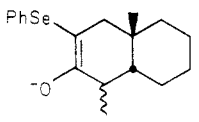

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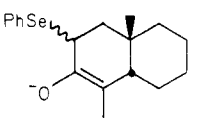

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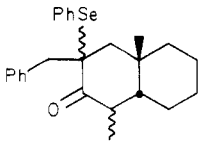

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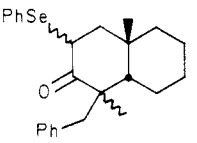
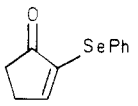
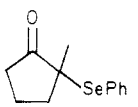


32

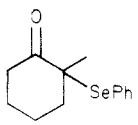
Finally, in the course of our studies we have found two α-phenylselenyl ketones which do not undergo the α,α' rearrangement. These are **33** and **34**. The only obvious



28



33



difference between these compounds and the ones given in Table I is that **33** and **34** lack any buttressing alkyl substituents. If this is indeed the reason for differences in reactivity between these compounds and the ones given in Table I, then the implication is that steric crowding at or around the α-carbon atom accelerates the α,α' rearrangement and may, in fact, be necessary for this process to be successful. Further studies involving both the synthetic and mechanistic aspects of this rearrangement will be the subject of future reports.

Acknowledgment. This work was supported by a grant from the National Institutes of Health.

Registry No. *cis*-**1**, 73825-08-8; *trans*-**1**, 73825-03-3; **2**, 80864-36-4; *cis*-**3**, 80864-37-5; *trans*-**3**, 80864-38-6; **7**, 80864-39-7; **8**, 80864-40-0; **9**, 24810-59-1; **10**, 80864-41-1; **11**, 80864-42-2; **12**, 80864-43-3; **13**, 80864-44-4; **14**, 80924-07-8; **15**, 78763-80-1; **16**, 80864-45-5; **17**, 80864-46-6; **18**, 80864-47-7; **19**, 80864-48-8; **20**, 80864-49-9; **21**, 80864-50-2; **22**, 80864-51-3; **23**, 80864-52-4; **24**, 80864-53-5; **31**, 80864-54-6; **33**, 80864-55-7; **34**, 65979-78-4.

Supplementary Material Available: Complete experimental details for all the reaction presented here (8 pages). Ordering information is given on any current masthead page.

(11) Fellow of the Alfred P. Sloan Foundation, 1980-1984. Recipient of a Camille and Henry Dreyfus Teacher-Scholar Fellowship, 1981-1986.

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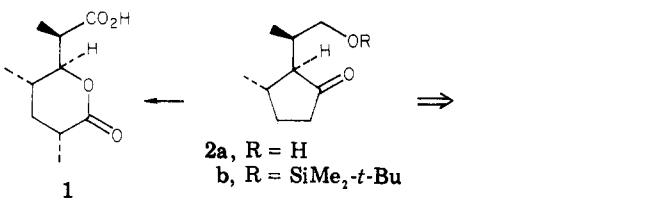
Received September 18, 1981

Synthesis of Racemic Prelog-Djerassi Lactone via a Regio- and Diastereoselective Ene Reaction†

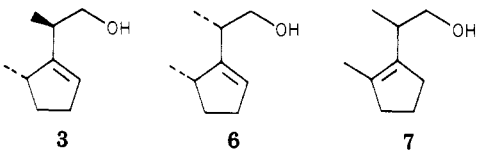
Summary: Examination of the regio- and stereochemical outcome of the ene reaction of 1-ethylidene-2-methylcyclopentanes with formaldehyde and the application to a synthesis of (±) Prelog-Djerassi lactone is described.

