,[18b,33] hydrogenation of the norbornene amino ester **29** delivered the saturated amino acid **30** (Table 4, entry 1). Although quite expensive, racemic **30** is commercially available and was recently used in a Ugi four-center three-component reaction to achieve the appropriate β-lactams.[34]

As indicated by entry 2 in Table 4 the application of this new protocol resulted in a simplified asymmetric synthesis of cispentacin **32**,[35] an antifungal antibiotic that was enantioselectively prepared first by Davies in 1993.[36] The enantiomeric ratio of 97:3 was confirmed by HPLC analysis of the corresponding amino ester **31**, using a racemic sample of this compound as reference. Recrystallization of **31** increased the e.e. to >99.7%.

Table 4. Preparation of protected and unprotected alicyclic β-amino acids **29**–**35**[a]



Entry	Mono-Benzyl Ester[b]	β-Amino Ester	E.e. [%][c]	Yield [%]	$[\alpha]^{25}_{D}$ (*c*, $CHCl_3$)	β-Amino Acid	Yield [%]	$[\alpha]^{25}_{D}$ (*c*, H_2O)
1	**24** (95% e.e.)	 **29**	93	72	+17.4 (2.63)	 **30**	97	−8.0 (1.40)
2	*ent*-**14** (94% e.e.)	 **31**	94[d]	77	−41.2 (1.83)	 **32**	98	−10.1 (2.81)
3	*ent*-**12** (93% e.e.)	 **33**	93	74	−61.6 (5.00)	 **34**	93	−80.0 (1.00)
4	**10** (92% e.e.)	 **35**	19	70	−7.3 (5.00)	—	—	—

[a] Reagents and conditions; for Curtius degradation: (*i*) ClCOOEt, Et_3N, THF, −20 °C; (*ii*) aq. NaN_3, −10 °C to r.t.; (*iii*) benzene, 80°C; (*iv*) BnOH, Et_3N, CH_2Cl_2, 40°C; for hydrogenation: see text and experimental part.

[b] The e.e.-values given in parentheses refer to the ones of the mono-benzyl esters obtained by the asymmetric opening of the corresponding anhydrides on a 15 mmol scale.

[c] Determined by HPLC-analysis using a chiral stationary phase.

[d] Recrystallization furnished an increase on >99.7 e.e. (HPLC-analysis).

In the first synthesis of the optically active cyclobutane amino acid **34**, Ortuño et al. used the methyl ester analogue of *ent*-**12** as a starting material, which was prepared by pig liver esterase-catalyzed chemoselective hydrolysis of the corresponding *meso*-diester.[23] The subsequent Curtius rearrangement afforded the amino methyl ester equivalent to **33**, whose saponification required particularly mild reaction conditions due to its tendency to epimerize. Finally, hydrolysis and hydrogenation led to the highly hygroscopic free amino acid **34** with 91% e.e. in 73% yield. It is noteworthy that the latter two reactions gave products, which were unsuitable for microanalysis.[23b] In light of these results, the reaction sequence for the preparation of **34** presented in Table 4 reveals a considerable improvement in terms of product purity, enantioselectivity and yield. Since the starting material used in both routes (*cis*-cyclobutane-1,2-dicarboxylic diacid) is rather expensive, the latter criterion (20% increase in yield) is particularly noteworthy.

The results shown in Table 4 were obtained from reactions towards amino acids performed on a 15 mmol laboratory scale. However, due to the ease of all the synthetic steps and the accessibility of the substrates, larger quantities are just as easily manageable. Only in a single case, the conversion of hemiester **10**, did we encounter difficulties. These were presumably due to the donor-acceptor substituted cyclopropane core of the corresponding β-amino acid which is prone to undergo rapid ring opening reactions.[37] Although the Curtius degradation has frequently been applied with such three-membered cyclic systems,[23b,37d,38] **35** was only obtained with a low e.e. (entry 4). Most likely, this partial racemization proceeded via an open-chain intermediate, which then underwent a stereospecific ring closure (as revealed by NMR spectroscopy). The instability of the three-membered ring also became apparent in the attempted hydrogenolytic deprotection of **35** to give the free amino acid. Even in the presence of HCl the desired product was not obtained and the only identifiable product (NMR spectroscopy) was the corresponding ring-opened achiral γ-amino acid. Along these lines another interesting observation was made in the hydrogenolytic deprotection of **33**. In this case, the corresponding free amino acid **34** was obtained in high yield, when the hydrogenation was performed under standard conditions. However, extending the reaction time to 12 h also led to C–C bond cleavage. Thus, with this substrate, the deprotection was substantially faster than the ring-opening of the cycloalkyl backbone allowing us to isolate the desired cyclobutane amino acid in high yield.

In conclusion, we have demonstrated that the desymmetrization of easily accessible *meso*-anhydrides by cinchona alkaloid-mediated opening with benzyl alcohol is applicable to a variety of structurally different substrates and leads to the corresponding optically active hemiesters with high enantioselectivities (up to 99% e.e.). A simple reaction protocol has been developed which allows the synthesis of either enantiomer selectively, generally without the additional need of purification of the resulting benzyl monoester by chromatography or recrystallization. Finally, we have described the transformation of such hemiesters into optically active β-amino acids through a reaction sequence involving a Curtius degradation as a key step. Their complete deprotection can be obtained in a single step by simple hydrogenation enabling the isolation of rather sensitive products. Currently, we are focusing our efforts on the application of this improved desymmetrization protocol toward the synthesis of β-peptides and new diamine ligands for asymmetric catalysis and highly organized pseudopeptidic systems.

