Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 79-82, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(94)00356-4

Methyl Methacrylate as Acceptor in the Asymmetric Michael Reaction Using Chiral β-Enaminoesters: Simultaneous, Complete Stereocontrol of a Quaternary Carbon Center and a Tertiary One in the β-Position

Christian Cavé, Valérie Daley, Jean d'Angelo

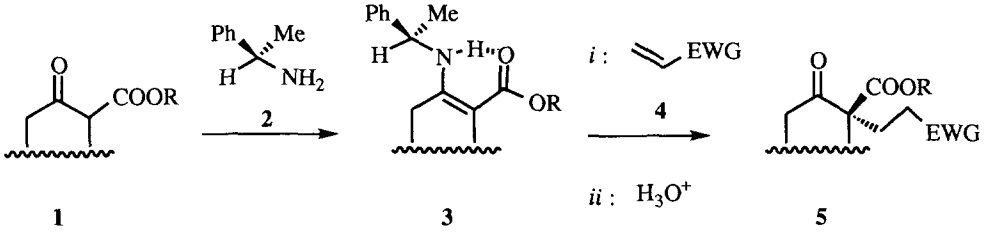
Unité de Chimie Organique Associée au CNRS, Centre d'Etudes Pharmaceutiques, Université Paris-Sud, 5, rue J.-B. Clément, 92296 Châtenay-Malabry (France).

André Guingant

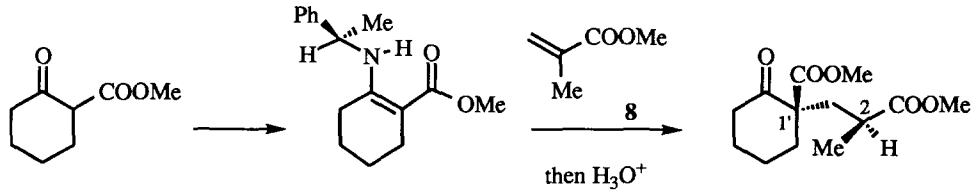
Laboratoire de Synthèse Organique Associé au CNRS, Université de Nantes, 2 rue de la Houssinière, 44072 Nantes (France).

Abstract : Addition of enaminoester (R)-7 to methyl methacrylate 8 led to adduct (2S, 1'R)-9 with a complete stereoselectivity.

It has been reported that chiral β-enaminoesters **3**, derived from cyclic β-ketoesters **1** and optically active 1-phenylethylamine **2**, add to electron-deficient alkenes **4** leading, after hydrolytic work-up, to adducts **5** with a high yield and an excellent stereoselectivity.[1-5] This reaction has been applied to the approach to several naturally occurring compounds, for example (-)-malyngolide[2] and *Nitraria* alkaloids.[3]

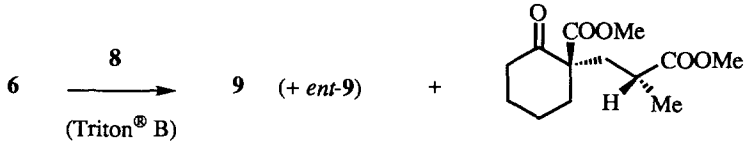


In this paper, we show that the addition of methyl methacrylate **8** to enaminoester **7** furnished adduct **9** as a *single* compound (de and ee ≥ 95 %), *thereby allowing the simultaneous, complete stereocontrol of a quaternary carbon center and a tertiary one in the β-position.* Enaminoester (*R*)-(-)-**7**[6] was prepared from keto-ester **6** and enantiopure (*R*)-1-phenylethylamine ($[\alpha]_D^{20}$ = +40.6, neat) (12 h in refluxing benzene, Dean-Stark trap, 86 % yield). This enaminoester was then added to methyl methacrylate **8** (Et_2O, 20 °C, 7 days, 1.2 eq of anhydrous $MgBr_2$ and 3.6 eq of **8**, both added in 12 times). After hydrolytic work-up (10 % AcOH in water, 20 °C, 24 h) adduct (2*S*, 1'*R*)-(+)-**9**[7] was isolated with a 72 % overall yield by flash chromatography on silica gel.