Scheme I

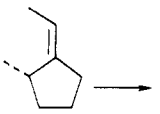


1 2a, R = H b, R = $SiMe_2$-*t*-Bu 3 4

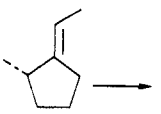
Scheme II



3 6 7



4 86:10:4



5 5:7:88 mixture of **3**, **6**, and **7**

Sir: The Prelog-Djerassi lactonic acid **1**, a degradation product of the macrolide antibiotics methymycin and narbomycin,[1] has attracted attention not only for its novel structure possessing four chiral centers but also because of its potential utility in the construction of more complex natural products.[2] A number of highly imaginative solutions to the problem of its synthesis have already appeared.[3]

Our own strategy evolved from a desire to gain some insight on the contribution of structural features to the very high stereoselectivity of the ene reaction with formaldehyde observed in our previous work regarding the generation of steroidal side chains bearing the natural C-20

(1) (a) Isolation from narbomycin degradation: Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* **1956**, *39*, 1785. (b) Isolation from methymycin degradation: Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 6390. (c) Final structure revision: Richards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025. Manwaring, D. G.; Rickards, R. W.; Smith, R. M. *Ibid.* **1970**, 1029.

(2) Synthesis of methymycin: Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513.

(3) (a) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23. (c) Brooks, D. W.; Lu, L. L.-D.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72. (d) Grieco, P.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749. (e) Hirama, M.; Garvey, D. S.; Lu, L. L.-D; Masamune, S. *Tetrahedron Lett.* **1979**, 3937. (f) Nakano, A.; Takimoto, S.; Inanaga, J.; Katsuki, T.; Ouchida, S.; Inoue, K.; Aiga, M.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1019. (g) Stork, G.; Nair, V. *J. Am. Chem. Soc.* **1979**, *101*, 1315. (h) White, J. D.; Fukuyama, Y. *Ibid.* **1979**, *101*, 226. (i) Bartlett, P. A.; Adams, J. L. *Ibid.* **1980**, *102*, 337. (j) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. (k) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479. (l) Jarosz, S.; Fraser-Reid, B. *Tetrahedron Lett.* **1981**, *22*, 2533. (m) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (n) Morgans, D. J. *Tetrahedron Lett.* **1981**, *22*, 3721. (o) Still, W. C.; Shaw, K. R. *Ibid.* **1981**, *22*, 3725. (p) Maruyama, K.; Ishihara, Y.; Yamamoto, Y. *Ibid.* **1981**, *22*, 4235. (q) Isobe, M.; Ichikawa, Y.; Goto, T. *Ibid.* **1981**, *22*, 4287.

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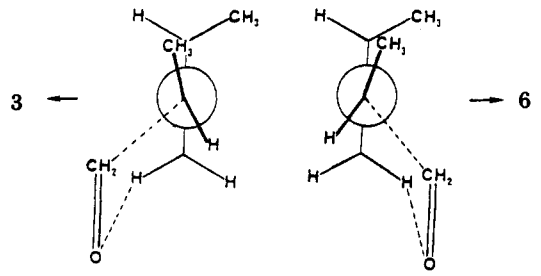


Figure 1.

configuration.[4] We have examined a more simplified version of the steroid D ring and now report the application of the ene reaction to the synthesis of the Prelog–Djerassi lactone.

The focal point for our work centered on the Grieco intermediate **2b**[3d] which we envisioned as being derived from the functionalized cyclopentene **3** which in turn would come from a regio- and stereoselective ene reaction of (*Z*)-1-ethylidene-2-methylcyclopentane (**4**) with formaldehyde (Scheme I).

Exposure of 2-methylcyclopentanone to ethylidenetriphenylphosphorane in dimethyl sulfoxide led to 55:45 mixture of olefins **4** and **5**, respectively. Spinning-band distillation (bp 128 °C) further enriched the lower boiling *Z* isomer **4** to 92% isomeric purity and provided pure **5**.[5,6] The *Z* olefin **4** when treated with paraformaldehyde in the presence of a catalytic amount of boron trifluoride etherate (ca. 4 mol %) in methylene chloride underwent a smooth reaction to give a mixture of ene adducts **3**, **6**, and **7** in a ratio of 86:10:4, respectively, in 60–70% yield (Scheme II).[7] The structure of **3** was determined by its ^1H and ^{13}C NMR spectral properties and by its conversion to **2b** (vide infra);[8] the structure of **6** was inferred from its NMR spectral properties and by exclusion of **3**; the structure of **7** was also consistent with its ^1H and ^{13}C NMR spectral properties. Similar treatment of the pure *E* olefin **5** with paraformaldehyde and $BF_3{\cdot}Et_2O$ produced a 5:7:88 mixture of **3**, **6**, and **7**, respectively (65% yield).[9,10]