3. Experimental

3.1. General information

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. Toluene and THF were distilled from sodium benzophenone ketyl radical, CH_2Cl_2 from CaH_2 under Ar. All other solvents were reagent grade and used as received. Unless otherwise noted all reactions were carried out under argon using standard Schlenk and vacuum line techniques. For the determination of the enantiomeric ratios of the opening products, see Ref. 9d. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 300 or Inova 400 spectrometer and were recorded relative to TMS as internal standard. Mass spectra were measured on a Finnigan SSQ 7000 instrument or on a Hewlett Packard GCMS apparatus-system (Column HP-5 MS, 30 m×0.25 mm×0.25 μm; Mass selective Detector 5973). HPLC analysis was performed using a Chiralpak AD column, 4.6×250 mm, $\lambda = 254$ nm. Melting points were measured in open glass capillaries with a Büchi apparatus and are uncorrected. Optical rotations were determined on a Perkin Elmer P241 instrument at rt (ca. 20°C) using solvents of Merck UVASOL-quality. Infrared spectra were recorded on a Perkin Elmer 1760 FT apparatus. All microanalyses were conducted on a Heraeus CHN RAPID instrument at the Institut für Organische Chemie der RWTH Aachen.

3.2. General procedure for the alkaloid-mediated ring opening of cyclic *meso*-anhydrides GP-1

Benzyl alcohol (0.310 mL, 3.0 mmol) was added dropwise to a stirred suspension of the anhydride (1.0 mmol) and the alkaloid (0.357 g, 1.1 mmol) in a 1:1 mixture of toluene and tetrachloromethane (5 mL in the case of quinidine, 20 mL in the case of quinine) at −55°C under argon. The reaction mixture was stirred at this temperature for 60 h. During this period the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuo to dryness and the resulting residue dissolved in ether (10 mL). The solution was washed with 2 M HCl (3×3 mL), followed by extraction of the aqueous phase with ether (5×5 mL) and the combined organic layers extracted with a saturated solution of sodium carbonate (5×15 mL). The resulting aqueous phase was washed with ether (1×25

mL) in order to remove the traces of benzyl alcohol, acidified with conc. HCl, extracted with CH_2Cl_2 (5×20 mL) and the organic layer dried over $MgSO_4$, filtered and concentrated providing the corresponding hemiester. Analogously, the quinidine- and quinine-mediated opening was performed in pure toluene using 5 or 10 mL solvent/mmol anhydride, respectively. The results are summarized in Table 3. To recover the alkaloid, the acidic aqueous phase was neutralized with Na_2CO_3 and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and filtered. Evaporation of the solvent yielded the alkaloid almost quantitatively.

3.2.1. (2*R*,3*S*)-3-*endo*-Ethoxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid 3. Compound (2*R*,3*S*)-**3** was obtained from the quinidine opening of anhydride **1** in the presence of ethanol in 97% yield: mp 71°C (rac), colorless oil (en) lit.[39] mp 74–75°C (rac); $[\alpha]_D^{25}=-5.8$ (*c* 3.13, $CHCl_3$); e.e. = 89%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.20$ (br t, $J=7.2$ Hz, 3H), 1.34 (br d, $J=8.6$ Hz, 1H), 1.48 (dt, $J=1.7$, 8.6 Hz, 1H), 3.17–3.18 (m, 2H), 3.27 (dd, $J=2.7$, 10.1 Hz, 1H), 3.33 (dd, $J=3.0$, 10.1 Hz, 1H), 4.03 (dq, $J=7.1$, 10.8 Hz, 1H), 4.07 (dq, $J=7.1$, 10.8 Hz, 1H), 6.21 (dd, $J=3.0$, 5.7 Hz, 1H), 6.31 (dd, $J=3.0$, 5.7 Hz, 1H), 10.54 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=14.3$, 46.4, 46.8, 48.3, 48.7, 49.0, 60.6, 66.6, 134.6, 135.7, 172.6, 179.0; IR (KBr): 2980, 1736, 1701, 1259, 1215, 1181 cm^{-1}; EI-MS: $m/z=210$ (M^+, 1), 192 (5), 165 (24), 164 (11), 145 (36), 137 (13), 127 (9), 119 (21), 99 (22), 91 (22), 66 (100), 65 (11). Anal. calcd for $C_{11}H_{14}O_4$ (210.23): C, 62.85; H, 6.71. Found: C, 62.83; H, 6.71.

3.2.2. (2*R*,3*S*)-3-*endo*-(2,2,2-Trifluorethoxycarbonyl)-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid 4. Compound (2*R*,3*S*)-**4** was obtained from the quinidine opening of anhydride **1** in the presence of 2,2,2-trifluoroethanol in 96% yield: mp 87.5°C (rac); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.37$ (d, $J=8.6$ Hz, 1H), 1.54 (dt, $J=1.7$, 8.6 Hz, 1H), 3.22 (br d, $J=10.1$ Hz, 2H), 3.25 (dd, $J=3.0$, 10.1 Hz, 1H), 3.41 (dd, $J=3.2$, 10.1 Hz, 1H), 4.23 (dq, $J=8.6$, 12.6 Hz, 1H), 4.47 (dq, $J=8.6$, 12.6 Hz, 1H), 6.21 (dd, $J=3.0$, 5.4 Hz, 1H), 6.34 (dd, $J=3.0$, 5.4 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=46.1$, 46.7, 47.7, 48.2, 48.8, 60.4 (q, $J=36.5$ Hz), 121.2 (q, $J=277.0$ Hz), 134.5, 135.6, 171.0, 178.5; IR (KBr): 2981, 1757, 1707, 1417, 1312, 1277, 1260, 1230, 1212, 1168, 1088 cm^{-1}; EI-MS: $m/z=164$ (12), 120 (12), 119 (9), 92 (36), 91 (100). Anal. calcd for $C_{11}H_{11}F_3O_4$ (264.20): C, 50.01; H, 4.20. Found: C, 50.28; H, 4.30.