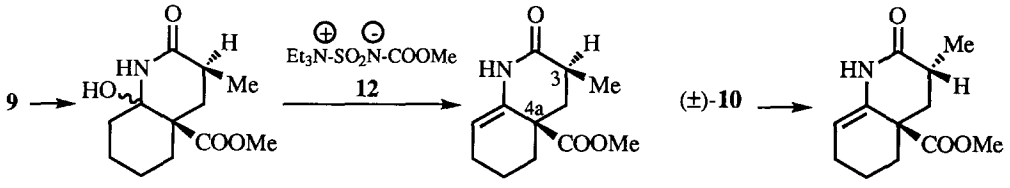
6 **7** **9**

This adduct proved to be homogeneous by (non-chiral)-GC analysis, ^{13}C and ^{1}H NMR spectroscopy (including in the latter case experiments using $Eu(FOD)_3$ and $Eu(hfc)_3$ as shift reagents). For comparison, a *racemic* specimen of **9**, accompanied with its diastereomer (±)-**10**, was prepared in a non-stereoselective fashion by addition [**6**+**8**] in the presence of Triton® B (3 eq of **8**, 0.1 eq of Triton® B, 12 h in refluxing THF).



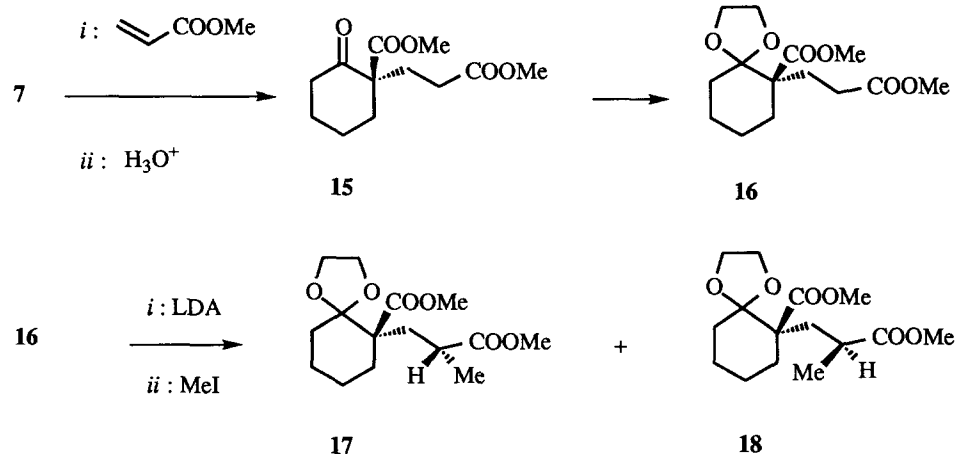
10 (+ *ent*-**10**)

The relative configuration of the two stereogenic centers in **9** was assigned by chemical correlation. For this purpose **9** was first cyclized into lactam **11** by addition of ammonia (NH_3 in MeOH, 48 h at 20 °C). Dehydration of **11** (Burgess inner salt **12**[8], 3 h in refluxing toluene) then led to (3*S*, 4a*R*)-(+)-**13**[9] (72 % overall yield), in which the methyl group at C-3 and the angular carbomethoxy substituent exhibit the *syn* relationship (by ^{1}H NMR, by comparison with diastereomer (±)-**14**[10], prepared from (±)-**10**, in a similar fashion to conversion [**9**→**13**]).

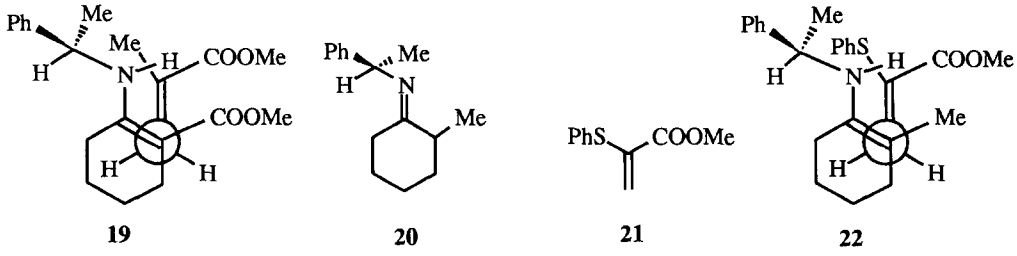


11 **13** **14** (+ *ent*-**14**)

The absolute configuration at the quaternary carbon center in adduct **9** (1'*R*) was determined as follows. Compound (*R*)-(+)-**15**[1,11] (prepared with an ee ≥ 95 % by condensation of enaminoester **7** with methyl acrylate in the presence of $MgBr_2$) was protected[12] as ketal derivative (*R*)-(+)-**16**.[13] Sequential deprotonation of **16** (LDA, THF, -78 °C) and methylation (MeI, -78 °C, 3 h) next produced with 76 % yield a mixture of diastereomers (2*R*, 1'*R*)-(+)-**17**[14] and (2*S*, 1'*R*)-(-)-**18**[15], easily separated by flash chromatography on silica gel (eluent: AcOEt/cyclohexane: 30/70), in the ratio of 4.5:1. Acidic hydrolysis of the minor isomer **18** led to the corresponding ketoester which proved to be identical in all respects with (+)-**9**[7], thereby establishing the *R* configuration of this adduct.



