Tetrahedron: Asymmetry Vol. 4, No. 2, pp. 173-176, 1993
Printed in Great Britain

0957-4166/93 \$6.00+.00
Pergamon Press Ltd

Unexpected Change of Absolute Configuration in Asymmetric *Michael* Addition of Methyl Vinyl Ketone to 2-Nitrocycloalkanones

Anita Latvala, Stephan Stanchev#, Anthony Linden and Manfred Hesse*

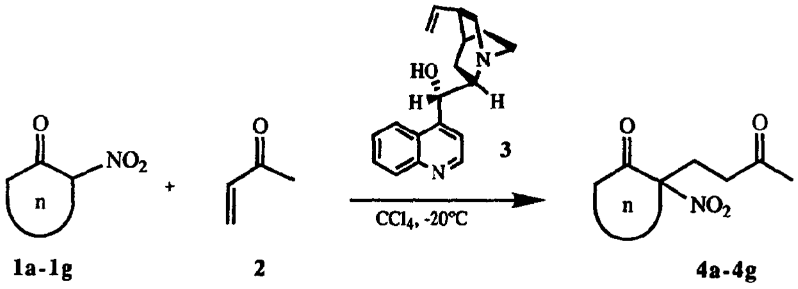
University of Zürich, Department of Organic Chemistry, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

(*Received in UK* 17 *December* 1992)

Abstract: *Michael* addition of methyl vinyl ketone **2** to 2-nitrocycloalkanones **1** catalyzed by the *Cinchona* alkaloid cinchonine **3** affords adducts in high chemical yields in up to 60% enantiomeric excess. The configuration of the products depends on the ring size. Absolute configuration of (-)-2-nitro-2-(3-oxobutyl)cyclooctanone and (+)-2-nitro-2-(3-oxobutyl)cyclododecanone derivatives were determined by X-ray diffraction.

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral catalysts. The use of *Cinchona* alkaloids for these purposes has been studied for many years[1].

We have studied *Michael* addition reactions of α,β-unsaturated ketones to 2-nitrocycloalkanones[2] catalyzed by chiral bases[3]. We obtained the best optical yields in CCl_4 in agreement with the findings of Hiemstra & Wynberg[4]. Here we report the addition of methyl vinyl ketone **2** to 2-nitrocycloalkanones **1** catalyzed by cinchonine **3** (*Cinchona* alkaloid) (Scheme 1).



a: n=6
b: n=7
c: n=8
d: n=9
e: n=10
f: n=12
g: n=16

Scheme 1

[#] Present address: Institute of Organic Chemistry, Bulgarian Academy of Sciences, 1113-Sofia, Bulgaria

The reactions were carried out as follows: 1.1 mmol of methyl vinyl ketone **2** was added to a stirred solution of 1.0 mmol 2-nitrocycloalkanone **1** and 1.0 mmol cinchonine **3** in 15 ml of CCl_4 under argon at -20°C and stirred at this temperature until no starting material was detected by TLC or GC. The mixture was then filtered either through a short silicic acid (*Serva, Mallinckrodt*, 100 mesh) or silica gel (*Merck, Kieselgel 60* PF_{254}) column, dried and evaporated. The resulting raw material was purified by flash chromatography or by crystallization. The enantiomeric excess of the products **4a**-**4g** were established by ^1H NMR in $CDCl_3$ using $Eu(hfc)_3$ as the chiral shift reagent. The results are shown in Table 1.

Table 1: *Michael* Addition of Methyl Vinyl Ketone **2** to 2-Nitrocycloalkanones **1** Catalyzed by Cinchonine **3** in CCl_4, t = -20°C

Product	Time h	Yield$^{a)}$ %	$[\alpha]_D^{22}$ $^{b)}$	e.e. %$^{c)}$
4a	60	84	−44.2	54.6
4b	30	95	+ 6.6	45.5
4c	45	92	−28.1	60.0
4d	48	95	+23.8	25.0
4e	22	91	+21.5	28.6
4f	90	87	+22.3	25.0
4g	64	97	+ 7.2	28.0

a) isolated yields; b) measured in $CHCl_3$ (c=0.6-1.4); c) determined by ^1H NMR analysis in $CDCl_3$ in the presence of $Eu(hfc)_3$, base-line separation of the methyl group

The oil **4c** was dissolved in a mixed solvent of diethyl ether and hexane, and the solution was kept at -20°C over night. In this case the racemic **4c** crystallized out, and the mother liquor yielded enantiomerically enriched (-)-**4c**[5], e.e. = 94.4%. The enantiomerically enriched (+)-**4f**[6], e.e. > 95%, obtained from the mother liquor fraction, was separated similarly in methanol at +4°C.

