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Catalytic Asymmetric Ring-Opening of Bridged Tricyclic Anhydrides

R Alan Aitken* and Jayalakshmi Gopal

Department of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife. KY16 9ST, UK.

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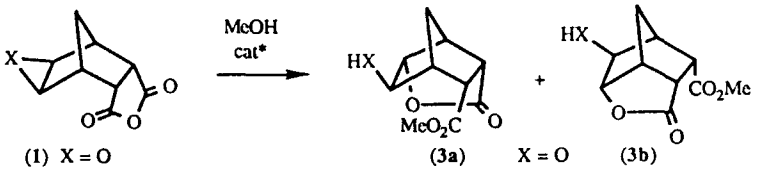
Abstract: Cinchona alkaloid catalysed methanolysis of three different achiral tricyclic anhydrides provides convenient access to either enantiomer of the corresponding half-esters in 35-67% enantiomeric excess; the absolute configuration of the products has been determined and a convenient procedure developed for preparation of multigram quantities of either enantiomer of one half-ester in ~90% e.e.

We recently reported[1] the enantioselective reaction of tetracyclic anhydrides (**1**) and (**2**) with methanol in the presence of cinchona alkaloids to give highly functionalised chiral products (**3**) and (**4**) in up to 76% enantiomeric excess (e.e.). Oda and coworkers[2] have developed similar procedures for asymmetric ring-opening of mono- and bicyclic anhydrides including *cis*-cyclohexene-4,5-dicarboxylic anhydride which was achieved in up to 52% e.e. using epiquinidine.



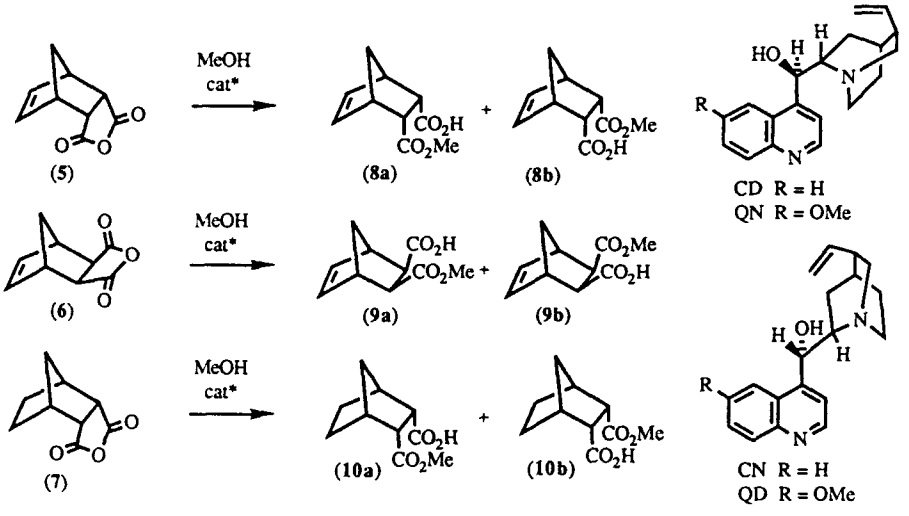
(1) X = O
(2) X = NPh

(3a) X = O (3b)
(4a) X = NPh (4b)

We now describe our results on the tricyclic anhydrides (**5-7**) which allow the simple preparation of either enantiomer of half esters (**8-10**) in up to 93% e.e. The lactones derived from reduction of these products have been used in racemic form for the synthesis of prostaglandin analogues[3] and the enantiomers of (**8**) obtained by resolution[4] provide valuable intermediates for iridoid synthesis. Our approach has considerable advantages over enzymatic methods in these cases since formation of (**9**) by pig liver esterase hydrolysis[5] of the corresponding dimethyl ester occurs with less than 10% e.e. and the diester precursor to (**8**) does not react at all. The alternative approach to the lactones derived from (**8-10**); oxidation of the diols by horse liver alcohol dehydrogenase is successful[6] but only provides one of the enantiomers in each case.