The remarkable complete stereocontrol of the two stereogenic centers in adduct **9** may be interpreted by evoking, as proposed earlier for related additions,[5] that reaction [**6**+**7**→**9**] proceeds through the compact approach **19** involving a *synclinal* arrangement of the enaminoester and the electrophilic alkene. According to such a model, the alkylation takes place *anti* to the phenyl ring of the chiral amine moiety, depicted in its energetically preferred conformation (the C-H nearly eclipsing the cyclohexane ring), thereby delivering the *R* configuration at the quaternary carbon center. The complete stereocontrol observed at the C-2 tertiary center requires that the N-H proton of enaminoester **7** should be transferred to the C-2 vinylic atom of methyl methacrylate **8**, *concertedly* to the creation of the C-C bond. Furthermore, in order to account for the observed stereochemistry, the electrophilic alkene should be arranged as indicated, namely the carbomethoxy group orientated in the *exo*-position relatively to the enaminoester partner. It should be pointed out that approach **22**, closely related to **19**, has been previously proposed in the addition of imine **20** to methyl 2-phenylthioacrylate **21**.[16]



If, as a rule,[5] the asymmetric Michael reaction using chiral imines (or enaminoesters) implicates compact approaches of the two reactants such as **19** and **22**, the *exo*-spatial arrangement of the electrophilic partner found in these two approaches does not appear to be general. We have thus recently demonstrated that additions of methyl 2-acetoxyacrylate or ethyl 2-deuteroacrylate to imine **20** arise both in the *endo*-fashion.[17] Factors responsible for the *endo*/*exo* orientation of the electrophile are currently under investigation.