It is interesting to note that **4a** and **4c** show negative optical rotation in $CHCl_3$ while the others show positive rotation. As shown in Figure 1, the CD spectra of (-)-**4c** and (+)-**4f** are opposite. This could mean that (-)-**4c** and (+)-**4f** possess opposite configurations. To clarify this, (-)-**4c** was derivatized with 1,3-propanedithiol. The absolute configuration of the resulting (-)-2-[2'-(2"-methyl-1",3"-dithian-2"-yl)ethyl]-2-nitrocyclooctanone **5**[3,7] was determined by X-ray diffraction, and is found to be *S*. (+)-**4f** was derivatized with (2*R*,3*R*)-(+)-1,4-bis(4-chlorobenzyloxy)-2,3-butanediol. The relative configuration of (+)-2-{2'-{4",5"-bis[(4-chlorobenzyloxy)methyl]-2"-methyl-1",3"-dioxolan-2"-yl}ethyl}-2-nitrocyclododecanone **6**[3,8] was determined by X-ray diffraction using the already known configuration at C-4" & C-5", the absolute configuration at C-2 of **6** was therefore assigned as *R*. The only compound in this series, which shows an abnormal solvent effect in $CHCl_3$ is **4b**; though its absolute configuration is the same as **4a** and **4c**.

In these *Michael* additions the enantioselectivity and absolute configuration of the products depend on the ring size. The optical yields of six- to eight-membered rings are up to 60% e.e. and they are lower (about 25%

e.e.) in the case of larger rings. The absolute configuration of six- to eight-membered rings is *S*, and nine-membered and larger rings possess the *R* configuration. The reaction mechanism will be discussed in Ref. 3.

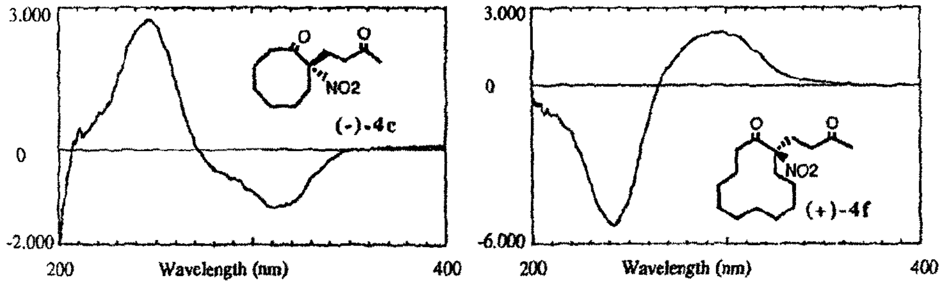


Fig. 1. CD spectra of (-)-4c and (+)-4f taken in $CHCl_3$

Acknowledgements: We thank the *Swiss National Science Foundation* for financial support of this work.

