



0957-4166(94)00356-4

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

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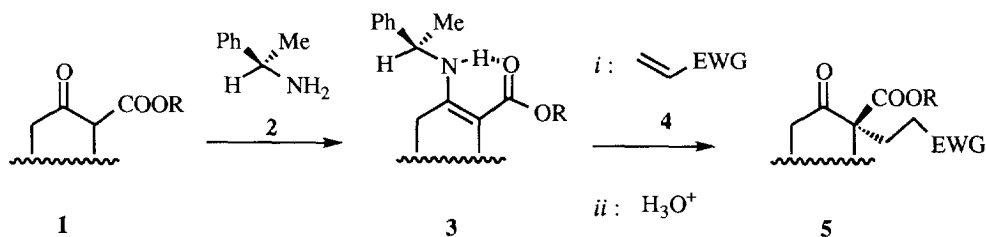
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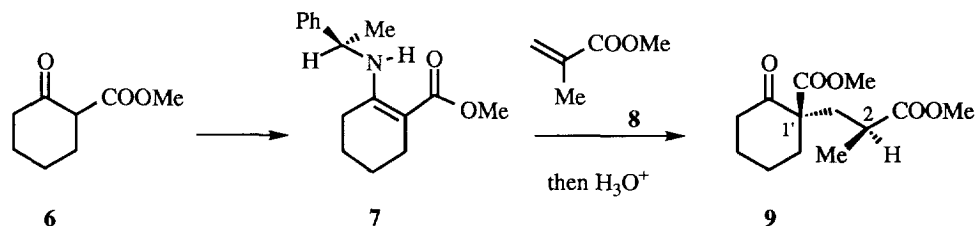
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*Abstract* : Addition of enaminoester (*R*)-**7** to methyl methacrylate **8** led to adduct (*2S*, *1'R*)-**9** with a complete stereoselectivity.

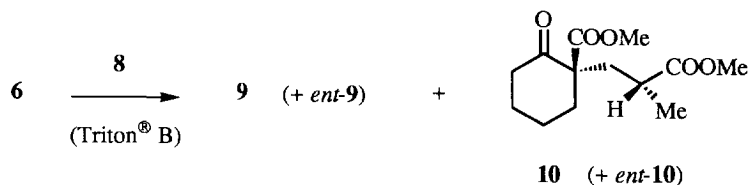
It has been reported that chiral  $\beta$ -enaminoesters **3**, derived from cyclic  $\beta$ -ketoesters **1** and optically active 1-phenylethylamine **2**, add to electron-deficient alkenes **4** leading, after hydrolytic work-up, to adducts **5** with a high yield and an excellent stereoselectivity.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



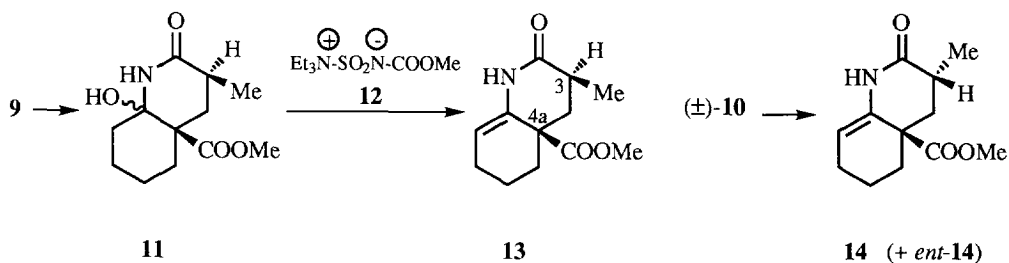
In this paper, we show that the addition of methyl methacrylate **8** to enaminoester **7** furnished adduct **9** as a *single* compound (de and ee  $\geq 95\%$ ), thereby allowing the simultaneous, complete stereocontrol of a quaternary carbon center and a tertiary one in the  $\beta$ -position. Enaminoester (*R*)-(-)-**7**<sup>6</sup> was prepared from ketoester **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<sub>2</sub>O, 20 °C, 7 days, 1.2 eq of anhydrous MgBr<sub>2</sub> and 3.6 eq of **8**, both added in 12 times). After hydrolytic work-up (10% AcOH in water, 20 °C, 24 h) adduct (*2S*, *1'R*)-(+)-**9**<sup>7</sup> was isolated with a 72% overall yield by flash chromatography on silica gel.



