Butenolide Synthesis Based upon a Contra-Electronic Addition in a Ruthenium-Catalyzed Alder Ene Reaction. Synthesis and Absolute Configuration of (+)-Ancepsenolide

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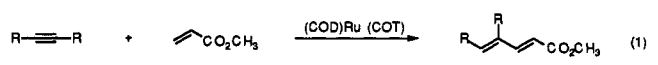
Additions of electron-rich reactants with electron-deficient olefins and acetylenes occur at the β-carbon: processes which prove to be very important approaches for C–C bond formation. The thermal Alder ene reaction represents one such reaction. Reorienting the reaction partners in an Alder ene type process to form the new C–C bond at the α-carbon would be an important adjunct to existing synthetic methodology. Transition metal catalyzed reactions which may rely more on coordination than on electronic effects to direct regioselectivity offer a conceptual approach to such a problem. As part of our program to develop atom economical reactions,[1] we considered the prospect of ruthenium-catalyzed additions of olefins and acetylenes as a possibility. On the one hand, ruthenium complexes have been reported to promote the addition of an acetylene with methyl acrylate with the new C–C bond formed at the *β-carbon* of the acrylate (eq 1).[2] On the other hand, we noted that a hydroxyl



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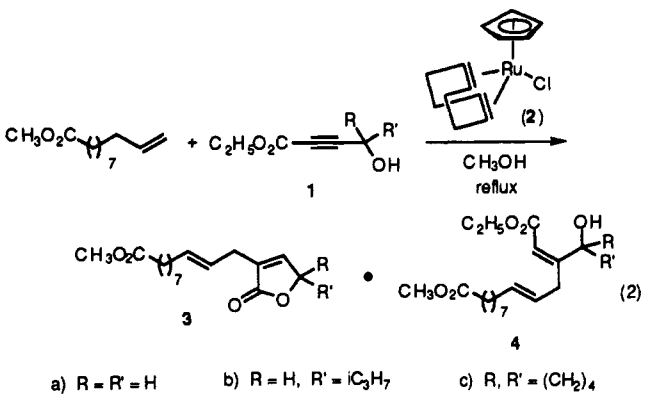
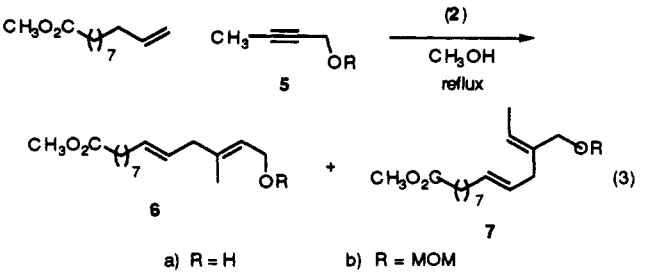
group at a propargylic position had a dramatic effect on the ruthenium-catalyzed addition of an acetylene to an allyl alcohol, which we attributed to a coordination effect.[3] We therefore explored the ruthenium-catalyzed addition of a simple olefin[4] to a γ-hydroxybutynoate in order to determine which substituent, the alcohol or the ester, would prevail in directing the regioselectivity in this metal-catalyzed version of an Alder ene reaction.

Methyl 10-undecenoate as the test olefin was reacted with 1 equiv of ethyl 4-hydroxybutynoate (**1a**) and 5 mol % Cp(COD)-RuCl (**2**)[5] in methanol at reflux (eq 2) to give two products in a 2.9:1 ratio in 51% isolated yield. Spectroscopic data clearly



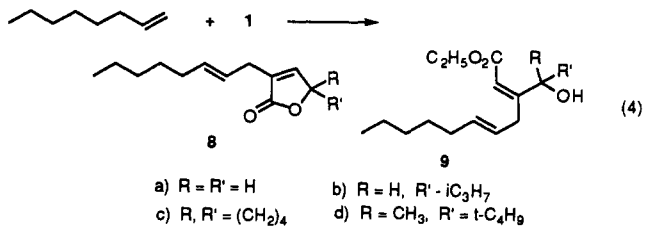
indicated that the major product was **3a**,[6] in which *the new C–C bond formed at the* α-carbon! The initial simple addition adduct spontaneously eliminated ethanol to give the butenolide in the case of the α-alkylation; whereas the product derived from β-attack was isolated as the hydroxy ester **4a**.[6] For evaluation of the effect of the ester, we performed the same reaction using 2-butyn-1-ol (**5a**), in which the adducts were isolated in a 1.8:1 ratio. Again, spectroscopy indicated the major adduct to be **6a**[6] (eq 3). In an