3.2.3. (2*R*,3*S*)-3-*endo*-Allyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid 5. Compound (2*R*,3*S*)-**5** was obtained from the quinidine opening of anhydride **1** in the presence of allyl alcohol in 97% yield: mp 84°C (rac), colorless oil (en), lit.[40] mp 83°C (rac); $[\alpha]_D^{25}=-1.7$ (*c* 3.20, $CHCl_3$); e.e. = 97%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.34$ (d, $J=8.6$ Hz, 1H), 1.49 (dt, $J=1.7$, 8.6 Hz, 1H), 3.18 (br s, 2H), 3.28–3.36 (m, 2H), 4.45 (ddt, $J=1.5$, 5.9, 13.1 Hz, 1H), 4.54 (ddt, $J=1.5$, 5.9, 13.1 Hz, 1H), 5.17–5.22 (m, 1H), 5.25–5.32 (m, 1H), 5.87 (ddt, $J=5.9$, 10.4, 16.3 Hz, 1H), 6.21 (dd, $J=3.0$, 5.5 Hz, 1H), 6.31 (dd, $J=3.0$, 5.5 Hz, 1H), 10.67 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=46.4$, 46.8, 48.3, 48.6, 49.0, 65.5, 118.5, 132.4, 134.6, 135.7, 172.3, 178.9; IR (KBr): 2980, 1736, 1703, 1342, 1261, 1216, 1173, 1153, 930 cm^{-1}; EI-MS: $m/z=222$ (M^+, 2), 204 (3), 176 (6), 165 (7), 157 (31), 139 (16), 137 (13), 119 (14), 99 (18), 91 (19), 66 (100), 65 (4). Anal. calcd for $C_{12}H_{14}O_4$ (229.24): C, 64.85; H, 6.35. Found: C, 64.79; H, 6.35.

3.2.4. (2*R*,3*S*)-3-*endo*-Propargyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid 6. Compound (2*R*,3*S*)-**6** was obtained from the quinidine opening of anhydride **1** in the presence of propargyl alcohol in 97% yield: mp 115°C (rac), colorless oil; $[\alpha]_D^{25}=-1.4$ (*c* 3.06, $CHCl_3$); e.e. = 79%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.34$ (d, $J=8.6$ Hz, 1H), 1.50 (dt, $J=1.7$, 8.6 Hz, 1H), 2.47 (t, $J=2.5$ Hz, 1H), 3.19–3.21 (m, 2H), 3.30 (dd, $J=3.0$, 10.1 Hz, 1H), 3.37 (dd, $J=3.2$, 10.1 Hz, 1H), 4.53 (dd, $J=2.5$, 15.8 Hz, 1H), 4.67 (dd, $J=2.5$, 15.8 Hz, 1H), 6.21 (dd, $J=3.0$, 5.7 Hz, 1H), 6.34 (dd, $J=3.0$, 5.7 Hz, 1H), 10.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=46.3$, 46.9, 48.1, 48.4, 49.0, 52.1, 75.1, 77.9, 134.6, 135.8, 171.8, 178.5; IR (KBr): 3284, 1744, 1705, 1344, 1260, 1216, 1169, 1073 cm^{-1}; EI-MS: $m/z=220$ (M^+, 1), 175 (3), 165 (5), 155 (22), 137 (13), 119 (12), 99 (20), 91 (16), 66 (100). Anal. calcd for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.24; H, 5.60.

3.2.5. (2*R*,3*S*)-3-*endo*-Benzyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid 7. Compound (2*R*,3*S*)-**3** was obtained from the quinidine opening of anhydride **1** in 92% yield as a white solid: mp 120°C (rac), 92°C (en); $[\alpha]_D^{25}=+8.0$ (*c* 1.95, $CHCl_3$); e.e. = 97%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.32$ (d, $J=8.5$ Hz, 1H), 1.47 (dt, $J=1.7$, 8.5 Hz, 1H), 3.18 (br s, 2H), 3.30–3.32 (m, 2H), 5.00 (AB-system, $J=12.4$ Hz, 2H), 6.21 (dd, $J=3.0$, 5.7 Hz, 1H), 6.28 (dd, $J=3.0$, 5.7 Hz, 1H), 7.27–7.36 (m, 5H), 9.50 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=46.4$, 46.8, 48.4, 48.6, 49.0, 66.7, 128.4, 128.6, 128.7, 134.7, 135.7, 136.2, 172.5, 178.8; IR (KBr): 3034, 2989, 2944, 1747, 1701, 1436, 1340, 1262, 1226, 1173, 1143, 1028 cm^{-1}; EI-MS: $m/z=272$ (M^+, 2), 254 (3), 226 (3), 181 (58), 163 (3), 137 (5), 119 (2), 91 (100), 66 (20). Anal. calcd for $C_{16}H_{16}O_4$ (272.30): C, 70.57; H, 5.92. Found: C, 70.55; H, 6.01.

3.2.6. (2*S*,3*R*)-3-*endo*-Benzyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*endo*-carboxylic acid *ent*-7. Compound (2*S*,3*R*)-**7** was obtained from the quinine opening of anhydride **1** in 93% yield as a white solid; $[\alpha]_D^{25}=-7.4$ (*c* 1.00, $CHCl_3$); e.e. = 96%.

3.2.7. (2*R*,3*S*)-3-*endo*-(4-Methoxy-benzyloxycarbonyl)-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid 8. Compound (2*R*,3*S*)-**8** was obtained from the quinidine opening of anhydride **1** in the presence of *p*-anisyl alcohol in 93% yield: mp 94°C (rac), colorless oil (en); $[\alpha]_D^{25}=+7.3$ (*c* 3.06, $CHCl_3$); e.e. = 97%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.32$ (br d, $J=8.6$ Hz, 1H), 1.48 (dt, $J=1.7$, 8.6 Hz, 1H), 3.18 (br d, $J=8.9$ Hz, 2H), 3.31-

3.32 (m, 2H), 3.79 (s, 3H), 4.95 (AB-system, $J=12.1$ Hz, 2H), 6.22 (dd, $J=3.0$, 5.4 Hz, 1H), 6.28 (dd, $J=3.0$, 5.4 Hz, 1H), 6.84–6.89 (m, 2H), 7.22–7.27 (m, 2H), 10.25 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=46.4$, 46.8, 48.4, 48.6, 49.0, 55.5, 66.5, 114.1, 128.3, 130.4, 134.6, 135.8, 159.8, 172.5, 178.8; IR (KBr): 2952, 1733, 1706, 1516, 1265, 1215, 1165, 1073 cm^{-1}; EI-MS: $m/z=302$ (M^+, 8), 121 (100), 91 (6). Anal. calcd for $C_{17}H_{18}O_5$ (302.32): C, 67.54; H, 6.00. Found: C, 67.49; H, 6.08.

