In summary, V emerges as an excellent synthon for the southern half of the avermectin, since the key transformations involving oxidation at C1, macrolactonization, and S_N2' rearrangement can be carried out confidently at the final stages without affecting the key C2 center. *In addition, the ability to move the biologically critical* Δ^3 *double bond of 1 into a safe exocyclic "holding position" presents novel opportunities for semisynthetic studies in the avermectins.*

Acknowledgment. We are indebted to Dr. Helmut Mrozik of Merck, Sharp and Dohme for many helpful discussions.

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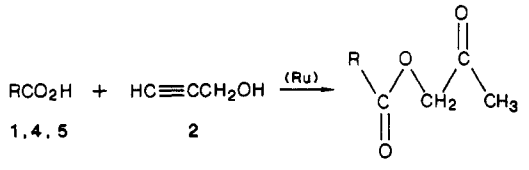
Synthesis of β-Oxopropyl Esters by Catalytic Addition of Carboxylic Acids and N-Protected Amino Acids to Propargyl Alcohol

Summary: The synthesis of β-oxopropyl esters results from the addition of saturated and unsaturated carboxylic acids or N-protected amino acids to propargyl alcohol in the presence of (arene)(phosphine)ruthenium(II) catalysts.

Sir: β-Oxoalkyl esters have been shown to be useful intermediates for access to heterocyclic derivatives such as furanones or imidazoles,[1] due to their reactive oxoalkyl carbonyl group, and for peptide synthesis,[2] as activated esters toward amino groups.

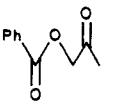
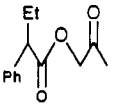
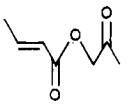
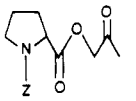
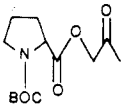
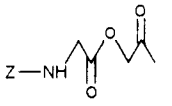
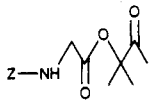
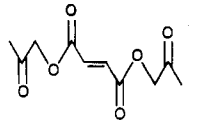
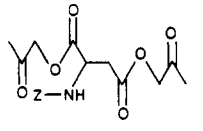
β-Oxopropyl esters are usually prepared by nucleophilic substitution of β-oxoalkyl halides by carboxylates in the presence of base[2,3] or by reaction of hydroxypropanone with acyl halides.[4] We report a new route to β-oxoalkyl esters by direct reaction of carboxylic acids with propargyl alcohols, thus avoiding the use of halide derivatives. This synthesis ensues from our studies on the addition of carboxylic acids to alkynes to afford enol esters.[5] We now show that the reaction of carboxylic acids with propargyl alcohol, catalyzed by $RuCl_2(PR_3)$(arene) complexes, proceeds differently: β-oxopropyl esters are formed in one step, under mild conditions (60 °C, 6 h), according to the following equation, and the reaction can be extended to diacids and N-protected amino acids. In a typical ex-



1, $PhCO_2H$ (a); Ph(Et)$CHCO_2H$ (b); $CH_3CH{=}CHCO_2H$ (c); Z-L-Pro (d); BOC-L-Pro (e); Z-L-Gly (f)
4, $HO_2CCH{=}CHCO_2H$
5, Z-L-Asp; Boc = $Me_3COC(O)$-; Z = $PhCH_2OC(O)$-

periment, Z-glycine (**1f**) (4.18 g, 20 mmol), $RuCl_2(PMe_3)$(*p*-cymene)[6] (0.072 g, 0.2 mmol), and propargyl alcohol (1.4 mL, 24 mmol) were dissolved under a nitrogen atmosphere in 10 mL of dry toluene. The reaction mixture was heated at 60 °C for 6 h. The ester **3f** which precipitated on partial evaporation of toluene was crystallized from a CH_2Cl_2/Et_2O (1/5) mixture to give pure product in 62% yield. Other esters **3**, **8**–**10** were obtained in a

Table I. Addition of Carboxylic Acids to Propargylic Alcohols with $RuCl_2(PMe_3)$(*p*-cymene)

acids	prepargylic alcohols[a]	esters (yield, %)[b]
1a	2[d]	 **3a** (92)
1b	2	 **3b** (30)
1c	2	 **3c** (85)
1d	2	 **3d** (74)
1e	2	 **3e** (41)
1f	2	 **3f** (62)
1f	6[c]	 **8** (45)
4	2	 **9** (30)
5	2	 **10** (40)

[a] General conditions: 60 °C; 6 h. [b] Isolated pure product. All compounds have been fully characterized spectrally (infrared, ^1H NMR) and by high resolution mass spectroscopy. Elemental composition has been established by combustion analysis for **3f** and **9**. [c] At 80 °C (6 h). [d] **2**, $HC{\equiv}CCH_2OH$; **6**, $HC{\equiv}CC(Me)_2OH$.