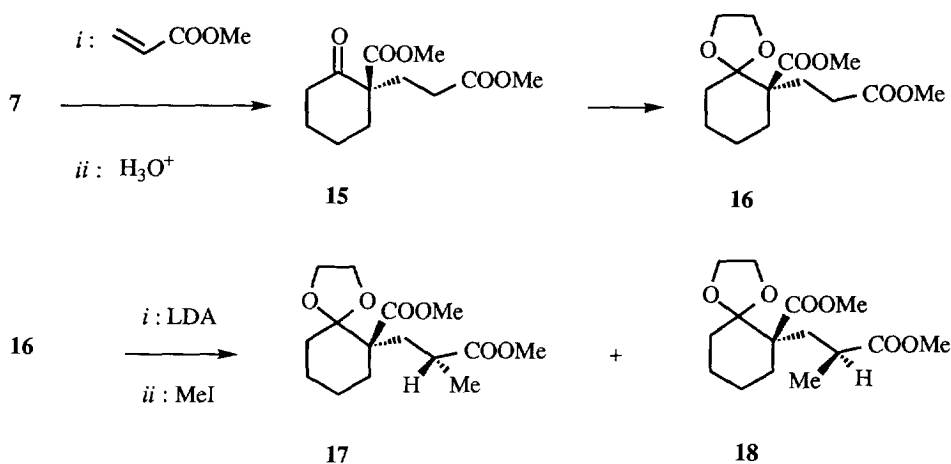
This adduct proved to be homogeneous by (non-chiral)-GC analysis,  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectroscopy (including in the latter case experiments using  $\text{Eu}(\text{FOD})_3$  and  $\text{Eu}(\text{hfc})_3$  as shift reagents). For comparison, a *racemic* specimen of **9**, accompanied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



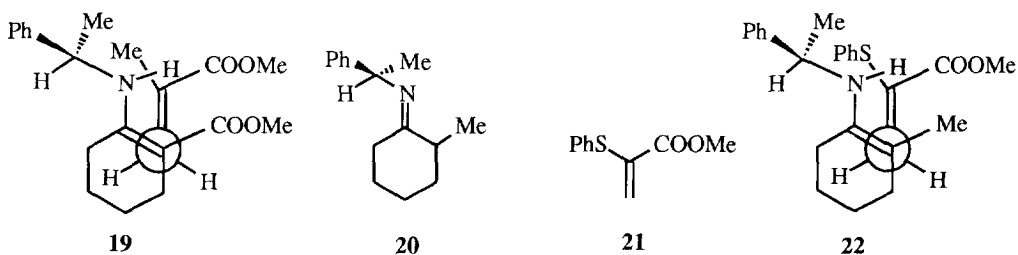
The relative configuration of the two stereogenic centers in **9** was assigned by chemical correlation. For this purpose **9** was first cyclized into lactam **11** by addition of ammonia ( $\text{NH}_3$  in MeOH, 48 h at 20 °C). Dehydration of **11** (Burgess inner salt **12**<sup>8</sup>, 3 h in refluxing toluene) then led to (3*S*, 4*aR*)-(+)-**13**<sup>9</sup> (72 % overall yield), in which the methyl group at C-3 and the angular carbomethoxy substituent exhibit the *syn* relationship (by  $^1\text{H}$  NMR, by comparison with diastereomer ( $\pm$ )-**14**<sup>10</sup>, prepared from ( $\pm$ )-**10**, in a similar fashion to conversion [9→13]).



The absolute configuration at the quaternary carbon center in adduct **9** (1'*R*) was determined as follows. Compound (*R*)-(+)-**15**<sup>11</sup> (prepared with an ee  $\geq 95\%$  by condensation of enaminoester **7** with methyl acrylate in the presence of  $\text{MgBr}_2$ ) was protected<sup>12</sup> as ketal derivative (*R*)-(+)-**16**.<sup>13</sup> 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**<sup>14</sup> and (2*S*, 1'*R*)-(-)-**18**<sup>15</sup>, 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**<sup>7</sup>, 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,<sup>5</sup> 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 relative 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**.<sup>16</sup>



If, as a rule,<sup>5</sup> 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-deutoxyacrylate to imine **20** arise both in the *endo*-fashion.<sup>17</sup> Factors responsible for the *endo/exo* orientation of the electrophile are currently under investigation.