3.2.8. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-3,3-dimethylcyclopropane-1-carboxylic acid 10. Compound (1*S*,2*R*)-**10** was obtained from the quinidine opening of anhydride **9** in 95% yield: mp 79°C (rac), colorless oil (en); $[\alpha]_D^{25}=-1.8$ (*c* 1.58, $CHCl_3$); e.e. = 92%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.26$ (s, 3H), 1.41 (s, 3H), 1.98 (AB-system, $J=8.8$ Hz, 2H), 5.15 (AB-system, $J=12.1$ Hz, 2H), 7.30–7.38 (m, 5H), 10.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.6$, 27.7, 28.4, 33.1, 33.1, 67.4, 128.6, 128.7, 128.8, 135.6, 170.7, 174.1; IR (KBr): 3042, 2961, 2881, 1741, 1691, 1502, 1445, 1257, 1191, 1097 cm^{-1}; EI-MS: $m/z=248$ (M^+, 7), 230 (1), 202 (1), 142 (5), 141 (3), 113 (19), 108 (7), 95 (4), 91 (100), 67 (3), 65 (6). Anal. calcd for $C_{14}H_{16}O_4$ (272.30): C, 67.73; H, 6.50. Found: C, 67.67; H, 6.54.

3.2.9. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-3,3-dimethylcyclopropane-1-carboxylic acid *ent*-10. Compound (1*R*,2*S*)-**10** was obtained from the quinine opening of anhydride **9** in 94% yield as a colorless oil: $[\alpha]_D^{25}=+1.7$ (*c* 1.00, $CHCl_3$); e.e. = 88%.

3.2.10. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-cyclobutane-1-carboxylic acid 12. Compound (1*R*,2*S*)-**12** was obtained from the quinidine opening of anhydride **11** in 90% yield: mp 72.5°C (rac), colorless oil (en), lit.[41] mp 66°C (rac); $[\alpha]_D^{25}=-10.9$ (*c* 1.75, MeOH); e.e. = 93%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.17$–2.28 (m, 2H), 2.36–2.45 (m, 2H), 3.41–3.49 (m, 2H), 5.11 (AB-system, $J=12.1$ Hz, 2H), 7.26–7.36 (m, 5H), 10.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=22.4$, 22.5, 40.8, 40.9, 66.9, 128.4, 128.5, 128.7, 135.9, 173.1, 179.3; IR (KBr): 2955, 1744, 1700, 1336, 1307, 1242, 1189, 1055 cm^{-1}; EI-MS: $m/z=234$ (M^+, 7), 216 (4), 188 (1), 127 (30), 110 (47), 108 (91), 99 (16), 91 (100), 82 (13), 77 (9), 66 (19), 55 (34). Anal. calcd for $C_{13}H_{14}O_4$ (234.25): C, 66.66; H, 6.02. Found: C, 66.72; H, 6.02.

3.2.11. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-cyclobutane-1-carboxylic acid *ent*-12. Compound (1*S*,2*R*)-**12** was obtained from the quinine opening of anhydride **11** in 85% yield as a colorless oil: $[\alpha]_D^{25}=+11.5$ (*c* 1.25, MeOH); e.e. = 90%.

3.2.12. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-cyclopentane-1-carboxylic acid 14. Compound (1*R*,2*S*)-**14** was obtained from the quinidine opening of anhydride **13** in 93% yield: mp 37.5°C (rac), colorless oil (en); $[\alpha]_D^{25}=+0.6$ (*c* 1.65, $CHCl_3$), +1.8 (*c* 0.94, MeOH); e.e. = 97%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.56$–1.71 (m, 1H), 1.79–2.11 (m, 5H), 3.03–3.14 (m, 2H), 5.08 (AB-system, $J=12.4$ Hz, 2H), 7.25–7.37 (m, 5H), 11.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=24.0$, 29.0, 47.1, 66.1, 66.7, 128.4, 128.4, 128.7, 136.1, 173.9, 180.7; IR (Capillary): 2961, 1736, 1706, 1183 cm^{-1}; EI-MS: $m/z=248$ (M^+, 8), 230 (6), 202 (9), 141 (46), 108 (100), 107 (89), 95 (19), 91 (87), 67 (27), 65 (16). Anal. calcd for $C_{14}H_{16}O_4$ (248.27): C, 67.73; H, 6.50. Found: C, 66.62; H, 6.58.

3.2.13. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-cyclopentane-1-carboxylic acid *ent*-14. Compound (1*S*,2*R*)-**14** was obtained from the quinine opening of anhydride **13** in 89% yield as a colorless oil; $[\alpha]_D^{25}=-1.3$ (*c* 0.90, MeOH); e.e. = 95%.

3.2.14. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-4,4-dimethylcyclopentane-1-carboxylic acid 16. Compound (1*R*,2*S*)-**16** was obtained from the quinidine opening of anhydride **15** according to GP-1 with a modified work-up: the crude product, obtained after washing the organic layer with 2 M HCl and evaporation of the solvent, was purified by column chromatography (pentane:EtOAc, 6:1 to 2:1) to give the hemiester **16** in 78% yield: mp 61°C (rac), colorless oil (en); $[\alpha]_D^{25}=+4.2$ (*c* 1.00, MeOH); e.e. = 97% [GC-analysis of the lactone:[9d] Lipodex E, $t_1=68.2$, $t_2=70.0$ (major)]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.90$ (s, 3H), 1.03 (s, 3H), 1.69–1.76 (dd, $J=8.2$, 13.4 Hz, 2H), 1.82–1.89 (dd, $J=8.4$, 11.4 Hz, 2H), 3.11–3.24 (m, 2H), 4.99 (AB-system, $J=12.4$ Hz, 2H), 7.20–7.30 (m, 5H), 9.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=29.0$, 29.7, 38.8, 43.7, 46.3, 66.8, 128.4, 128.5, 128.7, 136.1, 174.2, 180.8; IR (KBr): 2958, 2930, 1736, 1702, 1285, 1207 cm^{-1}; EI-MS: $m/z=276$ (M^+, 4), 258 (5), 230 (6), 169 (45), 123 (10), 108 (100), 107 (16), 95 (31), 91 (67), 65 (10). Anal. calcd for $C_{16}H_{20}O_4$ (276.33): C, 69.54; H, 7.30. Found: C, 69.53; H, 7.19.