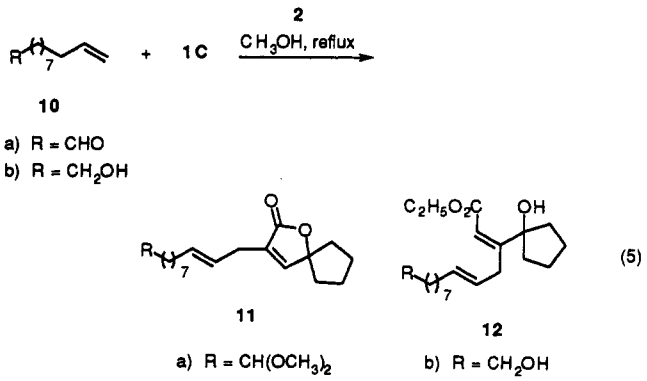
attempt to increase metal coordination and thereby enhance the regioselectivity, the MOM ether **5b** was added to methyl 10-undecenoate; however, no appreciable change in regioselectivity was observed (1.7:1 **6b**:**7b**). Comparing **1** and **5** suggests that the ester group not only does not exercise an electronic bias favoring β-attack but also seems to reinforce the directing influence of the hydroxyl group leading to α-attack.

Introducing alkyl substituents at the propargylic position of **1** enhanced the regioselectivity. A single substituent as in **1b** increased the product regioselectivity ratio to 4.4:1 (**3b**:**4b**,[6] 63% yield) and two substituents as in **1c** to 12.2:1 (**3c**:**4c**,[6] 67% yield).

A simple olefin, 1-octene, showed a similar trend (eq 4). Increasing the degree of steric hindrance at the propargylic position increased the ratio of **8** to **9**[6] from 2.6 for **1a** (47% yield) to 4.3 for **1b** (79% yield), to 6.6 for **1c** (68% yield), and to exclusive formation of **8d** from **1d** (60% yield).



Surprisingly, the remote substituent in the olefin substrate had some effect on regioselectivity. Notably, 10-undecenal (**10a**) gave a slightly diminished ratio of 7.9:1 (80% yield) of **11a**:**12a**[6] (eq 5) compared to 12.2:1 for the ester (eq 2). The alcohol **10b** enhanced the selectivity since **11b**[6] was the only regioisomer observed in 71% isolated yield.



The effectiveness of this new approach for the synthesis of butenolides leads us to consider its application toward the acetogenins, plant metabolites that have shown cytotoxic, antitumoral, antimalarial, and immunosuppressive activity as well as

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(5) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.
(6) This compound has been satisfactorily characterized spectroscopically.

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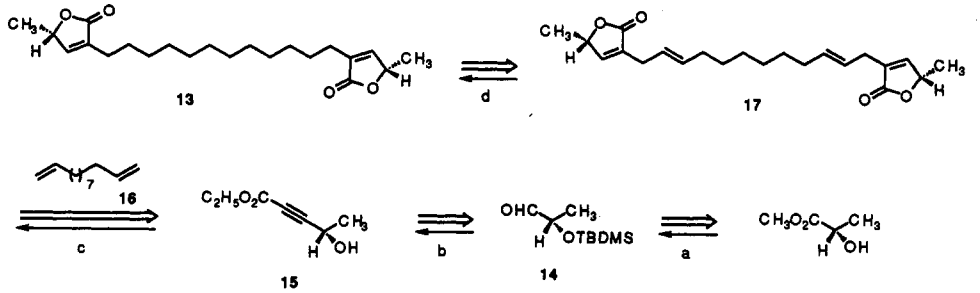
Scheme 1. **Scheme 1.** Retrosynthesis and Synthesis of (+)-Ancepsenolide[a]