(1) (a) Stoeck, V.; Schunack, W. *Arch. Pharm.* (Weinheim) **1976**, *309*, 421. (b) Erdmann, D.; Schuehrer, K.; Koch, W.; Schneider, G. Ger. Pat. 2116416, 1976; *Chem. Abstr.* **1973**, *78*, 16015e.
(2) Schwyzer, R.; Iselin, B; Feurer, M. *Helv. Chim. Acta* **1955**, *38*, 69.
(3) Corvello, M.; Piscopo, E.; Abignente, E. *Rend. Accad. Sci. Fis. Mat.* **1961**, *28*, 375.
(4) Bateman, N. E.; Woods, R. A.; Pharmaceutical Compounds. Eur. Pat. EP 89857, 1982.
(5) Ruppin, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1986**, *27*, 6323.
(6) Bennett, M. A.; Smith, K. A. *J. Chem. Soc., Dalton Trans.* **1974**, 233.

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Table II. Influence of the Catalyst on the Transformation 1f → 3f

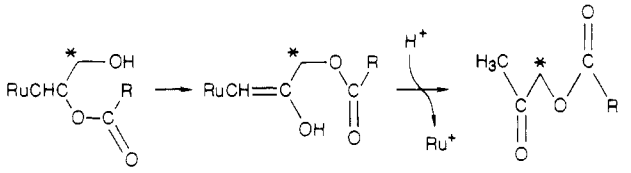
Ru catalyst	3f (% yield)
$RuCl_3 \cdot 3H_2O$	7
$RuCl_3 \cdot 3H_2O/2PBu_3$	43
$Ru_3(CO)_{12}$	33
$RuCl_2(PMe_3)(p\text{-cymene})$	62
$RuCl_2(PPh_3)(p\text{-cymene})$	64
$RuCl_2(P(OPh)_3)(p\text{-cymene})$	6
$RuCl_2(PMe_3)(C_6Me_6)$	61

similar way (Table I). They were isolated and purified by crystallization (**3f**, **8**, **9**) by reduced pressure distillation (**3a**, **3b**, **3c**), or by silica gel chromatography with ether (**3d**, **3e**, **10**).

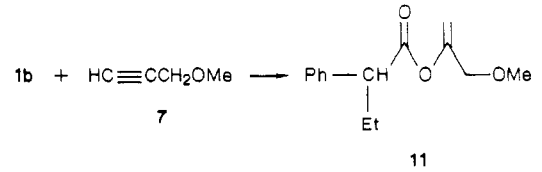
The addition of saturated (**1b**) and unsaturated (**1a**,**c**) carboxylic acids to propargyl alcohol (**2**) takes place under mild conditions (60 °C, 6 h) but mainly in the presence of ruthenium(II) catalysts. Amino acids do not add to **2** under similar conditions. However, N-protected amino acids give the corresponding esters (**3d-f**, **8**) in rather good yields (Table I). The ester formation takes place without deprotection of the amino group and the chiral esters **3d**, **3e**, and **10** retain optical activity.[7] Diacids such as **4** and **5** always yield a mixture of esters. However, when an excess of **2** was used, diesters **9** and **10** were isolated (Table I). The efficiency of the addition appears to be related to the steric hindrance of the acid (e.g. **3a** and **3b**; **3d** and **3e**).

The formation of esters **3** is catalyzed by a variety of ruthenium complexes. Thus, the ester **3f** was obtained from **1f**, under the above conditions, in yields which critically depended upon the nature of the Ru catalyst (Table II). The more efficient catalysts are the $RuCl_2(PR_3)$(arene) complexes containing basic phosphines (PPh_3, PMe_3).[8]

The formation of esters **3** may be similar to the addition of ammonium carbamates to propargyl alcohol:[9] initial addition of the carboxylate to the coordinated alkyne bond of **2** followed by intramolecular transesterification.