The reactions were carried out by stirring a suspension of the anhydrides in toluene containing 3 equiv. MeOH and 0.1-0.5 equiv. of either quinine (QN), quinidine (QD), cinchonine (CN) or cinchonidine (CD) at

room temperature for 24 hours. Removal of the alkaloid either by fractional crystallisation or rapid washing



with dilute HCl then afforded the desired half esters in pure form. The various reaction parameters were examined in turn and the optimised conditions for the formation of (**8-10**) are shown in **Table 1.**

The results of this study will be discussed in detail in a full paper[7] but the main features are as follows: (i) For all three substrates QN and QD gave higher e.e. than CN or CD. As expected QN and QD gave opposite enantiomers and the e.e. for QD was slightly higher. (ii) For (**5**) with QN and (**6**) with QN or QD the use of 0.5 equiv. catalyst resulted in a marked improvement in e.e. compared to 0.1 equiv. but for (**5**) with QD this was not the case. (iii) As in the reactions of (**1**) and (**2**)[1] the use of bulky alcohols, other solvents such as ethyl acetate or cyclohexane, and lower reaction temperatures gave no improvement in e.e.

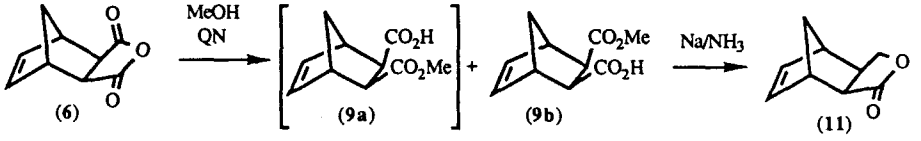
Table 1

Substrate	Catalyst	Yield	e.e.[a]	Major Enantiomer
(**5**)	0.5 equiv. QN	69%	61%	(**8a**)
(**5**)	0.1 equiv. QD	97%	52%	(**8b**)
(**6**)	0.5 equiv. QN	91%	58%	(**9b**)
(**6**)	0.5 equiv. QD	88%	67%	(**9a**)
(**7**)	0.1 equiv. QN	82%	35%	(**10a**)
(**7**)	0.1 equiv. QD	80%	44%	(**10b**)

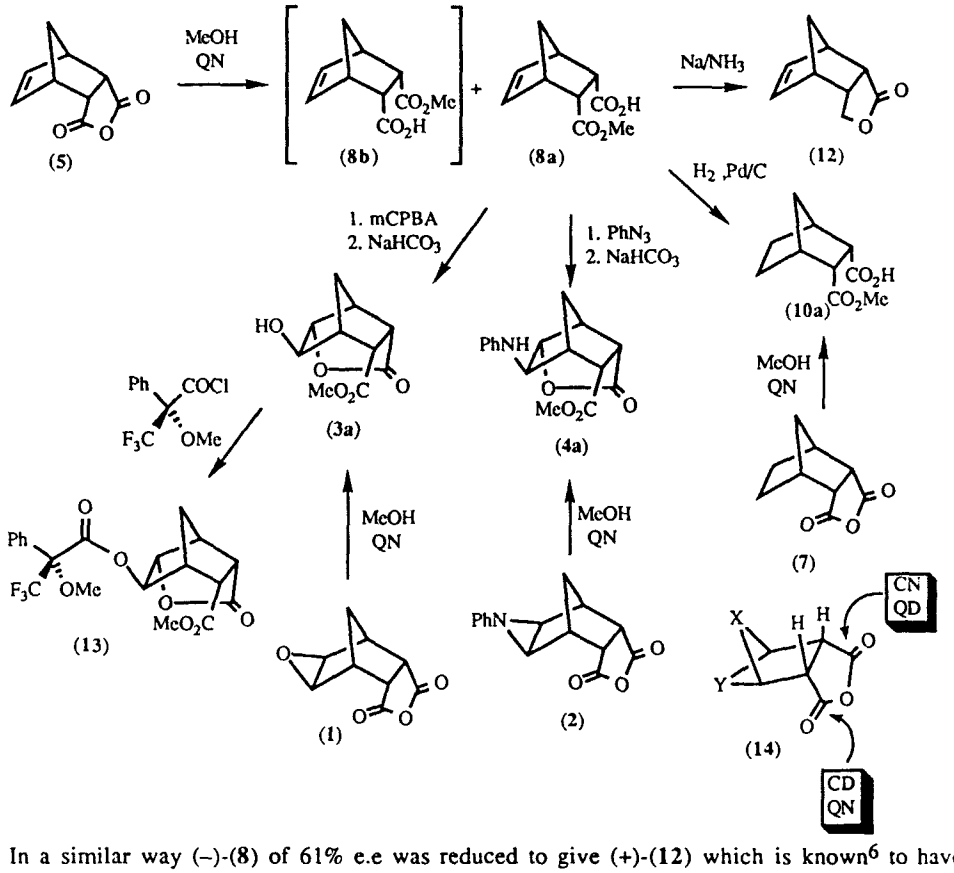
[a] Determined from 300 MHz ^{1}H n.m.r. of the diastereomeric salts formed with R-(+)-α-phenylethylamine (CO_2Me signal) (ref. 8).

