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THE CONTROL OF DIASTEREOSELECTIVITY IN THE MICHAEL REACTION OF KETONIC ENOLATES WITH CROTONIC ACID DERIVATIVES

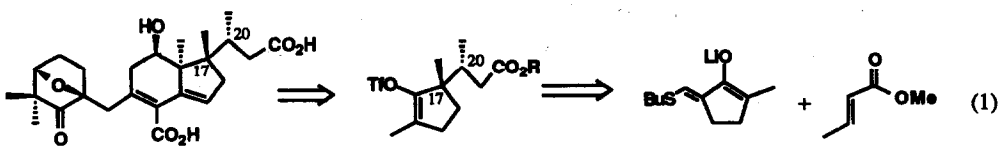
E. J. Corey and Ioannis N. Houpis

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *Methodology is described for the selective generation of either anti or syn Michael adducts from various ketone enolates and crotonic ester* **18** *or amide* **15**.

The Michael reaction to form 1,5-dicarbonyl compounds by C–C linkage has long been a powerful synthetic tool[1] for the construction of complex organic molecules, but until recently[2] very little has been known regarding control of stereochemistry with achiral components, in contrast to the Aldol reaction. Among the recent advances are control of both the relative and/or absolute stereochemistry in the addition of ester enolates to α,β-unsaturated esters[3] and in the addition of amide enolates to α,β-unsaturated ketones.[2c] More rare are additions of ketone enolates to α,β-unsaturated esters, since the equilibrium often favors the starting enolate instead of the enolate of the Michael adduct.[4]

During the synthesis of glycinoeclepin A[5] we required a convenient method for the construction of the side chain with the depicted *anti*-methyl stereochemistry at the C_{17}–C_{20} centers (eq 1), for which one possibility is a stereocontrolled Michael addition of the enolate of 2-methylcyclopentanone to methyl crotonate. This letter describes a solution to both the reactivity problem and the control of stereochemistry so that either the *anti* or *syn* stereochemistry can be obtained with high selectivity. The reactivity issue was resolved by introduction of an activating group at the alpha position of the crotonate, and diastereoselectivity was achieved by the proper selection of solvent, enolate counterion and activating group (X). The regiospecific generation of the enolate **2** was accomplished by reaction of the silyl ether **1** with MeLi in THF at 0 °C. Direct reaction of the enolate thus generated at -78 °C with methyl crotonate gave none of the expected Michael adduct **9** (X=H) but only starting material. Sufficient activation of the crotonate moiety could be achieved by the introduction of a thiophenyl group[6] at the alpha position and, indeed, reaction of **2** with **8** in THF at -78 °C afforded the



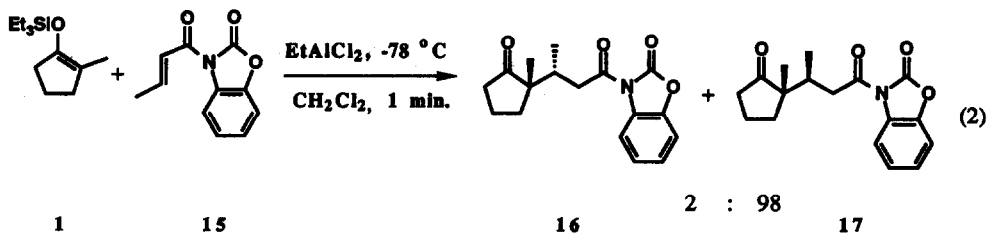
(1)

Glycinoeclepin A A

Michael products **9** and **10** (X=PhS, Table 1, entry 1) in 82% isolated yield.[7] In an attempt to improve the *anti* to *syn* ratio, the solvent and the activating group X in **8** were varied with the results shown in Table 1. Polar non-coordinating solvents favored (entries 1-4) the *anti*-diastereomer **9** (X=PhS), with reaction in CH_2Cl_2 giving the highest selectivity observed with the Li enolate. Interestingly, the rate of the reaction was not sensitive to changes in solvent polarity and donor coordination.