3.2.15. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-4,4-dimethylcyclopentane-1-carboxylic acid *ent*-16. Compound (1*S*,2*R*)-**16** was obtained in the same manner from the quinine opening of anhydride **15** in 83% yield as a colorless oil; $[\alpha]_D^{25}=-3.9$ (*c* 1.00, MeOH); e.e. = 95%.

3.2.16. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-cyclohexane-1-carboxylic acid 18. Compound (1*R*,2*S*)-**18** was obtained from the quinidine opening of anhydride **17** in 88% yield as a colorless oil; $[\alpha]_D^{25}=+2.9$ (*c* 1.95, $CHCl_3$); e.e. = 95%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.36$–1.56 (m, 4H), 1.76–1.80 (m, 2H), 2.01–2.07 (m, 2H), 2.86–2.89 (m, 2H), 5.12 (AB-system, $J=12.4$ Hz, 2H), 7.26–7.35 (m, 5H), 10.70 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=23.9$, 24.0, 26.3, 26.5, 42.7, 42.8, 66.6, 128.3, 128.3, 128.7, 136.2, 173.6, 180.5; IR (Capillary): 3064, 3034, 2940, 2864, 1733, 1740, 1453, 1256, 1218, 1176 cm^{-1}; EI-MS: $m/z=262$ (M^+, 8), 244 (8), 216 (3), 155 (30), 108 (89), 107 (87), 91 (99), 81 (40), 45 (100). Anal. calcd for $C_{15}H_{18}O_4$ (262.30): C, 68.68; H, 6.92. Found: C, 68.70; H, 6.98.

3.2.17. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-cyclohexane-1-carboxylic acid *ent*-18. Compound (1*S*,2*R*)-**18** was obtained from the quinine opening of anhydride **17** in 84% yield as a colorless oil; $[\alpha]_D^{25}=-2.8$ (*c* 1.09, $CHCl_3$); e.e. = 93%.

3.2.18. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-cyclohex-4-ene-1-carboxylic acid 20. Compound (1*R*,2*S*)-**20** was obtained from the quinidine opening of anhydride **19** in 84% yield: mp 65–67°C (rac), colorless oil (en); $[\alpha]_D^{25}=+11.0$ (*c* 1.13, MeOH); e.e. = 94%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.32$–2.43 (m, 2H), 2.52–2.68 (m, 2H), 3.08–3.13 (m, 2H), 5.13 (AB-system, $J=12.4$ Hz, 2H), 5.64–5.72 (m, 2H), 7.26–7.37 (m, 5H), 10.10 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=25.8$, 26.0, 39.8, 39.9, 66.8, 125.3, 125.4, 128.3, 128.4, 128.7, 136.1, 173.3, 180.0; IR (Capillary): 3031, 2924, 1735, 1707, 1296, 1255, 1190, 1163 cm^{-1}; EI-MS: $m/z=260$ (M^+, 1), 242 (13), 214 (11), 169 (4), 123 (18), 107 (5), 91 (100), 79 (26), 65 (9). Anal. calcd for $C_{15}H_{16}O_4$ (260.29): C, 69.22; H, 6.20. Found: C, 68.83; H, 6.27.

3.2.19. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-cyclohex-4-ene-1-carboxylic acid *ent*-20. Compound (1*S*,2*R*)-**20** was obtained from the quinine opening of anhydride **19** in 84% yield as a colorless oil; $[\alpha]_D^{25}=-12.1$ (*c* 1.00, MeOH); e.e. = 95%.

3.2.20. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonyl-4,5-dimethylcyclohex-4-ene-1-carboxylic acid 22. Compound (1*R*,2*S*)-**22** was obtained from the quinidine opening of anhydride **21** in 88% yield: mp 81–83°C (rac), colorless oil (en); $[\alpha]_D^{25}=+1.9$ (*c* 4.87, $CHCl_3$); e.e. = 98%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.60$ (s, 6H), 2.27–2.30 (m, 2H), 2.44–2.55 (m, 2H), 3.03–3.07 (m, 2H), 5.13 (AB-system, $J=12.4$ Hz, 2H), 7.25–7.37 (m, 5H), 9.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=19.1$, 19.2, 31.9, 32.1, 40.5, 40.6, 66.7, 124.2, 124.3, 128.2, 128.3, 128.7, 136.2, 173.4, 180.1; IR (Capillary): 2916, 2859, 1736, 1706, 1255, 1197, 1173 cm^{-1}; EI-MS: $m/z=288$ (M^+, 12), 270 (3), 242 (5), 197 (33), 179 (15), 151 (86), 107 (100), 91 (92), 79 (8), 65 (15). Anal. calcd for $C_{17}H_{20}O_4$ (288.34): C, 70.81; H, 6.99. Found: C, 70.70; H, 6.64.

3.2.21. (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-4,5-dimethylcyclohex-4-ene-1-carboxylic acid *ent*-22. Compound (1*S*,2*R*)-**22** was obtained from the quinine opening of anhydride **21** in 87% yield as a colorless oil; $[\alpha]_D^{25}=-2.3$ (*c* 1.00, $CHCl_3$); e.e. = 97%.