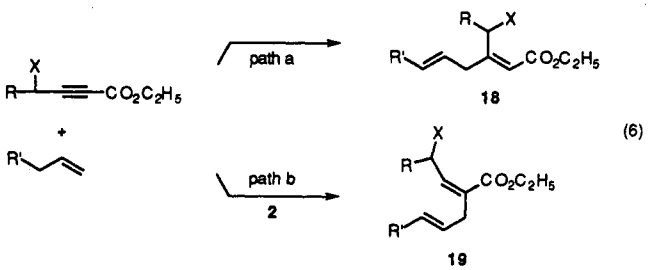


[a] (a) (i) TBDMSCl, $(C_2H_5)_3N$, DMAP, THF, 92%; (ii) DIBAL-H, hexane, −78 °C, 78%. (b) (i) Ph_3P, CBr_4, THF, −78 °C, 77%; (ii) nC_4H_9Li, THF, $ClCO_2C_2H_5$, −78 °C; (iii) HOAc, H_2O, THF, room temperature, overall 80%. (c) 10% **1**, CH_3OH, reflux, 75%. (d) $(Ph_3P)_3RhCl$, PhH–C_2H_5OH, room temperature, 2 atm of H_2, 93%.

pesticidal activity.[7,8] Ancepsenolide (**13**), from the gorgonia *Pterogorgia anceps* and *Pterogorgia guadalypenses*, whose reported $[\alpha]_D$ varies from +12.0° to +47.8°, represents one of the first butenolide acetogenins;[9,10] however, its absolute stereochemistry has not been established. The ability to annulate a butenolide ring onto a terminal olefin suggests the synthetic route outlined in Scheme 1, which addresses the question of a facile solution to the synthesis of acetogenins, the definition of the stereochemistry, and the ability to maintain the stereointegrity of the propargylic position of the acceptor in the ruthenium-catalyzed addition.

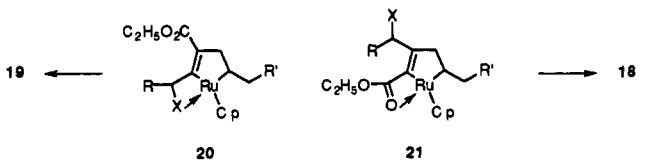
The known aldehyde **14**, readily available from methyl (*S*)-lactate,[11] undergoes olefination with (dibromomethylene)triphenylphosphorane.[12] Treatment of the resultant vinylidene dibromide with 2 equiv of C_4H_9Li and capping with ethyl chloroformate gave the acetylenic reaction partner **15**[6] after desilylation. The olefinic partner, 1,11-dodecadiene (**16**), was available by the olefination of 10-undecenal. Heating a 0.1 M solution of 2.4 equiv of acetylene **15** and 1 equiv of diene **16** with 10 mol % **2** gave a 75% yield of the double-addition product **17**,[6] $[\alpha]_D$ 38.7° (*c* 1.81, $CHCl_3$). Chemoselective hydrogenation with Wilkinson's catalyst did not proceed in benzene. On the other hand, in a 1:1 benzene–ethanol mixture, reduction proceeded completely at 2 atm to give ancepsenolide (**13**), $[\alpha]_D$ 39.6° (*c* 0.4, $CHCl_3$), mp 95.5–97.5 °C (lit.[9] mp 93–4 °C, $[\alpha]_D$ 13.2° (*c* 2.8, $CHCl_3$)). Since the sign of rotation of our synthetic product from (*S*)-lactic ester corresponds to that of the natural product, its absolute stereochemistry can now be assigned as *S*,*S*.[13] The synthesis proceeds in 31% overall yield in seven steps.

The thermal and Lewis acid catalyzed ene reactions with electron-deficient alkynes as enophiles are electronically controlled to produce predominantly the β-alkylated product (eq 6, path a) when they proceed at all.[14] In contrast to this fact, the ester



(6)

group appears to exercise no electronic effect on the ruthenium-catalyzed process. The metal-catalyzed version (eq 6, path b) reorients the reaction partners to give the α-alkylation products as well as expands the range of suitable enophiles. The steric demands of the catalyst dictate the use of terminal olefins as the ene partner. When X = OH, as in the cases illustrated herein, the regioselectivity is dominated by this substituent. A rationale for this effect envisions that coordination in a metallacycle intermediate as depicted in **20** is more efficient than in the regioisomeric metallacycle **21**.[15] These intermediates also explain



the steric effect on the regioselectivity since initial C–C bond formation should preferentially occur at the sterically more accessible carbon of the acetylenic acceptor as in **20**. Thus, coordination and steric effects rather than electronic effects dictate the regioselectivity. The utility of this new process is highlighted by the easy access it provides to butenolides as illustrated by the first synthesis of diastereo- and enantiopure (+)-ancepsenolide, which also established the absolute configuration.

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Supplementary Material Available: Characterization data for **3a–c**, **4a–c**, **6a,b**, **7a,b**, **8a–d**, **9a–c**, **11a,b**, **12a**, **13**, and **15–17** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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