The product distribution in each case reflects the powerful orienting effects of both the olefinic and ring methyl groups. The regioselectivity of the ene reaction is at least 96% with **4** (i.e., **3** + **6**/**7**)[11] and 88% with **5** (i.e., **7**/**3** + **6**) in a sense that proton abstaction occurs preferentially at the ring allylic carbon *anti* to the olefinic methyl group.[12,13] The source of this effect is most likely due to a greater steric interaction between formaldehyde–boron trifluoride and the olefinic methyl group in the transition state when proton abstraction occurs at the syn rather than anti allylic carbon. The control of stereoselectivity on the other hand does not appear to be solely the interaction of the incoming formaldehyde with the ring methyl group such as might be expected in the case of the steroid D ring where one face of the olefin is clearly more accessible than the other. The low selectivity observed for the approach of formaldehyde from the β vs. the α (ring methyl) face of the olefin **5** (i.e., **6**/**3** $\approx$ 7:5) in contrast to the ca. 9:1 preference (i.e., **3**/**6**) for β attack on **4** suggests that structural features present in **4** but absent in **5** are largely responsible for this stereoselectivity. In the transition state, en route to **3** from **4**, the olefinic methyl group tips out of the plane of the olefin toward the face where the allylic proton is removed, thus decreasing the nonbonded steric interaction between two methyl groups (Figure 1). Contrary to that, the less favorable conversion of **4** to **6** involves the movement of the olefinic methyl group toward the ring methyl, which results in an increased nonbonded interaction between the two methyl groups. Also since this methyl–methyl interaction would not occur in the conversion of **5** to either **3** or **6**, no differentiation of the two faces of the olefin would be expected except as a result of the ring methyl group hindering the approach of formaldehyde from the α face.

Stereoselective epoxidation of the major ene product **4** and subsequent stereospecific acid-catalyzed rearrangement of the epoxide form the basis on which its stereochemistry was deduced. Epoxidation (*t*-BuOOH, VO(acac)$_2$) of **3** produced in high yield a 95:5 mixture of epoxide **8a**[14,15] and its epimer (Scheme III). The high proportion of epoxidation to the same side of the cyclopentene ring as the methyl group is a consequence of participation by the free hydroxyl group in the preferred side chain rotamer **3′** (Newman projection). Acylation of **8a** with acetic anhydride in pyridine generated **8b** (95%)[14] which on exposure to a catalytic amount of boron trifluoride etherate in methylene chloride rearranged to acetoxy ketone **9** (85%).[14] Baeyer–Villiger oxidation with *m*-chloroperoxybenzoic acid ($NaHCO_3$, CH_2Cl_2) gave lactone **10** (73%),[14] the stereochemistry of which would be demonstrated by the following comparison.

Hydrolysis of the acetoxy ketone **9** with methanol and potassium carbonate was accompanied by epimerization to give ketone **2a** (73%), which was then converted to the *tert*-butyldimethylsilyl ether **2b** (*t*-BuMe$_2$SiCl, DMF, imidazole, 98%). The ketone **2b** was identical with authentic racemic material by TLC, IR, and ^1H and ^{13}C NMR com-

(4) Batcho, A. D.; Berger, D. E.; Davoust, S. G.; Wovkulich, P. M.; Uskokovic, M. R. *Helv. Chim. Acta* **1981**, *64*, 1682.