Greater activation of the crotonate by the use of more strongly electron withdrawing substituents (**8 a-c**) resulted in good yields of the Michael adduct upon reaction with **2**; however, complete erosion of the selectivity was observed (entries 5-7). Large ester substituents,[8] such as menthyl, gave poor diastereoselectivity (entry 8) at -78 °C while the *syn* adduct (**14b**, X=PhS) was obtained predominantly when the reaction was run at 0 °C (entry 9). Reaction of the $TiCl_3$ ($TiCl_4$, CH_2Cl_2) or EtAlCl enolates (Li enolate then $EtAlCl_2$), **3** or **4**, with **8** did not provide any of the desired Michael adducts (entries 10, 11) while the Bu_3Sn enolate **5** in toluene (Li enolate then Bu_3SnCl) gave predominantly the *syn* product (entry 12). Finally, excellent *anti* selectivity was obtained when the potassium enolate **6** (KHMDS, -78 °C, THF, 30 min) was employed in the condensation with **8** (entry 13).[9] The reaction was complete in 1 h at -78 °C to give the adducts **11** and **12** (X=PhS, ratio 97 : 3 respectively). Conversely, reaction of **8** with the *Li* enolate **7**, failed to give any of the Michael adduct even after 12 h at -78 °C, while higher temperatures led to decomposition (entry 14). We were gratified to find that the *syn* adduct could be obtained with high selectivity by reacting the silyl ether **1** with the oxazolidinone **15** ($EtAlCl_2$, CH_2Cl_2, -78 °C, 1 min) (eq 2). The adducts **16** and **17** (85% yield, ratio 2 : 98) could be separated by chromatography on silica gel and converted to the ketoesters **9** and **10** (X=H) by hydrolysis (LiOOH, THF–H_2O)[10] followed by esterification (CH_2N_2, ether).

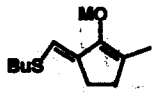
The potassium enolate addition can also be used to provide Michael adducts of high enantiomeric purity. For example, good face selectivity (95 : 5) was observed in the reaction of **6** with phenmenthyl (α-thiophenyl) crotonate **18**, although there was some deterioration of the C_{17}–C_{20} diastereoselectivity in this case (eq 3).[11] The desired diastereomer could be isolated and converted to glycinoeclepin A via the enol triflate **A**.



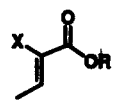
1 **15** **16** **17**

In conclusion , we have devised methodology that allows the Michael addition of a ketone enolate to an α,β-unsaturated carboxylic acid derivative with good diastereoselectivity and chemical yield. Either the *anti* or *syn* adduct can be formed selectively by the use of appropriate reaction conditions.[12]

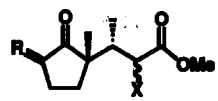
1 M=$SiEt_3$
2 M=Li
3 M=$TiCl_3$
4 M= EtAlCl
5 M= Bu_3Sn



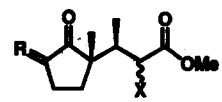
6 M=K
7 M=Li



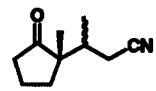
8 X= SPh, R= Me
8a X= SO_2Ph, R= Me
8b X= CO_2Me, R= Me
8c X= CN, R= Me
8d X= SPh, R= menthyl