NOTES AND REFERENCES

1- Guingant, A.; Hammami, H. *Tetrahedron : Asymmetry*, **1991**, *2*, 411-414.
2- Guingant, A. *Tetrahedron : Asymmetry*, **1991**, *2*, 415-418.
3- Guingant, A.; Hammami, H. *Tetrahedron : Asymmetry*, **1993**, *4*, 25-26.
4- For a related reaction using chiral β-enaminolactones, see: Felk, A.; Revial, G.; Viossat, B.; Lemoine, P.; Pfau, M. *Tetrahedron : Asymmetry*, **1994**, *5*, 1459-1462.
5- Review: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron : Asymmetry*, **1992**, *3*, 459-505.
6- **7**: solid, mp 40 °C (hexane); **IR** (KBr, cm^{-1}) 3275, 1748, 1652, 1600, 1493, 1448, 1375; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 9.40 (d, J = 6.0 Hz, 1H), 7.30 (m, 5H), 4.65 (dq, J = 6.0, 6.7 Hz, 1H), 3.70 (s, 3H), 2.40-1.60 (m, 8H), 1.50 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) 171.2 (C), 159.2 (C), 145.7 (C), 128.6 (2 CH), 126.8 (CH), 125.4 (2 CH), 90.2 (C), 51.9 (CH), 50.3 (CH_3), 26.5 (CH_2), 25.3 (CH_3), 23.7 (CH_2), 22.5 (CH_2), 22.1 (CH_2); $[\alpha]_D^{20}$ = -526 (c = 2.6, CCl_4); **Anal.** Calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.40. Found: C, 74.03; H, 8.14; N, 5.42.
7- **9**: oil; **IR** (neat, cm^{-1}) 1740, 1715, 1438, 1379; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.60 (s, 3H), 2.50-1.40 (m,11H), 1.16 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) 207.2 (C), 176.7 (C), 172.5 (C), 59.9 (C), 52.3 (CH_3), 51.5 (CH_3), 40.7 (CH_2), 37.8 (CH_2), 35.5 (CH_2), 35.2 (CH), 27.1 (CH_2), 22.2 (CH_2), 19.9 (CH_3); $[\alpha]_D^{20}$ = +56 (c = 1.7, CCl_4); **Anal.** Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 60.71; H, 7.94.
8- Burgess, E. M.; Penton, Jr., H. R.; Taylor, E.A. *J. Org. Chem.*, **1973**, *38*, 26-31.
9- **13**: amorphous solid; **IR** ($CHCl_3$, cm^{-1}) 1730, 1662, 791; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 5.03 (dd, J = 3.5, 3.5 Hz, 1H), 3.65 (s, 3H), 2.34-2.24 (m, 3H), 2.18-1.93 (m, 2H), 1.77-1.63 (m, 1H), 1.50-1.27 (m, 3H), 1.15 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$). 175.0 (C), 172.9 (C), 133.8 (C), 106.3 (CH), 52.5 (CH_3), 45.9 (C), 39.1 (CH_2), 33.9 (CH), 33.7 (CH_2), 23.2 (CH_2), 19.0 (CH_2), 16.1 (CH_3); $[\alpha]_D^{20}$ = +21.4 (c = 1.0, MeOH).
10- **14**: amorphous solid; **IR** ($CHCl_3$, cm^{-1}) 1729, 1657, 1446, 1232, 793; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (br s, 1H), 5.08 (dd, J = 3.7, 3.7 Hz, 1H), 3.71 (s, 3H), 2.64 (ddq, J = 1.8, 7.1, 7.8 Hz, 1H), 2.30 (br d, J = 10.5 Hz, 1H), 2.23 (dd, J =1.8, 14.0 Hz, 1H), 2.15-2.10 (m, 1H), 1.91 (dd, J = 7.1, 14.0 Hz, 1H), 1.74-1.71 (m, 1H), 1.50-1.22 (m, 3H), 1.15 (d, J = 7.8 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) 175.4 (C), 172.9 (C), 133.7 (C), 107.4 (CH), 52.5 (CH_3), 44.0 (C), 37.7 (CH_2), 35.2 (CH_2), 34.2 (CH), 23.5 (CH_2), 19.2 (CH_2), 18.0 (CH_3).
11- **15**: oil; **IR** (neat, cm^{-1}) 1741, 1714; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.55 (s, 3H), 2.42-1.24 (m, 12H); **^{13}C NMR** (50 MHz, $CDCl_3$) 207.5 (C), 173.5 (C), 172.3 (C), 60.1 (C), 52.5 (CH_3), 51.7 (CH_3), 41.1 (CH_2), 36.4 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 27.5 (CH_2), 22.6 (CH_2); $[\alpha]_D^{20}$ = +79 (c = 2.8, CCl_4); **Anal.** Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.48. Found: C, 59.48; H, 7.53.
12- Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.*, **1980**, *21*, 1357-1358.
13- **16**: oil; **IR** (neat, cm^{-1}) 1737, 957; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.80 (m, 4H), 3.57 (s, 3H), 3.53 (s, 3H), 2.30-1.20 (m, 12H); **^{13}C NMR** (50 MHz, $CDCl_3$) 177.3 (C), 173.7 (C), 110.6 (C), 64.7 (CH_2), 64.4 (CH_2), 53.9 (C), 51.7 (CH_3), 51.5 (CH_3), 31.9 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 26.6 (CH_2), 22.8 (CH_2), 20.8 (CH_2); $[\alpha]_D^{20}$ = +9.3 (c = 3.0, CCl_4); **Anal.** Calcd for $C_{14}H_{22}O_6$: C, 58.72; H, 7.74. Found: C, 58.61; H, 7.81.
14- **17**: oil; **IR** (neat, cm^{-1}) 1737, 1460, 1377, 948; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.90 (m, 4H), 3.70 (s, 3H), 3.66 (s, 3H), 2.40-1.20 (m, 11H), 1.07 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) 178.5 (C), 174.8 (C), 111.1 (C), 65.1 (CH_2), 64.9 (CH_2), 54.7 (C), 52.0 (CH_3), 51.9 (CH_3), 36.7 (CH), 34.7 (CH_2), 32.2 (CH_2), 29.6 (CH_2), 23.2 (CH_2), 20.7 (CH_2), 19.6 (CH_3); $[\alpha]_D^{20}$ = +27.7 (c = 1.4, CCl_4); **Anal.** Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.01; H, 8.11.
15- **18**: oil; **IR** (neat, cm^{-1}) 1737, 1462, 1379, 961; **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.90 (m, 4H), 3.66 (s, 3H), 3.63 (s, 3H), 2.60-1.30 (m, 11H), 1.15 (d, J = 6.1 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) 177.0 (C), 174.5 (C), 110.7 (C), 64.8 (CH_2), 64.3 (CH_2), 53.8 (C), 51.6 (CH_3), 51.5 (CH_3), 35.6 (CH), 35.5 (CH_2), 31.8 (CH_2), 30.8 (CH_2), 23.0 (CH_2), 21.1 (CH_2), 19.8 (CH_3); $[\alpha]_D^{20}$ = -1.0 (c = 5.8, CCl_4); **Anal.** Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.79; H, 7.98.
16- d'Angelo, J.; Guingant, A.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.*, **1988**, *29*, 2667-2670.
17- Ambroise, L.; Desmaële, D.; Mahuteau, J.; d'Angelo, J. submitted for publication.

Acknowledgment. *We thank Ms Claire Bouillon-Tallendier for performing preliminary experiments.*

(*Received in UK* 30 *September* 1994)