(5) The two isomers were readily distinguished by comparison of the methine ^{13}C NMR resonances: δ 34.4 for **4** and 39.5 for **5**. Conditions for gas chromatographic analysis: 25M PEG 20M capillary column, at ambient temperature.

(6) Variations of the reaction conditions did not significantly alter the isomer ratio.

(7) The ratio of this difficult to separate mixture was determined by integration of the ^1H NMR signals. **3**: δ ($CDCl_3$, 100 mHz) 1.08 (d, J = 7 Hz, 6 H), 5.35 (m, 1 H). **6**: 1.05 (d, J = 7 Hz, 3 H), 1.14 (d, J = 6.5 Hz, 3 H), 5.43 (m, 1 H). **7**: 0.97 (d, J = 7 Hz, 3 H), 1.66 (m, 3 H). These results were corroborated by ^{13}C NMR.

(8) For analytical purposes, a sample of **3** was separated from **6** and **7** by extensive silica gel chromatography of the alcohols and their THP ethers. **3**: (bulb to bulb distillation) bp 40 °C (0.08 mmHg).

(9) In an optically active series, **4** would produce one enantiomer of **7**, while **5** would generate the other. Since the olefins used here were racemic, **7** derived from **4** would be racemic and therefore indistinguishable from **7** derived from **5**.

(10) When much greater proportions of catalyst and paraformaldehyde were used, the yields and selectivities were somewhat diminished; cf. ref 26 in Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

(11) The regioselectivity is probably closer to 100% when the production of **7** from the 8% of the *E* isomer **5** present in the **4** used here is taken into consideration.

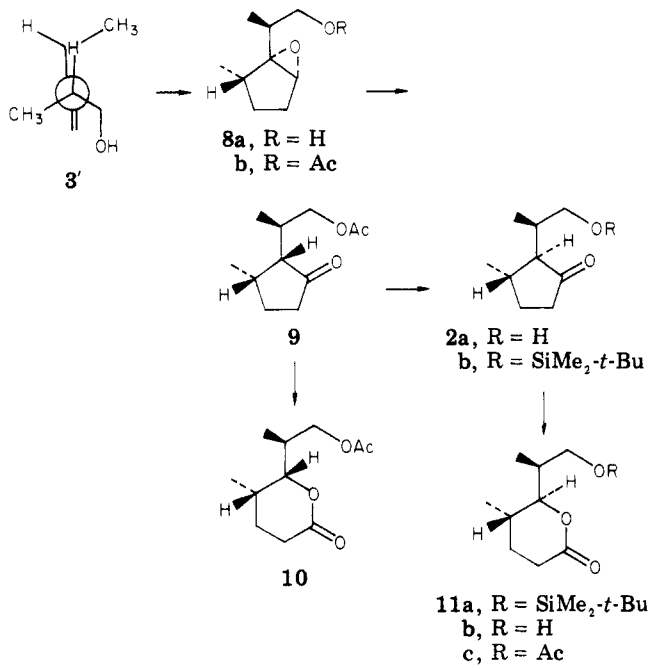
(12) Interestingly, in contrast to these results, essentially no regioselectivity was observed when 4-*tert*-butyl-1-ethylidenecyclohexane was exposed to the same reaction conditions.

(13) The analogous regioselectivity has been observed for the ene reaction of methyl chloroacrylate with the acyclic olefins (*E*)- and (*Z*)-3-methyl-2-pentene: Snider, B. B.; Duncia, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 5928.