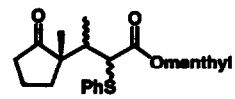
9 R=H,H
11 R=BuSCH



10 R=H,H
12 R=BuSCH



13a α-methyl
13b β-methyl

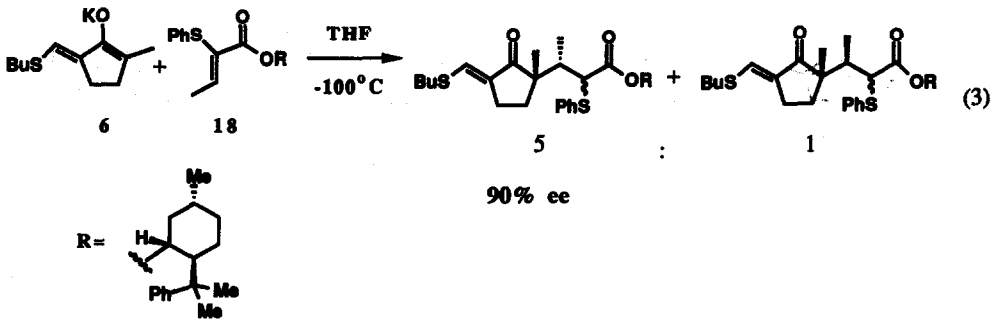


14a α-methyl
14b β-methyl

Table 1: Michael addition of ketone enolates to activated crotonates

Entry	Enolate	Crotonate	Solvent	Time / Temp.	Products	Ratio[a]	Yield[b]
1	2	8	THF	48 h / -78 °C	9 : 10	4 : 1	82%
2	2	8	THF-Hexane (1:1)	48 h / -78 °C	9 : 10	5 : 1	80%
3	2	8	$PhCH_3$	48 h / -78 °C	9 : 10	8 : 1	87%
4	2	8	CH_2Cl_2	48 h / -78 °C	9 : 10	15 : 1	81%
5	2	8a	$PhCH_3$	1 min / -78 °C	9 : 10	1 : 4	79%
6	2	8b	DME	5 min / -78 °C	9 : 10[c]	1 : 1	80%
7	2	8c	$PhCH_3$	2 min / -78 °C	13a : 13b[c]	2 : 1	83%
8	2	8d	THF	96 h / -78 °C	14a : 14b	1 : 1	50%
9	2	8d	THF	10 min / 0 °C	14a : 14b	1 : 30	83%
10	3	8	CH_2Cl_2	5 h / 0 °C	—	—	no reaction
11	4	8	CH_2Cl_2	5 h / 0 °C	—	—	no reaction
12	5	8	$PhCH_3$	48 h / -70 °C	9 : 10	1 : 3	70%
13	6	8	THF	1 h / -78 °C	11 : 12	31 : 1	85%
14	7	8	THF	96 h / -78 °C	—	—	no reaction

Notes: (a) Due to the diastereomers at the carbon alpha to the ester carbonyl the diastereomer ratio was determined after desulfurization with Raney Ni which proceeded in 80-85% yield.
(b) Yields are of isolated product.
(c) Ratio obtained after decarboxylation (LiCl, DMSO, 130 °C).



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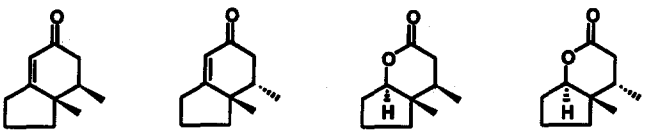
2. (a) Mulzer, J.; Chucholowski, A.; Lammer, O.; Jibril, J.; Huttner, G. *J. Chem. Soc., Chem. Com.* **1983**, 8. (b) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723. (c) For a thorough discussion of enolate and silyl enol ether addition to enones see Heathcock, C. H.; Sanner, M. A.; Henderson, M. A.; Oare, D. A. *J. Org. Chem.* **1990**, *55*, 132 and Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1990**, *55*, 157. (d) Bernardi, A.; Cappelli, M.-A.; Comotti, A.; Gennari, C.; Scolastico, C. *Tetrahedron Lett.* **1991**, *32*, 823. (e) For reviews see Oare, D. A.; Heathcock, C. H. *Topics in Stereochem.* **1989**, *19*, 227 and **1990**, *20*, 87.
3. Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, *26*, 5025.
4. See Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152.
5. Corey, E. J.; Houpis, I. N. *J. Am, Chem. Soc.* **1990**, *112*, 8997.
6. Prepared according to Trost, B. M.; Salzman, T. M.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.
7. Stereochemical assignments were made by conversion of **9** and **10** as well as the known enones *i* and *ii* (cf. Scanio, C. J. V.; Starrett, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1539) to the lactones *iii* and *iv*, spectral comparison and NOE experiments. All new compounds were identified by ^{1}H NMR, IR, MS and HRMS spectra.



i *ii* *iii* *iv*

8. In the reaction of amide enolates with enones, bulky substituents on the enone gave good diastereoselectivity: Heathcock, C. H.; Henderson, M. A.; Oare, D. A. Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3022.
9. For a discussion of the effect of Li vs. K enolate in the selectivity of the Michael reaction see refs. 2c, 2d.
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11. Because of the additional complication of diastereomers due to the thiophenyl group alpha to the ester carbonyl, enantiomeric excess was determined after conversion to the enol triflate **A** by sequential treatment (a) Raney (Ni) and (b) KHMDS, Tf_2NPh, THF.
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