## NOTES AND REFERENCES

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- 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  $\beta$ -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,  $\text{cm}^{-1}$ ) 3275, 1748, 1652, 1600, 1493, 1448, 1375;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 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<sub>3</sub>), 26.5 (CH<sub>2</sub>), 25.3 (CH<sub>3</sub>), 23.7 (CH<sub>2</sub>), 22.5 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>);  $[\alpha]_{\text{D}}^{20} = -526$  ( $c = 2.6$ ,  $\text{CCl}_4$ ); Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}_2$ : C, 74.09; H, 8.16; N, 5.40. Found: C, 74.03; H, 8.14; N, 5.42.
- 7- **9**: oil; IR (neat,  $\text{cm}^{-1}$ ) 1740, 1715, 1438, 1379;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  3.70 (s, 3H), 3.60 (s, 3H), 2.50-1.40 (m, 11H), 1.16 (d,  $J = 6.4$  Hz, 3H);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 207.2 (C), 176.7 (C), 172.5 (C), 59.9 (C), 52.3 (CH<sub>3</sub>), 51.5 (CH<sub>3</sub>), 40.7 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 35.5 (CH<sub>2</sub>), 35.2 (CH), 27.1 (CH<sub>2</sub>), 22.2 (CH<sub>2</sub>), 19.9 (CH<sub>3</sub>);  $[\alpha]_{\text{D}}^{20} = +56$  ( $c = 1.7$ ,  $\text{CCl}_4$ ); Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_5$ : 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 ( $\text{CHCl}_3$ ,  $\text{cm}^{-1}$ ) 1730, 1662, 791;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 175.0 (C), 172.9 (C), 133.8 (C), 106.3 (CH), 52.5 (CH<sub>3</sub>), 45.9 (C), 39.1 (CH<sub>2</sub>), 33.9 (CH), 33.7 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>), 19.0 (CH<sub>2</sub>), 16.1 (CH<sub>3</sub>);  $[\alpha]_{\text{D}}^{20} = +21.4$  ( $c = 1.0$ , MeOH).
- 10- **14**: amorphous solid; IR ( $\text{CHCl}_3$ ,  $\text{cm}^{-1}$ ) 1729, 1657, 1446, 1232, 793;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 175.4 (C), 172.9 (C), 133.7 (C), 107.4 (CH), 52.5 (CH<sub>3</sub>), 44.0 (C), 37.7 (CH<sub>2</sub>), 35.2 (CH<sub>2</sub>), 34.2 (CH), 23.5 (CH<sub>2</sub>), 19.2 (CH<sub>2</sub>), 18.0 (CH<sub>3</sub>).
- 11- **15**: oil; IR (neat,  $\text{cm}^{-1}$ ) 1741, 1714;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  3.64 (s, 3H), 3.55 (s, 3H), 2.42-1.24 (m, 12H);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 207.5 (C), 173.5 (C), 172.3 (C), 60.1 (C), 52.5 (CH<sub>3</sub>), 51.7 (CH<sub>3</sub>), 41.1 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>);  $[\alpha]_{\text{D}}^{20} = +79$  ( $c = 2.8$ ,  $\text{CCl}_4$ ); Anal. Calcd for  $\text{C}_{12}\text{H}_{18}\text{O}_5$ : 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,  $\text{cm}^{-1}$ ) 1737, 957;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  3.80 (m, 4H), 3.57 (s, 3H), 3.53 (s, 3H), 2.30-1.20 (m, 12H);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 177.3 (C), 173.7 (C), 110.6 (C), 64.7 (CH<sub>2</sub>), 64.4 (CH<sub>2</sub>), 53.9 (C), 51.7 (CH<sub>3</sub>), 51.5 (CH<sub>3</sub>), 31.9 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 22.8 (CH<sub>2</sub>), 20.8 (CH<sub>2</sub>);  $[\alpha]_{\text{D}}^{20} = +9.3$  ( $c = 3.0$ ,  $\text{CCl}_4$ ); Anal. Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_6$ : C, 58.72; H, 7.74. Found: C, 58.61; H, 7.81.
- 14- **17**: oil; IR (neat,  $\text{cm}^{-1}$ ) 1737, 1460, 1377, 948;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 178.5 (C), 174.8 (C), 111.1 (C), 65.1 (CH<sub>2</sub>), 64.9 (CH<sub>2</sub>), 54.7 (C), 52.0 (CH<sub>3</sub>), 51.9 (CH<sub>3</sub>), 36.7 (CH), 34.7 (CH<sub>2</sub>), 32.2 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>), 20.7 (CH<sub>2</sub>), 19.6 (CH<sub>3</sub>);  $[\alpha]_{\text{D}}^{20} = +27.7$  ( $c = 1.4$ ,  $\text{CCl}_4$ ); Anal. Calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_6$ : C, 59.98; H, 8.05. Found: C, 60.01; H, 8.11.
- 15- **18**: oil; IR (neat,  $\text{cm}^{-1}$ ) 1737, 1462, 1379, 961;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  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);  $^{13}\text{C NMR}$  (50 MHz,  $\text{CDCl}_3$ ) 177.0 (C), 174.5 (C), 110.7 (C), 64.8 (CH<sub>2</sub>), 64.3 (CH<sub>2</sub>), 53.8 (C), 51.6 (CH<sub>3</sub>), 51.5 (CH<sub>3</sub>), 35.6 (CH), 35.5 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 23.0 (CH<sub>2</sub>), 21.1 (CH<sub>2</sub>), 19.8 (CH<sub>3</sub>);  $[\alpha]_{\text{D}}^{20} = -1.0$  ( $c = 5.8$ ,  $\text{CCl}_4$ ); Anal. Calcd for  $\text{C}_{15}\text{H}_{24}\text{O}_6$ : 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.