(14) Satisfactory combustion analysis and IR, NMR, and mass spectral properties were obtained. Some NMR (100 MHz, $CDCl_3$) and IR ($CHCl_3$) data are as follows. **8a**: NMR δ 3.38 (m, 2 H), 3.14 (m, 1 H), 1.03 (d, J = 7 Hz, 3 H), 0.92 (d, J = 8 Hz, 3 H). **8b** NMR δ 4.11 (dd, J = 6, 11 Hz, 1 H), 3.85 (dd, J = 6, 11 Hz, 1 H), 3.30 (br s, 1 H), 2.04 (s, 3 H), 1.07 (d, J = 8 Hz, 3 H), 1.04 (d, J = 8 Hz, 3 H); IR 1730 cm^{-1}. **9**: NMR δ 4.45 (dd, J = 3.5, 11 Hz, 1 H), 4.25 (dd, J = 6, 11 Hz, 1 H), 2.04 (s, 3 H), 0.99 (d, J = 7 Hz, 3 H), 0.91 (d, J = 8 Hz, 3 H); IR 1732 cm^{-1}. **10**: NMR δ 4.36 (dd, J = 3, 11 Hz, 1 H), 4.15 (dd, J = 2, 10.5 Hz, 1 H), 4.14 (dd, J = 6, 11 Hz, 1 H), 2.05 (s, 3 H), 0.96 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H); IR 1735 cm^{-1}. **2a**: NMR δ 3.69 (d, J = 5 Hz, 2 H), 1.14 (d, J = 6 Hz, 3 H), 0.90 (d, J = 7 Hz, 3 H); IR 1725 cm^{-1}.

(15) On a preparative scale it was convenient to defer separation of any intermediate starting from the initial Wittig reaction to this point where all of the isomeric epoxides were easily resolved by silica gel chromatography.

Scheme III



parisons.[16] Then **2b** was converted to the acetoxy lactone **11c** by Baeyer–Villiger oxidation (**11a**), removal of the silyl group (**11b**), and acetylation. Thin-layer chromatography (hexane/ethyl aceatate, 2:1) and ^{1}H NMR cleanly distinguish between the two epimeric lactones **10** and **11c**. Since there is only one epimerizable center in the conversion of **9** to **11c** the stereochemistry of **10** as well as **9** must be as depicted. Compound **2b** was previously converted to the Prelog–Djerassi lactone **1** via **11a** by Grieco.[3d]

In summary, the ene reaction of (*Z*)-1-ethylidene-2-methylcyclopentane **4** has been found to proceed with a high degree of regio- and stereoselectivity which appears to be controlled by a combination of steric interactions. A formal total synthesis of racemic Prelog–Djerassi lactone was completed by the conversion of the major ene adduct **3** to a known synthetic intermediate.

Acknowledgment. We are indebted to Professor P. Grieco for providing a generous sample of the alcohol precursor for racemic **2b**. We also express our gratitude to the members of the Physical Chemistry Department of Hoffmann-La Roche Inc. for determinations of spectral and analytical data.

Registry No. (±)-**1**, 56781-39-6; (±)-**2a**, 80866-35-9; (±)-**2b**, 71828-72-3; (±)-**3**, 80866-36-0; (±)-**4**, 80866-37-1; (±)-**5**, 80866-38-2; (±)-**6**, 80866-39-3; (±)-**7**, 80866-40-6; (±)-**8a** (isomer 1), 80866-41-7; (±)-**8a** (isomer 2), 80924-11-4; (±)-**8b**, 80866-42-8; (±)-**9**, 80866-43-9; (±)-**10**, 80866-44-0; (±)-**11a**, 71828-73-4; (±)-**11b**, 80866-45-1; (±)-**11c**, 80866-46-2; 2-methylcyclopentanone, 32854-37-8.

† This manuscript is dedicated the the memory of Dr. Willy Leimgruber, deceased, July 8, 1981.

(16) We are indebted to Professor P. Grieco for providing a generous sample of the alcohol precursor for racemic **2b** which was then oxidized to **2b** according to his procedure.[3d] The ^{13}C NMR comparison included obtaining the spectrum of a 1:1 mixture of authentic material with **2b** prepared by the process described in the text. No doubling of the 12 signals was observed.