3.2.22. (2*R*,3*S*)-3-*exo*-Benzyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic acid 24. Compound (2*R*,3*S*)-**24** was obtained from the quinidine opening of anhydride **23** in 95% yield: mp 115°C (rac), 77°C (en); $[\alpha]_D^{25}=-24.6$ (*c* 1.17, $CHCl_3$); e.e. = 96%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.50$ (dt, $J=1.7$, 9.1 Hz, 1H), 2.13 (d, $J=9.1$ Hz, 1H), 2.64 (dd, $J=1.7$, 9.6 Hz, 1H), 2.69 (dd, $J=1.7$, 9.6 Hz, 1H), 3.10–3.13 (m, 2H), 5.06 (AB-system, $J=12.4$ Hz, 2H), 6.21 (br t, $J=1.7$ Hz, 2H), 7.26–7.37 (m, 5H), 10.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=45.6$, 45.8, 46.1, 47.7, 47.8, 67.0, 128.4, 128.5, 128.8, 136.0, 138.2, 138.3, 173.5, 180.2; IR (KBr): 2979, 1744, 1694, 1437, 1327, 1259, 1223, 1186, 1151, 1018 cm^{-1}; EI-MS: $m/z=272$ (M^+, 3), 254 (7), 226 (1), 181 (5), 165 (9), 163 (7), 120 (9), 108 (47), 91 (100), 66 (40). Anal. calcd for $C_{16}H_{16}O_4$ (272.30): C, 70.57; H, 5.92. Found: C, 70.67; H, 5.99.

3.2.23. (2*S*,3*R*)-3-*exo*-Benzyloxycarbonyl-bicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic acid *ent*-24. Compound (2*S*,3*R*)-**24** was obtained from the quinine opening of anhydride **23** in 81% yield as a white solid; $[\alpha]_D^{25}=+21.6$ (*c* 1.00, $CHCl_3$); e.e. = 92%.

3.2.24. (2*S*,3*R*)-3-*exo*-Benzyloxycarbonyl-7-oxabicyclo-[2.2.1]hept-5-ene-2-*exo*-carboxylic acid 26. Compound (2*S*,3*R*)-**26** was obtained from the quinidine opening of anhydride **25** according to GP-1 with a modified work-up: the crude product, obtained after washing the organic layer with 2 M HCl and evaporation of the solvent, was purified by column chromatography (CH_2Cl_2:Et_2O, 1:1, +1% AcOH) to give the hemiester **26** in 84% yield as a white solid: mp 121°C (rac), 123°C (en); $[\alpha]_D^{25}=-27.8$ (*c* 3.23, MeOH). e.e. = 99%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=2.86$ (AB-system, $J=8.9$ Hz, 2H), 5.11 (AB-system, $J=12.4$ Hz, 2H), 5.25 (br s, 1H), 5.32 (br s, 1H), 6.43–6.48 (m, 2H), 7.28–7.38 (m, 5H), 8.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=46.9$, 47.3, 67.2, 80.4, 80.7, 128.4, 128.5, 128.6, 135.5, 136.4, 136.8, 171.1, 176.8; IR (KBr): 3022, 1737, 1677, 1334, 1313, 1288, 1214, 1198, 1168, 1008 cm^{-1}; EI-MS: $m/z=$ 228 (1), 206 (19), 139 (9), 121 (6), 108 (23), 107 (81), 100 (55), 91 (100), 79 (30), 68 (90), 65 (26), 55 (12), 51 (14). Anal. calcd for $C_{15}H_{14}O_5$ (274.24): C, 65.69; H, 5.15. Found: C, 65.69; H, 5.33.

3.2.25. (2*R*,3*S*)-3-*exo*-Benzyloxycarbonyl-7-oxabicyclo-[2.2.1]hept-5-ene-2-*exo*-carboxylic acid *ent*-26. Compound (2*R*,3*S*)-**26** was obtained in the same manner from the quinine opening of anhydride **25** in 77% yield as a white solid; $[\alpha]_D^{25}=+29.8$ (*c* 1.00, MeOH); e.e. = 94%.

3.2.26. (2*S*,3*R*)-3-*exo*-Benzyloxycarbonyl-7-oxabicyclo-[2.2.1]heptane-2-*exo*-carboxylic acid 28. Compound (2*S*,3*R*)-**28** was obtained from the quinidine opening of anhydride **27** according to GP-1 with a modified work-up: the crude product, obtained after washing the organic layer with 2 M HCl and evaporation of the solvent, was purified by column chromatography (CH_2Cl_2:Et_2O, 1:1, +1% AcOH) to give the hemiester **28** in 79% yield as a white solid: mp 135°C (rac), 126°C (en), lit.[42] mp 122–124°C (rac); $[\alpha]_D^{25}=-10.8$ (*c* 1.00, MeOH); e.e. = 96%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.42–1.48 (m, 2H), 1.70–1.78 (m, 2H), 2.95 (AB-system, $J=9.4$ Hz, 2H), 4.81–4.89 (m, 2H), 5.00 (AB-system, $J=12.4$ Hz, 2H), 7.21–7.30 (m, 5H), 8.20 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=29.3$, 52.5, 52.6, 67.3, 78.7, 78.9, 128.5, 128.6, 128.8, 135.7, 170.8, 176.5; IR (KBr): 2982, 1736, 1681, 1332, 1301, 1196, 1001 cm^{-1}; EI-MS: $m/z=276$ (M^+, 1), 258 (9), 169 (10), 141 (5), 123 (25), 108 (77), 91 (100), 79 (18), 68 (19), 65 (15). Anal. calcd for $C_{15}H_{16}O_5$ (276.28): C, 65.21; H, 5.84. Found: C, 65.32; H, 5.96.

3.2.27. (2*R*,3*S*)-3-*exo*-Benzyloxycarbonyl-7-oxabicyclo[2.2.1]heptane-2-*exo*-carboxylic acid *ent*-28. Compound (2*R*,3*S*)-**28** was obtained in the same manner from the quinine opening of anhydride **27** in 85% yield as a white solid; $[\alpha]_D^{25}=+10.5$ (*c* 1.05, MeOH); e.e. = 90%.