References and Notes

1. See e.g. Wynberg, H. in "Topics in Stereochemistry", Ed. Eliel, E. L.; Wilen, S. H.; Allinger, N. L., John Wiley & Sons, New York, 1986, Vol. 16, p. 87. Fujii, M.; Sato, Y.; Aida, T.; Yoshihara, M. *Chem. Express* **1992**, *7*, 309. Nerinckx, W.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 265. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. *J. Chem. Soc., Chem. Commun.* **1991**, 485. Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.
2. Bischoff, C.; Schröder, E. *J. Prakt. Chem.* **1972**, *314*, 891. Dampawan, P.; Zajac, W. W., Jr. *Synthesis* **1983**, 545. Feuer, H.; Pivawer, P. M. *J. Org. Chem.* **1966**, *31*, 3152. Kostova, K.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 1713. Stanchev, S.; Hesse, M. *Helv. Chim. Acta* **1987**, *70*, 1389. Hesse, M. "Ring Enlargement in Organic Chemistry", VCH, Weinheim, 1991.
3. Latvala, A. Ph.D. Thesis Univ. Zürich in preparation. Stanchev, S. Ph.D. Thesis Univ. Zürich, 1989. Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Helv. Chim. Acta* in preparation.
4. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.
5. (*S*)-4c: colorless oil; $[\alpha]_D^{22} = -42.3$ (c=1.39, $CHCl_3$); CD ($1.27 \cdot 10^{-4}$ M, $CHCl_3$): 207 (0.00), 246 (+2.75), 272 (0.00), 311 (-1.17), 353 (0.00). *IR* ($CHCl_3$): 2920, 2860, 1725, 1550, 1538, 1470, 1450, 1435, 1170, 1080. *^1H NMR* (400 MHz, $CDCl_3$): 2.74-2.46 (*m*, 5 H); 2.40-2.15 (*m*, 5 H), therein by 2.14 (*s*, CH_3); 1.93-1.58 (*m*, 8 H); 1.20-1.03 (*m*, 1 H). *^{13}C NMR* (50 MHz, $CDCl_3$): 205.9 (*s*, C(3')); 204.8 (*s*, C(1)); 97.5 (*s*, C(2)); 38.2, 37.7, 32.0 (3 *t*); 29.7 (*q*, CH_3); 28.4, 27.6, 25.3, 24.3, 22.3 (5 *t*). *CI-MS*: 242 $[M+1]^+$. Anal. calc. for $C_{12}H_{19}NO_4$ (241.292): C 59.73, H 7.94, N 5.80; found: C 59.99, H 8.19, N 5.91.
6 (*R*)-4f: colorless crystals; mp 94-95°C; $[\alpha]_D^{22} = +85.0$ (c=0.96, $CHCl_3$); CD ($1.24 \cdot 10^{-4}$ M, $CHCl_3$): 198 (0.00), 242 (-5.30), 265 (0.00), 298 (+2.08), 359 (0. 00). *IR* (KBr): 2940, 2920, 2865, 1725, 1548, 1538, 1475, 1440, 1170, 1080.

^1H NMR (200 MHz, $CDCl_3$): 2.85-2.74 (*m*, 1 H); 2.52-2.03 (*m*, 11 H), therein by 2.13 (*s*, CH_3); 1.42-1.00 (*m*, 15 H). *^{13}C NMR* (50 MHz, $CDCl_3$): 205.8 (*s*, C(3')); 200.9 (*s*, C(1)); 100.1(*s*, C(2)); 37.3, 32.7, 30.5 (3 *t*); 29.9 (*q*, CH_3); 26.9, 26.4, 26.2, 23.3, 22.6, 21.9, 21.8, 21.3, 19.1 (9 *t*). *CI-MS*: 298 $[M+1]^+$. Anal. calc. for $C_{16}H_{27}NO_4$ (297.393): C 64.62, H 9.15, N 4.71; found: C 64.65, H 9.20, N 4.55.