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Received January 18, 1982

Synthesis and Transmetalation of Alkyl (*E*)-2,3-Bis(trimethylstannyl)-2-alkenoates, Novel Organotin Compounds

Summary: Reaction (THF, 0 °C) of α,β-acetylenic esters with 2.5 equiv of the (trimethylstannyl)copper reagents **3** or **5** provides, stereoselectively, the corresponding alkyl (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates. The potential synthetic utility of the latter substances is demonstrated by the conversion of ethyl (*E*)-2,3-bis(trimethylstannyl)-2-butenoate (**17**) into the stereochemically homogeneous compounds **25–30**, inclusive.

Sir: We have shown[1,2] recently that α,β-acetylenic esters **1** react smoothly with (trimethylstannyl)cuprate (**2–4**)[3] or copper (**5**)[3] reagents to produce, after protonation of the presumed intermediates **6**[4] and/or **7**[4], the conjugate addition products **8** and/or **9**. Clearly, the synthetic utility of this methodology would be enhanced significantly if **6** and/or **7** could be trapped with electrophiles ("E$^+$") other than proton. For example, reduction of the ester group of the resultant product(s) (general structures **10** and/or **11**), followed by sequential protection of the hydroxyl function and transmetalation (CH_3Li) of the Me_3Sn moiety, would provide organolithium reagents corresponding to the geometrically isomeric general synthons[5] **12** and/or **13**. We report herein that (a) although our attempts to trap **6** and/or **7** with electrophiles other than proton have been unsuccessful thus far, investigations into possibility have led to the discovery of an efficient method for the synthesis of alkyl (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates (**14**),[6] and (b) treatment of the latter substances with CH_3Li results in the selective transmetalation of the α-trimethylstannyl group to provide nucleophilic species which may be trapped by carbon electrophiles.

Treatment of a solution (THF, −78 or −48 °C)[1,2] of 1.2 equiv of the cuprate reagent **3** with 1.0 equiv of ethyl 2-butynoate (**15**),[9,10] followed by addition of methyl iodide, benzyl bromide, or cyclohexanone and stirring of the reaction mixture at −78 or −48 °C for 2–3 h, failed to provide any of the desired products **16** (E = CH_3, $C_6H_5CH_2$, or 1-hydroxycyclohexyl). In each case, appropriate workup gave only the product (**16**, E = H) resulting from protonation of the intermediate.[12] In efforts to find conditions

(1) Piers E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263.
(2) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905.
(3) For the preparation of these reagents, see ref 2.
(4) The formulas **6** and **7** are not meant to imply actual structures, but are used only for the sake of clarity. See also Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. Siddall, J. B.; Biskup, M.; Fried, J. H. *Ibid.* **1969**, *91*, 1853. Anderson, R. J.; Corbin, V. L.; Cotterrell, G.; Cox, G. R.; Henrick, C. A.; Schuab, F.; Siddall, J. B. *Ibid.* **1975**, *97*, 1197.
(5) Cf. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(6) Although 1,2-bis(trialkylstannyl)ethylenes are known,[7,8] to the best of our knowledge organotin compounds of general structure **14** have not been reported previously.
(7) Bulten, E. J.; Budding, H. A.; Noltes, J. G. *J. Organomet. Chem.* **1970**, *22*, C5.
(8) (a) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* **1974**, *96*, 5581. (b) *J. Org. Chem.* **1975**, *40*, 3788.
(9) The α,β-acetylenic esters employed in this work were prepared by reaction of the appropriate lithium acetylides with ethyl (or methyl) chloroformate. The required acetylenes are commercially available or were prepared via standard methods. Details will be given in a full paper.
(10) All compounds reported herein exhibited spectral data in full accord with structural assignments. New compounds gave satisfactory elemental analyses and/or high-resolution mass spectrometric measurements. Although the mass spectra of the organotin compounds did not exhibit molecular ion peaks, in accord with previous observations concerning trimethylstannyl compounds,[11] all showed $m/e = M^+ - 15$ peaks, and, in each case, the high-resolution measurement was carried out on this fragment.
(11) Kuivila, H. G.; Tsai, K.-H.; Kingston, D. G. I. *J. Organomet. Chem.* **1970**, *23*, 129.

0022-3263/82/1947-1602$01.25/0