Tetrahedron Letters No. 46, pp 4057 - 4060, 1975. Pergamon Press. Printed in Great Britain.

ASYMMETRIC INDUCTION IN THE ALKALOID-CATALYSED MICHAEL REACTION

Hans Wynberg and R. Helder

Department of Organic Chemistry, The University,

Zernikelaan, Groningen, The Netherlands.

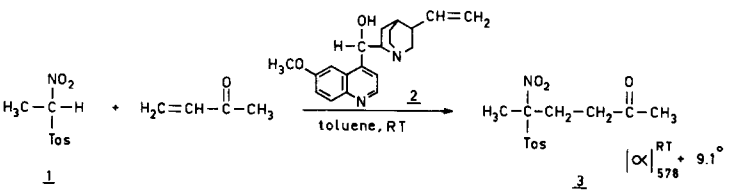
(Received in UK 26 September 1975; accepted for publication 6 October 1975)

The route to chiral molecules via asymmetric catalysis has obvious theoretical as well as practical significance, with nature as our teacher.[1]

We have chosen the versatile Michael reaction[2] as subject for study since only two previous examples of asymmetric catalysis in this reaction have come to our attention. The first one is a Russian report[3] of a reaction on optically active quartz. The second is the recent work of Langström and Bergson[4] using an optically active synthetic amine. In neither of these cases has the optical purity or enantiomeric excess of the products been determined.

We have found that for 11 Michael reactions, using optically inactive donors and acceptors in the presence of catalytic amounts of optically active quinine, optically active products were obtained. In one case the enantiomeric excess was determined and amounted to 68%.

In a typical run, 458 mg (2 mmole) of nitrosulfone 1 was dissolved in a standard solution containing 8 mg of quinine (mp 176-7°, $[\alpha]^{RT}_{578}$ - 172°, c = 0.96, ethanol) in 8 ml toluene, and 280 mg (4 mmole) of methyl vinyl ketone (MVK) was added:



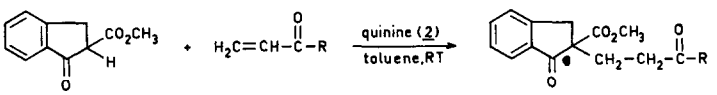
The optical rotation of the solution rose from 0.020° (578 mμ, 10 cm cell), 0.210° (20 min.), 0.335° (40 min.), 0.400° (70 min.) to 0.435° (16 hr). After work-up and crystallization from ethanol, 519 mg (87%) of 3 (mp 112-5°, $[\alpha]^{RT}_{578}$ + 10.0°, c = 2.20, C_6H_6), chemically pure according to PMR was obtained.

Recrystallization afforded 465 mg (78%), mp 117-8°, $[\alpha]^{RT}$ (c = 2.15, C_6H_6) + 9.1° (578 mμ), + 10.0° (546 mμ), + 10.0° (436 mμ) and + 4.7° (405 mμ). The IR and PMR were identical with those of an authentic sample synthesized by Zeilstra and Engberts.[5]

Compound 1 was chosen as the starting material since it gives the crystalline adduct (3) in high yield when triethylamine is used as the catalyst.[5] In addition adduct 3 was expected and found not to racemize substantially under the reaction conditions used.

The solvent effect on the asymmetric induction (but not on the chemical yield!) was significant. The following values of $[\alpha]^{RT}_{578}$ (solvent C_6H_6) were found for 3, after work-up and crystallization:[6] ethanol 0.0°, CH_2Cl_2 + 2.6°, dioxane + 2.8°, C_6H_6 + 7.2° and CCl_4 + 14.1°. Thus, toluene and CCl_4 were the solvents of choice in our subsequent experiments.

An attempt to determine the enantiomeric excess of 3 by PMR spectroscopy was not successful in this particular case. However, we were able to determine this important parameter for adduct 5 using the reaction between 4 and MVK. Reaction at room temperature in toluene under the influence of quinine (2) gave 5 in 87% yield, after crystallization from ether/hexane {mp 104-6°, $[\alpha]^{RT}_{578}$ - 42.9° - 51.0° (546 mμ), - 117.6° (436 mμ) and - 167.8° (405 mμ), c = 2.05, C_6H_6}.



4

5. R=CH_3
6. R=H

After another crystallization ($[\alpha]^{RT}_{578}$ - 42.8°, c = 1.94, C_6H_6), the enantiomeric excess of this material was determined with the aid of PMR spectroscopy. Addition of $Eu(TFC)_3$ to 5 dissolved in $CDCl_3$ gave rise to two nicely separated singlets for the ester methyl group. The integration ratio of these peaks was estimated to be 1:3.5, which is in accord with 56% enantiomeric excess. From these data optically pure 5 is calculated to have $[\alpha]^{RT}_{578}$ - 77.0°.

Variation of parameters as given below had only little influence on the chemical yield of 5 but affected the enantiomer ratio considerably. This will be clear from $[\alpha]^{RT}_{578}$ that was found (after crystallization):[6] a) quinine, CCl_4, RT, - 49.2°; b) quinine, CCl_4, 0°, - 55.4°; c) quinine, toluene, 0°, - 57.4°; d) quinine, toluene, - 20°, - 54.8° (not recrystallized!); e) cinchonidine, toluene, RT, - 41.9°; f) cinchonine, toluene, RT, + 29.0°. Hence, depending upon the choice of the catalyst either of the enantiomers could be formed in excess.