3.3. General procedure for the preparation of *N*-Cbz protected amino acid benzyl esters GP-2

Ethyl chloroformate (2.86 mL, 30 mmol) was added to a mixture of the appropriate monoester (15 mmol) and Et_3N (6.27 mL, 45 mmol) in dry THF (25 mL) at −20°C. The reaction mixture was stirred at this temperature for 1 h. An aqueous solution of NaN_3 (2.93 g, 45 mmol; in 18 mL water) was added at −10°C. The temperature was gradually increased to rt and stirring continued for 2 h. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated providing the corresponding acyl azide. The crude acyl azide was dissolved in anhydrous benzene (18 mL) and heated under reflux for 2 h. After removal of the benzene, benzyl alcohol (1.55 mL, 15 mmol) and Et_3N (4.18 mL, 30 mmol) were added to a solution of the isocyanate in dry CH_2Cl_2 (20 mL). The reaction mixture was heated under reflux for 4 h. Evaporation of the solvent delivered an oily residue, which was purified by column chromatography providing the corresponding *N*-protected amino acid benzyl ester.

3.3.1. (2*S*,3*R*)-3-*exo*-Benzyloxycarbonylamino-bicyclo-[2.2.1]hept-5-ene-2-*exo*-carboxylic acid benzyl ester 29. Compound (2*S*,3*R*)-**29** was synthesized according to GP-2 by the reaction of the dicarboxylic acid monoester **24** with benzyl alcohol. The crude reaction product was purified by flash chromatography (petroleum ether:EtOAc, 4:1) delivering **29** in 72% yield as a white solid: mp 44°C (en); e.e. = 93% [HPLC-analysis: Chiralpak AD at rt, *n*-heptane:2-propanol = 94:6, 0.5 mL/min, 254 nm, $t_1 = 30.1$ min, $t_2 = 46.8$ min (major)]; $[\alpha]_D^{25} = +17.4$ (*c* 2.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.57$ (dt, $J = 1.7$, 9.4 Hz, 1H), 1.97 (d, $J = 9.4$ Hz, 1H), 2.69 (d, $J = 8.4$ Hz, 1H), 2.73 (br s, 1H), 2.95 (br s, 1H), 4.03 (t, $J = 8.4$ Hz, 1H), 4.95–5.13 (m, 4H), 5.52 (d, $J = 9.6$ Hz, 1H), 6.15–6.25 (m, 2H), 7.24–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 44.7, 46.2, 46.7, 48.8, 53.5, 66.8, 67.0, 128.3, 128.4, 128.5, 128.7, 128.8, 135.9, 136.8, 137.5, 138.7, 158.0, 174.3; IR (KBr): 3352, 2978, 1718, 1529, 1337, 1267, 1252, 1235, 1189, 1032 cm^{-1}; EI-MS: $m/z = 353$ (M^+, 1), 262 (9), 218 (39), 91 (100). Anal. calcd for $C_{23}H_{23}NO_4$ (353.41): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.46; H, 6.92; N, 4.01.

3.3.2. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonylamino-cyclopentane-1-carboxylic acid benzyl ester 31. Compound (1*R*,2*S*)-**31** was synthesized according to GP-2 by the reaction of the dicarboxylic acid monoester *ent*-**14** with benzyl alcohol. The crude reaction product was purified by flash chromatography (pentane:EtOAc, 4:1) delivering **31** in 77% yield as a white solid: mp 55°C (rac), 77°C (en); e.e. = 94% (99.7% after recrystallization) [HPLC-analysis: Chiralpak AD at rt, *n*-heptane:2-propanol = 90:10, 0.8 mL/min, 254 nm, $t_1 = 14.9$ min (major), $t_2 = 19.2$ min]; $[\alpha]_D^{25} = -41.1$ (*c* 1.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.55$–1.85 (m, 3H), 1.89–2.03 (m, 3H), 3.05 (q, $J = 7.2$ Hz, 1H), 4.24–4.34 (m, 1H), 5.04 (AB-system, $J = 18.3$ Hz, 2H), 5.06 (AB-system, $J = 12.4$ Hz, 2H), 5.25 (d, $J = 8.4$ Hz, 1H), 7.26–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.1$, 27.8, 32.1, 46.8, 54.3, 66.4, 66.6, 128.1, 128.2, 128.2, 128.5, 128.6, 135.8, 136.5, 155.8, 174.1; IR (KBr): 3333, 2950, 1719, 1688, 1529, 1455, 1319, 1244, 1184, 1044 cm^{-1}; EI-MS: $m/z = 353$ (M^+, 2), 262 (3), 218 (4), 156 (53), 138 (14), 107 (42), 91 (100); Anal. calcd for $C_{21}H_{23}NO_4$ (353.41): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.09; H, 6.75; N, 4.18.

3.3.3. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonylamino-cyclobutane-1-carboxylic acid benzyl ester 33. Compound (1*R*,2*S*)-**33** was synthesized according to GP-2 by the reaction of the dicarboxylic acid monoester *ent*-**12** with benzyl alcohol. The crude reaction product was purified by flash chromatography (pentane:EtOAc, 6:1) delivering **33** in 74% yield as a colorless oil: e.e. = 93% [HPLC-analysis: Chiralpak AD at rt, *n*-heptane:2-PrOH = 95:5, 0.5 mL/min, 254 nm, $t_1 = 38.9$ min (major), $t_2 = 45.0$ min]; $[\alpha]_D^{25} = -61.6$ (*c* 5.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.97$–2.03 (m, 2H), 2.23–2.33 (m, 1H), 2.35–2.38 (m, 1H), 3.45 (s, 1H), 4.57 (p, $J = 8.8$ Hz, 1H), 5.05 (AB-system, $J = 12.2$ Hz, 2H), 5.13 (AB-system, $J = 12.4$ Hz, 2H), 5.69 (d, $J = 8.8$ Hz, 1H), 7.29–7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.0$, 30.2, 45.6, 46.5, 66.7, 67.0, 128.3, 128.4, 128.5, 128.7, 128.8, 136.0, 136.6, 155.4, 174.2; IR (Capillary): 3350, 2952, 1724, 1515, 1334, 1251, 1213, 1169, 1049 cm^{-1}; EI-MS: $m/z = 311$ (4), 220 (5), 204 (14), 177 (7), 132 (8), 107 (7), 91 (100). Anal. calcd for $C_{20}H_{21}NO_4$ (339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.64; H, 6.17; N, 4.41.