In order to obtain multi-gram quantities of (**8**) of higher e.e. we exploited the very ready enantiomeric enrichment which occurred on recrystallisation. Thus reaction of (**5**) (18 g) with methanol in the presence of 0.5 equiv. QN gave , after washing with acid, 19 g (88%) of (**8**) with an e.e. of 55%. A single recrystallisation gave racemic crystals (8.3 g) and, upon evaporation of the filtrate, 9.1 g (48%) of (**8**) having an e.e. of 88% in favour of enantiomer (**8a**) . The same procedure using 0.1 equiv. QD gave 20.8 g (97%) crude product of 52%

e.e. which was similarly enriched on recrystallisation giving 10.9 g (52%) of (**8**) with an e.e. of 93% in favour of enantiomer (**8b**). Unfortunately similar enrichment for (**9**) was not possible since this compound was obtained as an oil. Procedures for the enantiomeric enrichment of (**10**) as well as the effect of increasing the quantity of catalyst are still under investigation although (**10**) of high e.e. can of course be obtained by hydrogenation of (**8**).



Of the products (**3**), (**4**), (**8**), (**9**) and (**10**), only (**8**) has previously been prepared in non-racemic form so we have determined the absolute configurations of each of these products. In the case of (**9**) this was relatively easy since reduction with sodium in liquid ammonia[9] is known to proceed regioselectively on the ester group. When the (–)- product (**9**) of 58% e.e from reaction with quinine was reduced it gave the (+)-lactone whose absolute configuration has already been established[6] as (**11**). Thus the absolute configuration (**9b**) is that of the major (–)- enantiomer formed in the quinine reaction.



In a similar way (–)-(**8**) of 61% e.e was reduced to give (+)-(**12**) which is known[6] to have the configuration shown. Thus (–)-(**8**) has the configuration (**8a**) in agreement with that established by a previous

chemical correlation[4]. This was then correlated with the products from reaction of (**1**), (**2**) and (**7**) by treatment of (–)-(**8**) with mCPBA, PhN_3 and catalytic hydrogenation respectively. The resulting samples of (–)-(**3**), (–)-(**4**), and (–)-(**10**) all had the same sign of rotation as the products from the three quinine reactions which must therefore have the absolute configurations (**3a**), (**4a**) and (**10a**) shown. Since these assignments all depend on the reported absolute configuration of (**12**) we thought it wise to double check them by means of an X-ray structure determination. To aid determination of the absolute configuration (–)-(**3**) was converted to its ester (**13**) with *R*-(+)-MTPA[10]. A single crystal X-ray diffraction study[11] of (**13**) gave the structure depicted thus confirming the previous assignments.

Having thus demonstrated that catalysis by quinine (and cinchonidine) gives products with the absolute configurations (**9b**), (**8a**), (**3a**), (**4a**), and (**10a**) while quinidine and cinchonine give primarily the opposite enantiomers we feel that some comment on the mechanism is in order. It can be seen that the site of methanol attack (and thus presumably initial attack by the quinuclidine nitrogen of the alkaloids) is on the front of the *endo* structures (**5**), (**1**), (**2**) and (**7**) but on the rear side of *exo* anhydride (**6**). This clearly indicates that, perhaps not surprisingly, it is the anhydride ring itself which is the primary site of molecular recognition by the alkaloid and that, regardless of the nature of the bridges X and Y, quinine and cinchonidine attack at the front carbonyl in structure (**14**) while quinidine and cinchonine attack at the rear. The nature of X and Y do however appear to be critical in allowing highly enantioselective reaction as shown by the results for very similar substrates, such as the tricyclic anhydrides derived from cycloaddition of maleic anhydride to cyclohexa-1,3-diene and furan where, although methanolysis occurs readily, the e.e. of the products never exceeds 10% under any conditions so far examined.Further detailed studies are needed to shed more light on the mechanism of these reactions.

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11. Full details of the structure determination of (**13**) will be given in a forthcoming paper.