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A Facile and Stereoselective Synthesis of Dienediones and 6-Oxo-2,4-dienoic Esters

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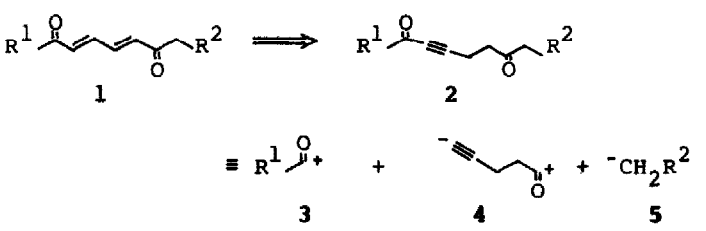
Abstract. Ostopanic acid and ethyl 6-oxodocosa-2,4-dienoate were synthesized by a short route based on the palladium catalyzed isomerization of ynone and ynoic ester, respectively, using pent-4-ynal as a starting material.

There are various classes of natural products such as alcohols,[1] aldehydes,[2] ketones,[3] and acids[4] containing a conjugated polyene structure, with a specific double-bond geometry being a requirement of primary importance for biological activity. Thus, it is not surprising that considerable effort has been paid in seeking stereoselective methods for the synthesis of such conjugated systems. In the course of our study on the transition metal complexes catalyzed organic synthesis, a novel isomerization of α,β-ynones[5] and 2-ynoic esters[6] to corresponding diene compounds was developed. The good yields and high stereoselectivity stimulated us to apply this reaction to the synthesis of natural products.

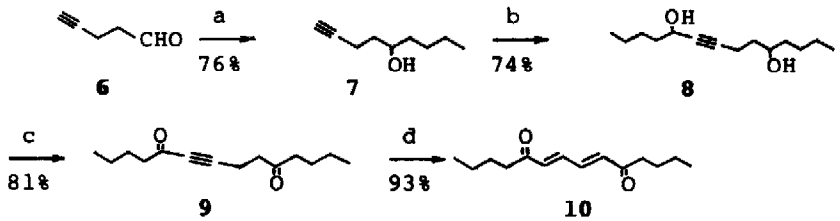
Ostopanic acid(**16**), a cytotoxic fatty acid, recently[7] isolated in minute quantity(0.009%) from the stem and fruits of Ostodes paniculata Blume(Euphorbiaceae), has been shown to inhibit the growth of P-388 lymphocytic leukemia test system in vitro. To date, only two reports[8,9] have described the total synthesis, one in low yield and its key step being nonstereoselective, the other requiring a multistep preparation of the disilyl derivatives. Our approach was based on the isomerization of ynones. The strategy is described in Scheme I.

Tetradec-6-yne-5,10-dione (**9**) was first prepared and it was successfully converted to tetradeca-6,8-diene-5,10-dione(**10**) as a model (Scheme II).

Scheme I



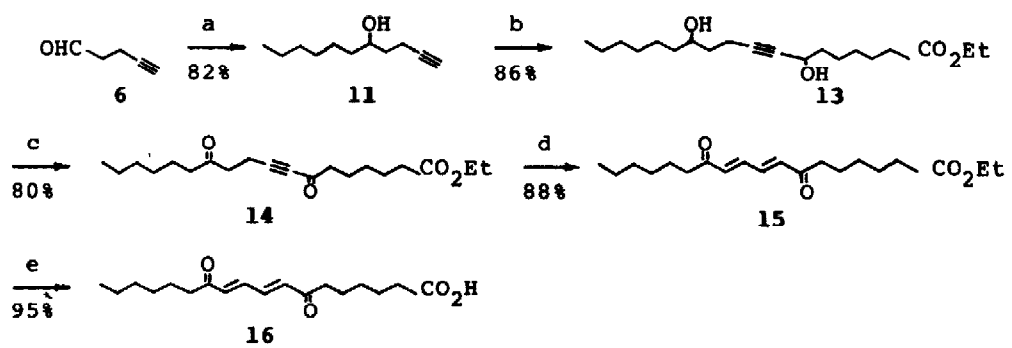
Scheme II



(a) i. n-C_4H_9MgBr, Et_2O; ii. aq.NH_4Cl. (b) i. EtMgBr, THF; ii. n-C_4H_9CHO, THF; iii. aq.NH_4Cl. (c) CrO_3, dil.H_2SO_4, CH_3COCH_3. (d) $Pd(OAc)_2$ (2.5 mol%), PPh_3 (35 mol%), benzene, reflux, 27 h.

