Pergamon

Tetrahedron Letters, Vol. 35, No. 40, pp. 7351-7354, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01590-2

Highly Stereoselective 1,4-Addition Reactions of Alkylidene Malonate Substituted η^4-(1,3-Butadienyl)iron(tricarbonyl) Complexes

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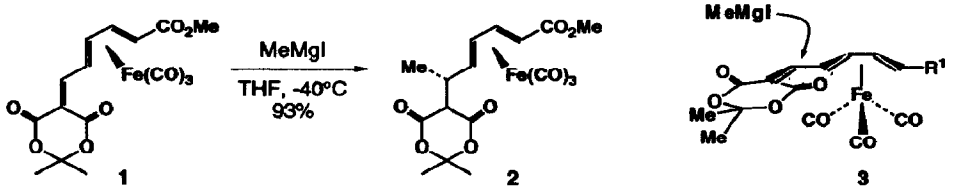
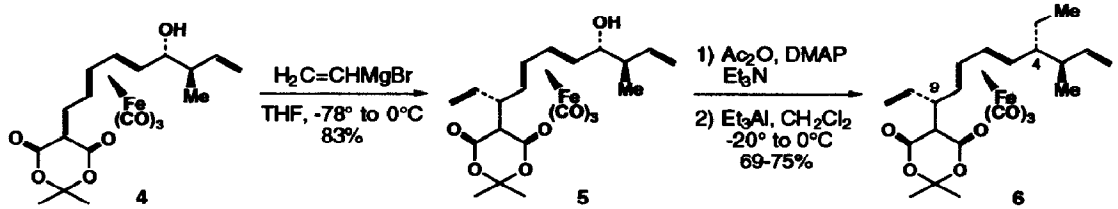
Abstract. Alkylidene malonate substituted η^4-(1,3-butadienyl)iron(tricarbonyl) complexes **4** and **10** undergo highly diastereoselective 1,4-addition reactions with various nucleophiles, including Grignard reagents, organolithium reagents, ketene silyl acetal **14** and allyltributylstannane.

The conjugate addition of organometallic nucleophiles to alkylidene malonates is well documented in the literature.[1] Grée and Laabassi have demonstrated the highly diastereoselective addition of MeMgI to the η^4-(1,4-butadienyl)iron(tricarbonyl) substituted alkylidene malonate **1** in the synthesis of (-)-verbenalol and (-)-epiverbenalol.[2] The -$Fe(CO)_3$ unit controls the stereochemical course of the 1,4-addition reaction by blocking the bottom face of the alkylidene malonate unit, thereby directing the addition of the carbon nucleophile *anti* to the metal carbonyl substituent (see **3**).[3]