Indeed, when **1b** was treated with methyl propargyl ether (**7**), the addition occurred only under more drastic conditions (120 °C, 15 h, 44%) and gave the enol ester **11** corresponding to the expected addition product.[5]



The intramolecular transesterification is also supported by the reaction of **1f** with the dimethyl disubstituted propargyl alcohol $HC{\equiv}CC(CH_3)_2OH$ (**6**) which gave the ester **8** (Table I).

(7) $(\alpha)^{20}_D$ (*c* 2, EtOH): -67° (**3d**); -70° (**3e**); +14° (**10**). The optical purity has not been determined.

(8) One example of similar addition involving acetic acid and propargyl alcohol has just been reported, but using as a catalyst the three component system $Ru(\eta^5\text{-}C_8H_{11})_2/2PBu_3$/(maleic anhydride)$_2$. Mitsudo, T. A.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2330.

(9) Bruneau, C.; Dixneuf, P. H. *Tetrahedron. Lett.* **1987**, *28*, 2005.

The facile one-step formation of β-oxopropyl esters **3**, particularly from chiral acids and N-protected amino acids, allows the use of these compounds as synthesis intermediates.

Acknowledgment. We are grateful to Dr. S. Lecolier for helpful discussions and to CNRS and SNPE for support of this work.

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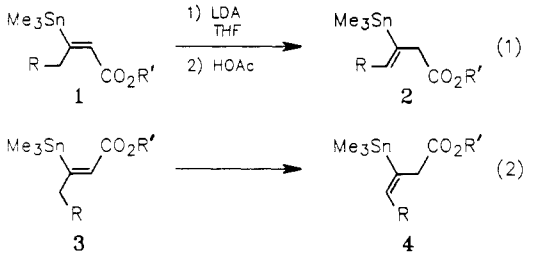
Received August 7, 1987

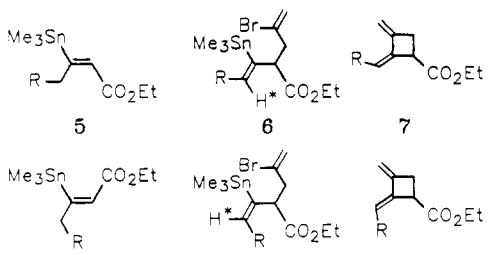
Deconjugation-Alkylation of Ethyl 3-(Trimethylstannyl)-2-alkenoates. Stereocontrolled Synthesis of Ethyl 2-Alkylidene-3-methylenecyclobutanecarboxylates

Summary: Alkylation of ethyl (*E*)- and (*Z*)-3-(trimethylstannyl)-2-alkenoates with 2,3-dibromopropene, followed by $(Ph_3P)_4Pd$-catalyzed cyclization of the resultant products, provides ethyl (*Z*)- and (*E*)-2-alkylidene-3-methylenecyclobutanecarboxylates, respectively, in good yields (60-79%).

Sir: Recently, we reported[1] that alkyl 3-(trimethylstannyl)-2-alkenoates **1** and **3** can be deconjugated stereospecifically to provide excellent yields of the corresponding alkyl 3-(trimethylstannyl)-3-alkenoates **2** and **4**, respectively (eq 1 and 2). We have subsequently found,



not surprisingly, that alkylative deconjugation of ethyl (*E*)- and (*Z*)-3-(trimethylstannyl)-2-alkenoates **5** and **8**, respectively, can also be accomplished readily. More importantly, we report herein that the products **6** and **9**, respectively, derived from alkylation of **5** and **8** with 2,3-dibromopropene cyclize smoothly in the presence of a palladium(0) catalyst to afford, stereospecifically, ethyl (*Z*)- and (*E*)-2-alkylidene-3-methylenecyclobutanecarboxylates **7** and **10**, respectively. It may be noted that 1,2-di-



a R=Me b R=$(CH_2)_2OCH_2OMe$
c R=$(CH_2)_3OSiMe_2Bu^t$ d R=OCH_2OMe e R=H

(1) Piers, E.; Gavai, A. V. *J. Chem. Soc., Chem. Commun.* **1985**, 1241.

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