Asymmetric Reduction of Methyl Benzoylformate with a Chiral NAD(P)H-Model Compound

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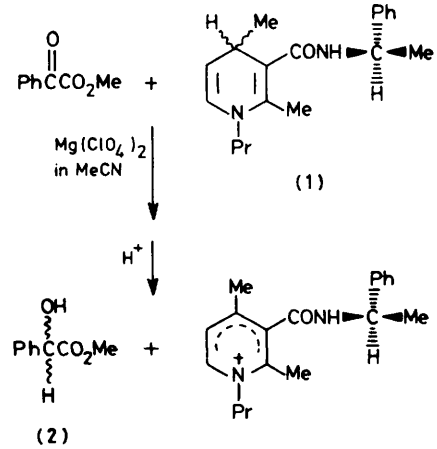
Summary The title reaction with *N*-(*R*)-α-methylbenzyl-1-propyl-2-methyl-4-(*R*)-methyl-1,4-dihydronicotinamide or its 4-(*S*)-methyl isomer affords methyl mandelate in 97% optical yield and quantitative chemical yield.

ONE of the purposes of biomimetic organic reactions is to imitate the high stereospecificity of enzymic reactions. In this sense a mimesis of the mild and stereospecific reduction with NAD(P)H-dependent dehydrogenases has been a target for organic chemists.

We have reported that α-keto-esters are reduced, in the presence of bivalent metal ions, by chiral *N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide or its analogues in 20—25% optical yields.[1-4] Since the chiral centres in these NAD(P)H-model compounds are well separated (5 atoms) from the reaction centre there arises a limitation in the enantiospecificity of the reduction unless the substrate to be reduced has an effective chiral centre(s) in itself. Recently, 70—80% optical yields were claimed for the reduction of menthyl esters of α-keto acids with a Hantsch ester-type model compound.[5]

We have now synthesized diastereoisomers of *N*-(*R*)-α-methylbenzyl-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (**1**) and studied the stereochemistry of the reduction of methyl benzoylformate, an achiral substrate. These model compounds have chiral centres at the reaction centre and high enantiospecificity is expected for reduction with them. A mixture of the diastereoisomers of (**1**) was obtained in 79% yield by reduction of the corresponding pyridinium bromide with sodium dithionite.[4] The pyridinium bromide was prepared from 2,4-dimethylnicotinyl chloride hydrochloride by successive reactions with (*R*)-(+)-α-methylbenzylamine and propyl bromide.[4] Fractional recrystallization of the mixture of (**1**) from ethanol–water gave one isomer as the first fraction and the other isomer as the third fraction. Since we do not know the absolute configuration at C(4) in these isomers, we shall denote the former as (*XR*)-(**1**) and the latter as (*YR*)-(**1**). Repeated recrystallization of each iosmer from aqueous ethanol afforded analytically and optically pure materials: (*XR*)-(**1**): m.p. 118 °C; $[\alpha]_D$ −115·9° (MeCN); n.m.r. δ ($CDCl_3$; Me_4Si) 0·88 (t, 3H), 1·03 (d, 3H), 1·49 (d, 3H), 1·20—1·70 (m, 2H), 2·02 (s, 3H), 3·11 (tq, 2H), 3·24 (dq, 1H), 4·77 (dd, 1H), 5·22 (q, 1H), 5·66 (broad s, 1H), 5·74 (d, 1H), and 7·28 (s, 5H); (*YR*)-(**1**): m.p. 99 °C; $[\alpha]_D$ +85·3° (MeCN); n.m.r. δ ($CDCl_3$; Me_4Si) 0·88 (t, 3H), 1·01 (d, 3H), 1·49 (d, 3H), 1·20—1·70 (m, 2H), 2·02 (s, 3H), 3·11 (tq, 2H), 3·26 (dq, 1H), 4·77 (dd, 1H), 5·22 (q, 1H), 5·66 (broad s, 1H), 5·74 (d, 1H), and 7·28 (s, 5H).



Methyl benzoylformate, (*XR*)- or (*YR*)-(**1**), and magnesium perchlorate (1 mmol each) were allowed to react in 10 ml of acetonitrile at 30 °C in the dark under argon for 44 h. The reaction proceeded completely giving methyl

mandelate (**2**) in quantitative chemical yield (g.l.c.). After the usual work-up and purification[4] analytically pure (**2**) was isolated. The optical rotations of (**2**) isolated from the reaction mixtures with (*XR*)- and (*YR*)-(**1**), measured on a Perkin-Elmer 241 polarimeter, were $[\alpha]_D^{26}$ −130·7° and $[\alpha]_D^{26}$ +129·2° (each 1·030, EtOH), respectively, and the accuracy of the observed values was confirmed with authentic samples of (**2**) {$[\alpha]_D^{26}$ ±134·0 (*c* 1·030, EtOH)}.[6] The optical yield of the reduction was calculated to be 97%. This is the highest value so far reported, to the best of our knowledge, for the asymmetric reduction of α-keto-esters or -acids.

It is interesting that the chirality in the α-methylbenzyl group of (**1**) does not affect the enantiospecificity of the reduction. in contrast to the reduction with *N*-α-methylbenzyl-1-propyl-1,4-dihydronicotinamide. A CPK-model for (**1**) indicates that the amide carbonyl group in (**1**) is twisted out of the plane of dihydropyridine ring because of steric repulsion with the C(2)-methyl group, and, consequently, the α-methylbenzyl group is well separated from the reaction centre. Thus, the extremely high enantiospecificity of the present reduction is induced almost entirely by the one chiral centre at the C(4)-position. Such a high efficiency may be accounted for by a tight transition state involving the magnesium ion as a binder.[3,7]

The absolute configuration of (**1**) is under investigation.

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