3.3.4. (1*R*,2*S*)-*cis*-2-Benzyloxycarbonylamino-3,3-dimethylcyclopropane-1-carboxylic acid benzyl ester 35. Compound (1*R*,2*S*)-**35** was synthesized according to GP-2 by the reaction of the dicarboxylic acid monoester **10** with benzyl alcohol. The crude reaction product was purified by flash chromatography (pentane:EtOAc, 6:1) delivering **35** in 70% yield as a colorless oil: e.e. = 19% [HPLC-analysis: Chiralpak AD at rt, *n*-heptane:2-PrOH = 94:6, 0.7 mL/min, 254 nm, $t_1 =$ 17.8 min, $t_2 = 21.3$ min (major)]; $[\alpha]_D^{25} = -7.3$ (*c* 5.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.13$ (s, 3H), 1.20 (s, 3H), 1.69 (d, $J = 7.7$ Hz, 1H), 3.20 (t, $J = 7.4$ Hz, 1H), 5.09 (br s, 2H), 5.11 (br s, 2H), 6.26 (d, $J = 6.0$ Hz, 1H), 7.27–7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$, 26.2, 26.6, 27.9, 41.5, 66.8, 67.1, 128.3, 128.5, 128.6, 128.7, 128.8, 136.0, 136.8, 157.1, 171.5; IR (Capillary): 3401, 2957, 1725, 1510, 1344, 1221, 1154, 1065 cm^{-1}; EI-MS: $m/z = 353$ (M^+, 1), 262 (9), 218 (39), 91 (100). Anal. calcd for $C_{21}H_{23}NO_4$ (353.41): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.46; H, 6.92; N, 4.01.

3.4. General procedure for the synthesis of the free β-amino acids GP-3

A solution of the *N*-protected β-amino acid benzyl ester in dry MeOH was hydrogenated over 10% Pd/C for 1–2 h at rt and at 1 atm. The complete conversion of the reaction was monitored by TLC, the catalyst was removed by filtration through Celite, washed with MeOH and the filtrate was evaporated to give the corresponding free amino-acid.

3.4.1. (2*S*,3*R*)-3-*exo*-Amino-bicyclo[2.2.1]heptane-2-*exo*-carboxylic acid 30. Compound (2*S*,3*R*)-**30** was synthesized from the β-amino ester **29** according to GP-3 in 97% yield as a white solid: mp (dec) >250°C (rac), (dec) >250°C (en), lit.[43] mp 275–278°C (rac); $[\alpha]_D^{25} = -8.0$ (*c* 1.40, H_2O); ^1H NMR (300 MHz, D_2O): $\delta = 1.16$–1.18 (m, 2H), 1.23 (d, $J = 10.9$ Hz, 1H), 1.43–1.60 (m, 2H), 1.66 (d, $J = 10.9$ Hz, 1H), 2.30 (s, 1H), 2.42 (s, 1H), 2.53 (d, $J = 7.9$ Hz, 1H), 3.30 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 25.8$, 28.0, 33.5, 41.1, 41.9, 51.3, 54.7, 178.9; IR (KBr): 3424, 2955, 2676, 1632, 1537, 1395, 1367, 1316 cm^{-1}; EI-MS: $m/z = 155$ (M^+, 70), 138 (13), 127 (52), 110 (43), 82 (45), 70 (100), 56 (90). HRMS for $C_8H_{13}NO_2$: calcd 155.0946, Found: 155.0945.

3.4.2. (1*R*,2*S*)-*cis*-2-Amino-cyclopentane-1-carboxylic acid 32. Compound (1*R*,2*S*)-**32** was synthesized from the β-amino ester **31** according to GP-3 in 98% yield as a white solid: mp (dec) 194°C (rac), (dec) 192°C (en), lit.[36b] mp 194–197°C (en); $[\alpha]_D^{25} = -10.1$ (*c* 2.81, H_2O), lit.[35f] $[\alpha]_D^{25} = -9.6$ (*c* 1.00, H_2O); ^1H NMR (300 MHz, D_2O): $\delta = 1.52$–1.74 (m, 4H), 1.86–2.00 (m, 2H), 2.71 (dt, $J = 6.4$, 8.4 Hz, 1H), 3.56 (dt, $J = 4.2$, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 21.3$, 28.0, 29.5, 47.6, 53.0, 180.8; IR (KBr): 3420, 2955, 1627, 1577, 1506, 1461, 1440, 1411, 1311, 1122, 1073 cm^{-1}; EI-MS: $m/z =$ 129 (M^+, 12), 100 (8), 82 (7), 69 (7), 56 (100). Anal. calcd for $C_6H_{11}NO_2$ (129.16): C, 55.80; H, 8.58; N, 10.84. Found: C, 55.52; H, 8.46; N, 11.19.

3.4.3. (1*R*,2*S*)-*cis*-2-Amino-cyclobutane-1-carboxylic acid 34. Compound (1*R*,2*S*)-**34** was synthesized from the β-amino ester **33** according to GP-3 in 93% yield as a white solid: mp (dec) 130°C (en), lit.[44] mp (dec) 129–132°C (rac), lit.[23b] mp (dec) 130°C (en); $[\alpha]_D^{25} = -80.0$ (*c* 1.00, H_2O); ^1H NMR (300 MHz, D_2O): $\delta =$ 1.90–2.00 (m, 1H), 2.07–2.30 (m, 3H), 3.09–3.17 (m, 1H), 3.79–3.86 (m, 1H); ^{13}C NMR (75 MHz, D_2O): $\delta = 21.1$, 25.0, 41.3, 45.5, 181.0; IR (KBr): 3433, 2956, 2190, 1541, 1405, 1293 cm^{-1}; MS (FAB): 114 (M^+–H); Anal. calcd for $C_5H_9NO_2$ (115.13): C, 52.16; H, 7.88; N, 12.17. Found: C, 51.80; H, 7.97; N, 11.81.

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