7. (*S*)-5: colorless crystals; mp 88.0-89.4°C; $[\alpha]_D^{22}$ = -41.8 (c=0.62, $CHCl_3$); *IR* (KBr): 2940, 2895, 2860, 2820, 1730, 1545, 1532, 1475, 1465, 1445, 1420, 1372, 1345, 1330, 1245, 1230, 1150, 1118, 1085, 1075, 905, 865, 845, 820, 765. *^1H NMR* (200 MHz, $CDCl_3$): 2.91-2.82 (*m*, 2 H); 2.78-2.68 (*m*, 4 H), 2.52-2.27 (*m*, 3 H); 2.07-1.24 (*m*, 14 H), therein by 1.54 (*s*, CH_3). *^{13}C NMR* (50 MHz, $CDCl_3$): 204.7 (*s*, C(1)); 98.1 (*s*, C(2)); 48.0 (*s*, C(2")); 38.0, 34.4, 31.4, 29.3, 28.4 (5 *t*); 27.5 (*q*, CH_3); 26.4, 26.3, 25.4, 24.8, 24.1, 22.4 (6 *t*). *CI-MS*: 349 $[M+1+NH_3]^+$. Crystal data: $C_{15}H_{25}NO_3S_2$, Mr= 331.49, orthorhombic; space group $P2_12_12_1$ (#19), a = 12.502 (2), b = 18.870 (3), c = 7.252 (3) Å, V = 1710.7 (6) Å^3, Z = 4, D_{calc} = 1.287 g cm^{-3}, F(000) = 712, μ (MoK_α) = 3.060 cm^{-1}, *Rigaku AFC5R* diffractometer, T= -100 ± 1°C, R=0.0311, R_w=0.0263 for 4154 reflections with $I>3\sigma(I)$. After the full structure was refined to convergence using the *TEXSAN* program package of Molecular Structure Corporation, the reflection data and atomic coordinates were transferred to the program *CRYSTALS* on which it is possible to refine the enantiopole, or Flack's χ, parameter. This parameter refined to 0.02 (6) which confidently confirms that the refined coordinates represent the correct configuration. Full details of the crystal structure have been deposited at the Cambridge Data Centre.

8. (2*R*,4"*R*,5"*R*)-6: colorless crystals; mp 105-107°C; $[\alpha]_D^{22}$ = +49.6 (c=1.19, $CHCl_3$); *IR* (KBr): 2930, 2860, 1720, 1595, 1535, 1492, 1470, 1445, 1410, 1135, 1110, 1090, 1015, 865, 838, 802. *^1H NMR* (200 MHz, $CDCl_3$): 7.33-7.22 (*s*, 8 arom. H); 4.53 (*d*, *J*=1.9 Hz, 4 H, CH_2-C_6H_4); 4.12-4.06 (*m*, *CH*-O); 4.00-3.94 (*m*, *CH*-O); 3.64-3.54 (*m*, 4 H, CH-CH_2-O); 2.87-2.76 (m, 1 H); 2.38-2.03 (*m*, 6 H); 1.75-1.24 (*m*, 20 H), therein by 1.37 (*s*, CH_3). *^{13}C NMR* (50 MHz, $CDCl_3$): 201.2 (*s*, C(1)); 136.3 (*s*, 2 arom. *C*-CH_2); 133.3 (*s*, 2 arom. *C*-Cl); 128.8; 128.5 (2 *d*, 8 arom. CH); 110.0 (*s*, C(2")); 100.7 (*s*, C(2)); 77.7, 77.3 (2 *d*, C(4"), C(5")); 72.6 (*t*, 2 CH_2-C_6H_4); 70.4, 69.9 (2 *t*, C(4")-CH_2, C(5")-CH_2)); 33.0, 32.2, 29.1, 26.7, 26.2 (5 *t*, 6 CH_2), 25.5 (*q*, CH_3), 23.1, 22.5, 21.8, 21.6, 21.3. 18.8 (6 *t*, 6 CH_2). *CI-MS*: 650 $[M+1]^+$ with $^{35}Cl_2$. Crystal data: $C_{34}H_{45}Cl_2NO_7$, Mr= 650.64, monoclinic; space group $P2_1$ (#4), a = 11.810 (2), b = 8.716 (2), c = 17.295 (2) Å, β = 106.93 (1)°, V = 1703.1 (5) Å^3, Z = 2, D_{calc} = 1.269 g cm^{-3}, F(000) = 692, μ (MoK_α) = 2.340 cm^{-1}, *Nicolet-R3* diffractometer, T= -60°C, R=0.0522, R_w=0.0497 for 2964 reflections with $I>2\sigma(I)$. Structure solution was performed using the direct methods routine of *SHELXS86*. Data reduction and refinement of the structure was performed with the *TEXSAN* program package of Molecular Structure Corporation. Empirical absorption corrections were applied using *DIFABS*. Full details of the crystal structure have been deposited at the Cambridge Data Centre.