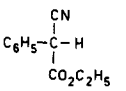
In case d) the asymmetric induction of the conversion 4 → 5 was determined. A PMR experiment

(vide supra) was carried out on the crude product obtained after work-up, but before crystallization, in order to avoid changing of the enantiomer ratio by crystallization. The peak area ratio was estimated to be 1:5.3 corresponding with 68% asymmetric induction. After two recrystallizations the optical purity of 5 was raised to 89% ($[\alpha]_{578}^{RT}$ - 68.4°, c = 1.82, C_6H_6).

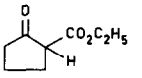
The reaction between 4 and acrolein, which was described by Bergson[4] in his elegant work, was carried out by us in toluene at room temperature using quinine (2) as the catalyst. We obtained the adduct 6 in 93% yield, $[\alpha]_{546}^{RT}$ - 61.1° (c = 3.46, CCl_4).

In order to investigate the scope of this catalytic asymmetric synthesis, the Michael donors 7-14 were added to MVK (quinine, toluene, RT).

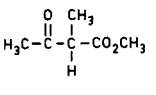
7, R=C_6H_5
8, R=C_2H_5



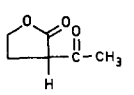
9



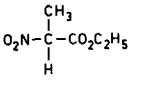
10



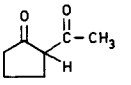
11



12



13



14

Except for 14, all of these donors gave the corresponding Michael adducts in high yield. The IR and PMR spectra of the adducts of 7 and 8 were identical to those of authentic material.[5] The remaining adducts were characterized by their elemental analysis and spectroscopic properties. The specific rotations (in C_6H_6) of the Michael adducts 7b-14b derived from 7-14, are given below. Ad 7b: $[\alpha]_{578}^{RT}$ + 2.2° (c = 5.31), this value diminishes when 7b is recrystallized; ad 8b: $[\alpha]_{578}^{RT}$ + 18.6° (c = 2.2), this value also diminishes upon recrystallization; ad 9b: $[\alpha]_{365}^{RT}$ + 0.3° (c = 6.32); ad 10b: $[\alpha]_{578}^{RT}$ - 10.7° (c = 11.4); ad 11b: $[\alpha]_{578}^{RT}$ - 0.1°, $[\alpha]_{365}^{RT}$ - 3.5° (c = 23.1); ad 12b: $[\alpha]_{578}^{RT}$ + 26.4° (c = 8.0) after distillation, + 10.6° (c = 2.46) after distillation followed by one recrystallization; ad 13b: $[\alpha]_{365}^{RT}$ - 7.1° (c = 2.17, toluene); ad 14b: $[\alpha]_{578}^{RT}$ + 18.3° (c = 5.45).

Since the optical purity or enantiomeric excess of the adducts 7b-14b has not yet been determined, nothing definite can be said about the amount of asymmetric induction in these cases. However, the order of magnitude of $[\alpha]$ suggests a reasonable enantioselectivity in most cases.

The work by Meurling[7] and Pracejus[8] as well as the classical work by Prelog[9] has revealed that

minute differences in the parameters (structure, solvent, temperature) control alkaloid-catalyzed reactions. Our results are in agreement with these facts.

We are unaware of any data indicating that alkaloids bound or unbound to biopolymers might fulfill an asymmetric catalysis role in biogenetic processes.

Acknowledgement

We are much indebted to Dr. J.H. Wieringa who carried out the PMR experiments with $Eu(TFC)_3$ and recorded and interpreted the PMR and CMR spectra of the adducts 10b, 12b and 14b. We thank Mr. R. Arends for the synthesis of 8b and 13b, and Dr. J.J. Zeilstra and Dr. J.B.F.N. Engberts for providing us with samples of 1, 7 and 8 and the IR and PMR spectra of the corresponding adducts.

References and notes

1. For a recent review: J.W. Scott and D. Valentine, Jr., Science 184, 943 (1974).
2. E.D. Bergmann, D. Ginsburg and R. Pappo in "Organic Reactions", J. Wiley and Sons, N.Y. 1959, Volume 10, p. 179-555.
3. A.P. Terent'ev, E.I. Klabunovskii and E.I. Budovskii, Chem. Abstracts 49, 5263b (1955).
4. B. Langström and G. Bergson, Acta Chem. Scand., 27, 3118 (1973).
5. J.J. Zeilstra and J.B.F.N. Engberts, J. Org. Chem., 39, 3215 (1974).
6. The recrystallization, as well as small differences in reaction temperature might have influenced the specific rotation of the adduct.
7. L. Meurling, Chemica Scripta 7, 90 (1975).
8. H. Pracejus, Fortschr. chem. Forsch., Bd. 8/4, 493 (1967).
9. V. Prelog and M. Wilhelm, Helv. Chim. Acta 37, 1634 (1954).