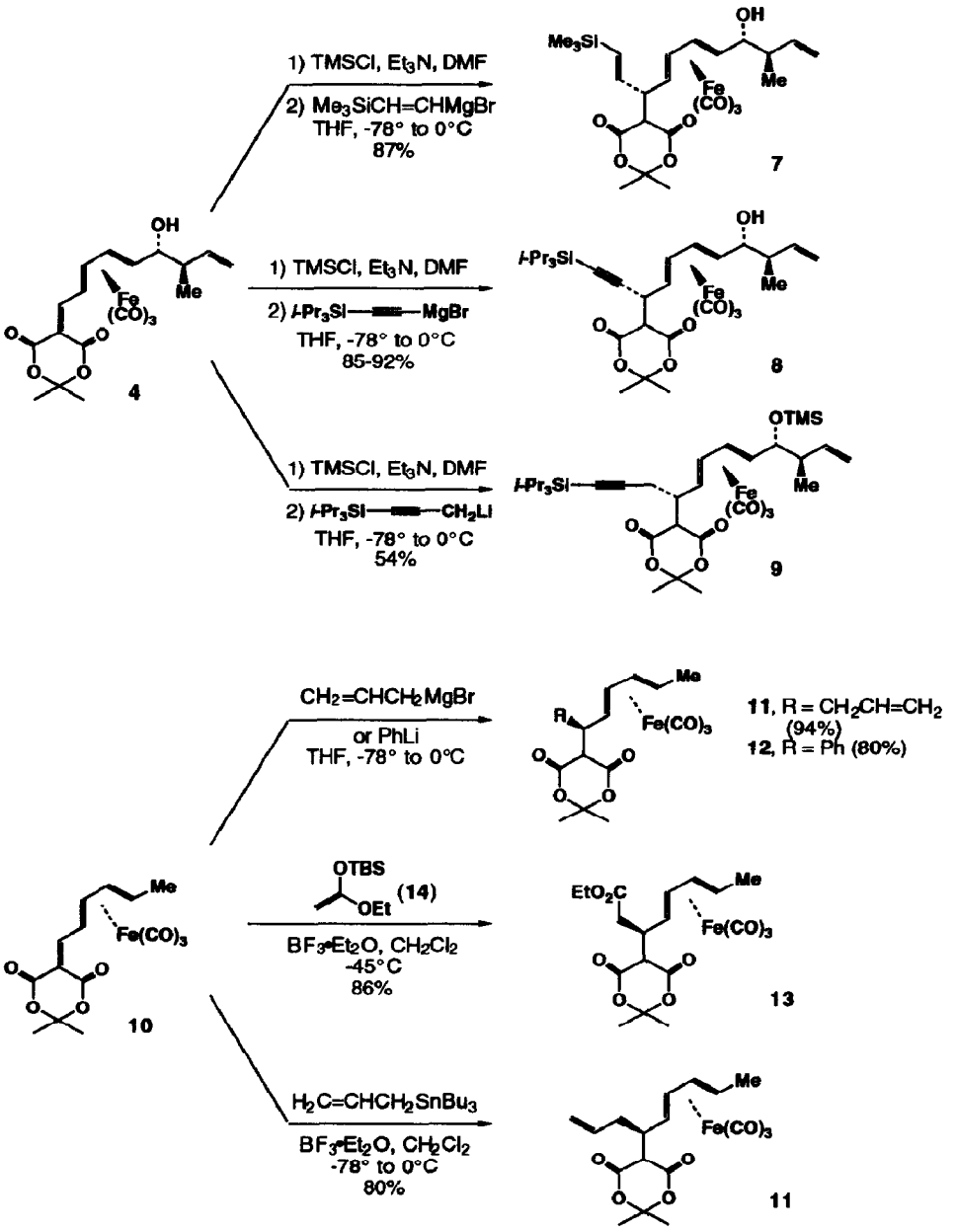


1 **2** **3**

We have recently employed this conjugate addition methodology in the highly stereoselective synthesis of the *as*-hydrindacene unit of (+)-ikarugamycin.[4] Specifically, the Meldrum's acid derivative **4** was treated with vinylmagnesium bromide to provide the 1,4-adduct **5** in 83% yield as the only observed stereoisomer (500 MHz ^{1}H NMR analysis). This reaction coupled with the stereospecific substitution at the carbinol center[5,6] provided a novel means of controlling the remote stereochemical relationship between C(4) and C(9) of **6**. We report herein studies that define more broadly the scope of the nucleophilic 1,4-addition reactions of η^4-(1,3-butadienyl)iron(tricarbonyl) substituted alkylidene malonates, using complexes **4** and **10** as representative electrophilic substrates.[7]



4 **5** **6**

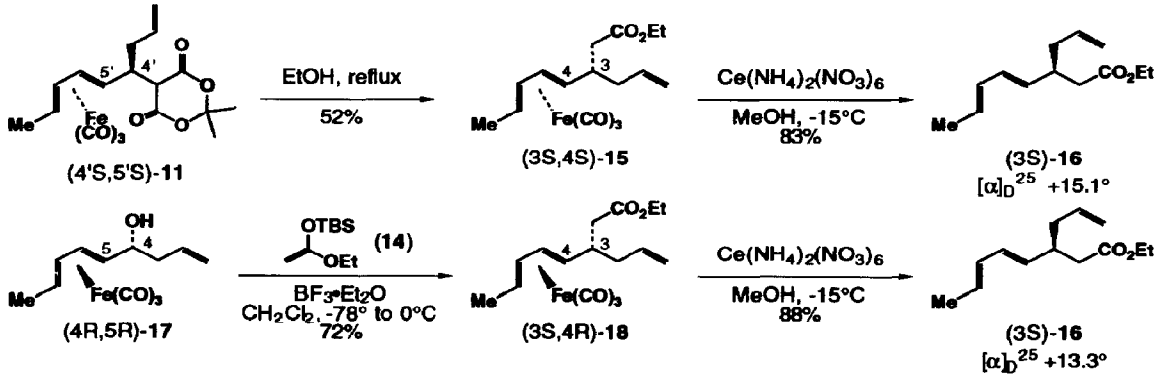


We first examined the reactions of **4** and **10** with several Grignard reagents. The TMS ether of **4** was used in these initial experiments, although our experience with the reaction of **4** and H_2C=CHMgBr suggests that this may not be necessary in all cases.[4] A -78°C THF solution of the alkylidene malonate complex was treated with a solution of the appropriate Grignard reagent (1.5-2.5 equiv.), and the reaction mixture was allowed to warm slowly

to 0°C. Aqueous saturated NH_4Cl was then added, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude products were purified by flash chromatography to provide the 1,4-adducts **7**, **8** and **11** in excellent yield (87-94%).[8]

