Simple and Highly Enantioselective Nonenzymatic Ring Opening of Cyclic Prochiral Anhydrides[1]

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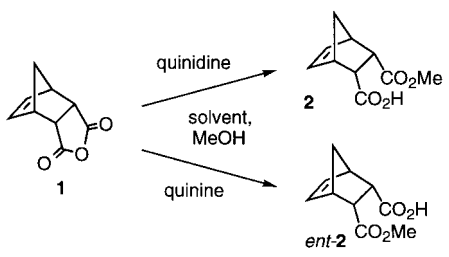
Abstract: A convenient highly enantioselective methanolysis of cyclic *meso*-anhydrides only requires one equivalent cinchona alkaloid and low temperature. Both enantiomers can be easily obtained with up to 98% *ee* by using either quinine or quinidine.

Key words: alkaloids, asymmetric reactions, anhydrides, stereoselection

As yet, numerous enzymatic[2] and nonenzymatic[3-7] methods for the desymmetrization of *meso*-dicarboxylic acid derivatives have been developed. Although a few catalytic versions are known[3,7b] most transformations of this kind require stoichiometric amounts of chiral reagents such as alcohols,[4] amines,[5] amino alcohols,[6] or titanium reagents (Ti-TADDOLates)[7a] to accomplish high enantiotopic differentiation. In addition they suffer from moderate stereoselection, use of sophisticated enantiomerically pure compounds or complex reaction conditions.

Given the findings of Aitken *et al.*[3a-b] and Oda and coworkers[3c-d] we developed a new stoichiometric method employing inexpensive and readily available cinchona alkaloids and methanol. With this convenient metal free procedure cyclic *meso*-anhydrides are easily transferred to their corresponding methyl monoesters with very high enantiomeric excess (*ee*) in excellent yield.

In our initial studies, we screened the use of various cinchona alkaloids for the methanolysis[8] of anhydride **1**. The highest enantiomeric excess for methyl monoester **2** was observed in reactions with commercially available quinidine. Quinidine derivatives, other chiral amino alcohols and tertiary amines gave lower asymmetric induction. Quinine, the pseudo-enantiomer of quinidine, provided the best stereoselection for the preparation of *ent*-**2**.



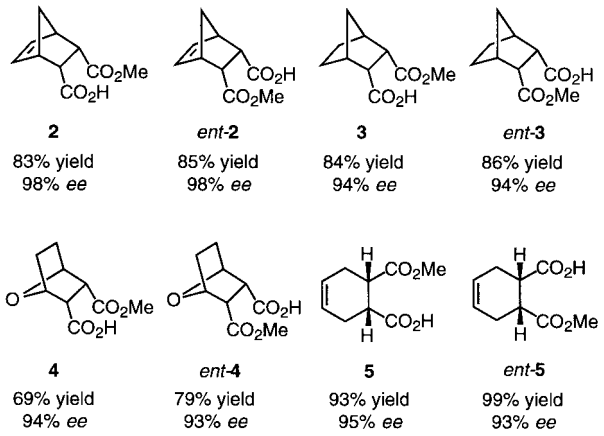
Searching for the optimal reaction conditions we first examined the effect of the alkaloid amount on the enantioselectivity of the ring opening. Using anhydride **1** as test substrate we found that the enantiomeric excess of the product increased when larger quantities of the alkaloid were employed. The highest asymmetric induction was observed in reactions with one equivalent of quinidine. Thus, in toluene solution at ambient temperature *(2R,3S)*-**2** was formed in 83% yield having 78% *ee*. It is noteworthy that more alkaloid did not lead to further improvement.

Since the reaction medium often affects chemical transformations,[12] we also studied the influence of the solvent polarity on the ring-opening of **1**. When the desymmetrization was performed in benzene or tetrachloromethane the highest asymmetric inductions were obtained. The enantiomeric excess still remained high when the solvent system toluene/CCl_4 1:1 was employed.

Lowering the temperature also had a positive effect on the stereoselectivity. Eventually, the best results were obtained in reactions run at -50 °C in toluene/CCl_4 mixtures, using 1.1 eq. of the alkaloids. Thus, use of quinidine led to the formation of methyl monoester **2** with 98% *ee*.[9] Its enantiomer, *ent*-**2**, was obtained with the same enantiomeric excess using quinine as promoter. After acidic extraction of the reaction mixture no further purification of the crude methyl monoesters by chromatography or recrystallization was required, and the cinchona alkaloids could easily be recovered quantitatively as their hydrochloride salts.

Under identical reaction conditions the corresponding saturated monoesters **3** and *ent*-**3** as well as the heteroatom-containing bicyclic compounds **4** and *ent*-**4** were obtained with slightly lower enantiomeric excesses (93-94% *ee*). Interestingly, highly enantioenriched *mono*cyclic esters **5** and *ent*-**5** are also available by this method. Compounds of such type have been used for the preparation of the corresponding β-amino acids by means of Curtius degradation of the corresponding acyl azide.[13]

In summary, we developed an enantioselective ring-opening of bi- and tricyclic anhydrides which gives products with very high enantioselectivity. Compared to the existing methods our protocol is simple and more convenient to perform. Currently, we are focusing our efforts on the application of this transformation towards the synthesis of enantiomerically pure unnatural β-amino acids and new ligands for asymmetric catalysis.



Acknowledgment

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References and Notes

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(8) When more hindered alcohols such as ethanol or 2-propanol were used as nucleophiles decreased reaction rates and lower enantioselectivities were observed. Primary and secondary amines as well as thiols also gave less satisfactory results.
(9) Representative procedure: Methanol (0.122 mL, 3.0 mmol) was added dropwise to a stirred suspension of *cis-endo*-bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic anhydride (**1**) (0.164 g, 1.0 mmol) and quinidine (0.357 g, 1.1 mmol) in toluene (2.5 mL) and tetrachloromethane (2.5 mL) at -50 °C under argon. The reaction mixture was stirred at that temperature for 36 h. During this period it gradually changed from heterogeneous to homogeneous. Subsequently, the resulting clear solution was concentrated *in vacuo* to dryness, then the resulting residue was dissolved in ethyl acetate (40 mL). The solution was washed with 2 N HCl (2 x 4 mL) and after phase separation the organic layer was dried over $MgSO_4$, filtered, and concentrated providing 0.163 g (83 %) of (2*R*,3*S*)-(+)-*cis-endo*-3-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**2**) as a white solid {purity > 98 % (NMR, GC-MS), mp 75-78 °C (Lit.:[10] 76-78.5 °C), $[\alpha]_D^{20}$ = + 7.7 (CCl_4, *c* = 4.23) (Lit.:[11] + 7.9, *c* = 4.8), 98% *ee* [HPLC-analysis of the methyl-4-bromophenyl diester: Chiralcel OD-H at rt, 2% 2-propanol/*n*-heptane, 0.5 mL/min, 254 nm, t_R = 20.27 min (2*S*,3*R*)-(-) and 23.15 min (2*R*,3*S*)-(+)}. The absolute configuration was determined by selective reduction of the methylester group with $LiBEt_3H$ followed by catalyzed lactonization providing a known lactone.[11] The alkaloid was quantitatively recovered by neutalization of the aqueous layer with $NaHCO_3$ and extraction with ethyl acetate.
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