After completing the preparation of the compound **10**, we started the total synthesis of ostopanic acid(**16**) as depicted in Scheme III. Pent-4-ynal(**6**), the equivalent of synthon **4**, reacted with Grignard reagent prepared from hexyl bromide afforded undecyn-5-ol(**11**). Treatment of **11** with n-butyllithium in THF, followed by ethyl 7-oxoheptanoate(**12**), which was prepared from 1-ethoxycycloheptene by ozonization, provided the ynediol(**13**). This ynediol was then transformed to ynedione(**14**) by Jones oxidation. The key step for construction of the diene structure was achieved when subjecting the precursor **16** to $Pd(OAc)_2/PPh_3$. Ethyl ostopanoate(**15**) was obtained in high yield. Sheu et al. has prepared ostopanic acid(**16**) through ethyl ostopanoate(**15**). However, they failed to

Scheme III

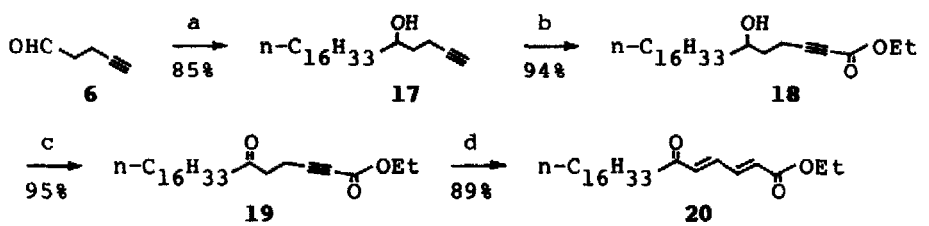


(a) i. n-$C_6H_{13}MgBr$, Et_2O; ii. aq.NH_4Cl. (b) i. n-BuLi, THF; ii. OHC-(CH$_2$)$_5$-CO_2Et(**12**), THF; iii. H_2O. (c) CrO_3, dil.H_2SO_4, CH_3COCH_3. (d) $Pd(OAc)_2$ (2.5 mol%), PPh_3 (35 mol%), benzene, reflux, 35 h. (e) LiOH, i-PrOH-H_2O.

afford ostopanic acid(**16**) directly by hydrolysis of **15** with hydrochloric acid and sulfuric acid or bases like sodium or potassium hydroxide. The failure of this reaction presumably arose from the vulnerable conjugated diene diketone present in compound **15**. Using less basic lithium hydroxide and carrying out the reaction at lower temperature, we successfully obtained ostopanic acid(**16**).

By a similar strategy, ethyl 6-oxodocosa-2,4-dienoate(**20**), a deoxygenation product of the natural compound Chondrillin,[10] was prepared (Scheme IV). The introduction of hexadecyl group to pent-4-ynal(**6**) by n-$C_{16}H_{33}MgBr$ gave heneicosyn-5-ol(**17**). After protection of the hydroxyl group with THP, generation of the lithium acetylide derivative of **17** with n-butyllithium, followed by quenching with ethyl chloroformate, yielded ethyl ynoate, which gave ethyl 6-hydroxydocos-2-ynoate(**18**) on deprotection. Jones oxidation of **18** afforded ethyl 6-oxodocos-2-ynoate(**19**). Finally, palladium catalyzed isomerization of **15** produced ethyl 6-oxodocosa-2,4-dienoate(**20**).

Scheme IV



(a) i. n-$C_{16}H_{33}MgBr$, Et_2O; ii. aq.NH_4Cl. (b) i. DHP, CH_2Cl_2, cat.PPTS; ii. n-BuLi, THF; iii. $ClCO_2Et$, THF; iv. aq.NH_4Cl; v. EtOH, cat.PPTS. (c) CrO_3, dil.H_2SO_4, CH_3COCH_3. (d) $Pd(OAc)_2$(2.5 mol%), PPh_3(35 mol%), toluene, reflux, 27 h.

Obviously, the above synthetic approach affords an easy access to the structurally modified analogues of **15** and **20**. Thus, a facile and stereoselective route to dienediones and 6-oxo-2,4-dienoic esters starting from pent-4-ynal is provided.

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10. Wells, R. J. Tetrahedron Lett. 1976, 2637.
11. The ^{1}H NMR, IR, and mass spectral data of ethyl ostopanoate(15) and ostopanic acid(16) were in agreement with those reported.[7,8] Ethyl 6-oxodocosa-2,4-dienoate(**20**), which had no reported data, was fully characterized by ^{1}H NMR, IR, MS, and elemental analysis. ^{1}H NMR(200 MHz, $CDCl_3$) δ 0.88(br t, 3H), 1.25(br s, 28H), 1.62(br t, 3H), 2.60(t, J=7.0 Hz, 2H), 4.26(q, J=7.0 Hz, 2H), 6.24(d, J= 15.0 Hz, 1H), 6.46(d, J=15.0 Hz, 1H), 7.15(dd, J=15.0,12.0Hz, 1H), 7.33(dd, J=15.0, 12.0 Hz, 1H); IR(nujol) 1705, 1685, 1590, 1090, 990cm^{-1}; MS, m/e 379(M^++H), 378(M^+), 349, 333, 305, 253, 195, 183, 168, 153, 125, 99, 73. Anal. Calcd for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 75.83; H, 11.25.

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