Thus, alkylidene malonate derivatives **1**,[2] **4** and **10** undergo highly efficient 1,4-addition reactions with a range of Grignard reagents, including MeMgI, $H_2C{=}CHMgBr$,[4] (E)-$Me_3SiCH{=}CHMgBr$,[9a] and *i*-Pr_3Si-$C{\equiv}CMgBr$.[9b] Organolithium reagents may also be used, as illustrated by the reaction of **4** with *i*-Pr_3Si-$C{\equiv}CCH_2Li$[9c] (54% yield of **9**) and of **10** with PhLi (80% yield of **12**). Finally, it is also interesting to note that complex **1** readily undergoes $BF_3{\bullet}Et_2O$ catalyzed 1,4-addition reactions with ketene silyl acetal **14** (86% yield of **13**) and allyltributylstannane (80% yield of **11**). The alkylidene malonate unit also readily reacts with Et_3Al.[10]

A single stereoisomeric 1,4-addition product was produced in each of the reactions summarized herein.[11] The stereochemistry indicated in structures **7-9** and **11-13** was assigned by analogy to the precedent provided by the conversion of **1** to **2**,[2] and by our successful elaboration of **5** to the *as*-hydrindacene nucleus of ikarugamycin.[4] Additional support for these assignments is provided by the correlation experiment described below. Decarboxylation of the Meldrum's acid unit of (4'S,5'S)-**11**[12] by heating in EtOH at reflux provided ethyl ester (3S,4S)-**15**, which was then treated with $Ce(NH_4)_2(NO_3)_6$ in MeOH at -15°C provided triene ethyl ester (S)-**16** ($[\alpha]_D^{25}$ +15.1° (*c* 0.57, $CHCl_3$)). This compound proved identical to the triene ethyl ester (S)-**16** ($[\alpha]_D^{25}$ +13.3° (*c* 0.64, $CHCl_3$)) prepared from (4R,5R)-**17**[7] ($[\alpha]_D^{25}$ +32.8° (*c* 0.40, $CHCl_3$)) by stereospecific $BF_3{\bullet}Et_2O$ catalyzed substitution with ketene silyl acetal **14**[6] and oxidative removal of the -$Fe(CO)_3$ unit of **18**. Because retention of stereochemistry has been established for substitutions of the type **17** to **18**,[6] it follows that the stereochemistry of the addition of nucleophiles to the (η^4-diene)$Fe(CO)_3$ substituted alkylidene malonates occurs anti to the -$Fe(CO)_3$ unit, as formulated in transition structure **3**.[13] It also follows from this analysis that the stereoselectivities of these two processes are complimentary, since the conjugate addition route provides **15** which is a diastereomer of the diene complex **18** produced by the substitution reaction of **17**.



In summary, we have shown that a wide range of carbon nucleophiles undergo highly stereoselective 1,4-addition reactions with η^4-(dienyl)$Fe(CO)_3$ substituted alkylidene malonates of type **4** and **10**. Further applications of the η^4-(dienyl)$Fe(CO)_3$ unit as a stereochemical control element in organic synthesis will be reported in due course.

Acknowledgment: Financial support provided by the National Institute of General Medical Sciences (GM 26782), and fellowship support to C. K. W. from Procter and Gamble and the Department of Education, is gratefully acknowledged.

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8. The spectroscopic properties (^{1}H NMR, ^{13}C NMR, IR, HRMS and/or C,H combustion analysis) of all new compounds were in complete agreement with the assigned structures.
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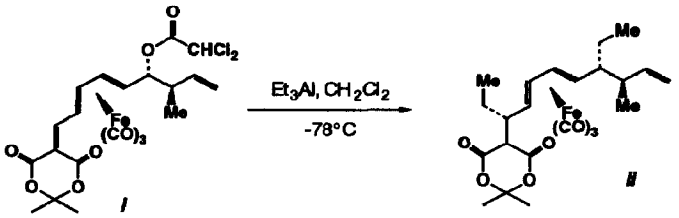
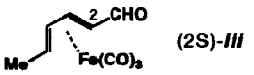
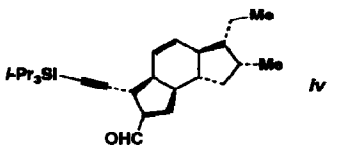
10. The bis-alkylated product ***ii*** was obtained as the major product of the reaction of dichloroacetate derivative ***i*** with Et_3Al at -78°C.



11. Crude reactions mixtures were analyzed by 500 MHz ^{1}H NMR spectroscopy. Conservatively, the diastereoselectivity of these reactions is ≥97 : 3.
12. (4'S,5'S)-**10** was synthesized starting from the kinetically resolved[7] sorbaldehyde-Fe(CO)$_3$ complex (2S)-***iii*** ($[\alpha]_D^{25}$ +103.8° (*c* 0.40, $CHCl_3$)).



13. The stereostructure of **8** also has been verified following its elaboration to ***iv*** (by using methods similar to those reported in ref. 4). We thank Dr. John. C. Huffmann for performing the X-ray analysis of ***iv*** (Indiana University Molecular Structure Center Report No. 92316).



(*Received in USA* 20 *July* 1994; *accepted* 10 *August* 1994)