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A New Methodology to Key Intermediates for Synthesizing Polyene Compounds

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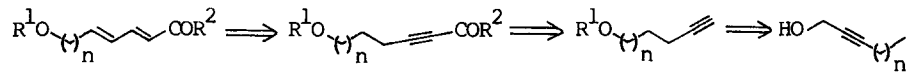
Abstract: ω-Alkoxy-(2E,4E)-dienoates, ω-oxo-(2E,4E)-dienoates and δ-oxo-α,β:γ,δ-dienones were prepared according to a new methodology shown in scheme I. High yield and high stereoselectivity were achieved by using transition metal catalyzed isomerization of ynoates or ynones instead of using Wittig-Horner-wadsworth-Emmons reaction to constitute the diene moiety. The usefulness of this methodology was demonstrated by the preparation of important synthetic precursors to polyene compounds and natural products such as 10-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-decadienoates, methyl 8-[(tetrahydropyran-2'-yl)-oxy]-(2E,4E)-octadienoate, methyl 10-benzyloxy-(2E,4E)-decadienoate, 6-oxo-(2E,4E)-tetradecadienal, methyl 8-oxo-(2E,4E)-octadienoate, and retrofractamide A.

Introduction

ω-alkoxy-(2E,4E)-dienoates, ω-oxo-(2E,4E)-dienoates, and δ-oxo-α,β:γ,δ-dienones are a class of compounds that play an important role in organic synthesis. Many complex natural products including insecticidal lipid isobutylamides,[1] macrocyclic or polycyclic compounds with bactericidal and anticancer activity,[2] insect pheromones,[3] and Leukotriene B3 or its derivatives[4] are conveniently synthesized from these conjugated diene building blocks. Recently, several novel preparations of these dienes have been reported,[1-4] however, these procedures rely on either Wittig-Horner-Wadsworth-Emmons olefinations or elemination reactions for the introduction of the diene functionality and are typically plagued by both low yields and stereoselectivity.[1-4] On the other hand, transition metal complexes catalyzed isomerization of alkynes to dienes has been demonstrated to be a very efficient and mild method for highly stereoselective synthesis of trans, trans-conjugated dienones,[5] dienoates, and dienamides[6], which makes it possible to develop a new methodology (Scheme I) to synthesize these functionalized dienes. Herein, we would like to describe this methodology in detail.

Scheme I



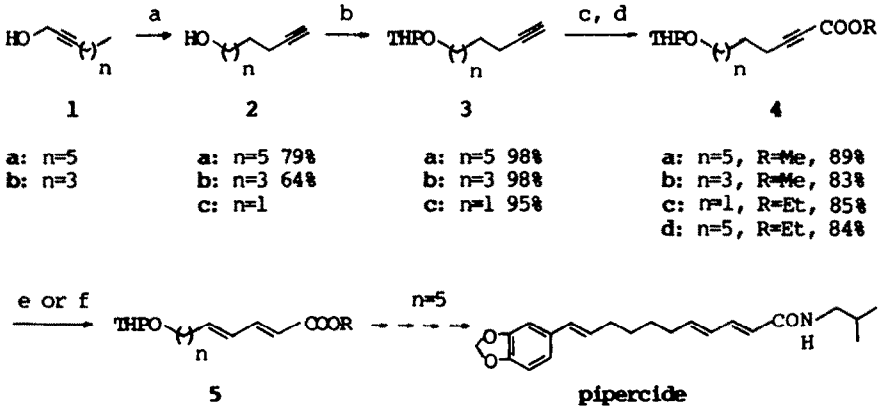
R^1=alkyl, R^2=alkyl or alkoxyl.

Results and discussion

ω-Alkoxy dienoates

As outlined in Scheme II, ω-hydroxyl terminal alkynes (**2**), which are readily available via base catalyzed isomerization of 2-ynol (**1**),[7] were protected with dihydropyran to give ω-(tetrahydropyran-2'-yl)oxy terminal alkynes (**3**). Compounds **3** were converted to the corresponding lithium alkynylides (with an equimolar amount of n-BuLi in n-hexane) followed by trapping with alkyl chloroformates to produce the ω-[(tetrahydropyran-2'-yl)oxy]-2-ynoates (**4**).[8] The conjugated dienoates could be readily obtained by the isomerization of **4** catalyzed by $IrH_5(i\text{-}Pr_3P)_2$ + 4n-Bu_3P or $RuH_2(Ph_3P)_4$ + 6n-Bu_3P.[6] The trans, trans stereochemistry of the products was confirmed by ^1H NMR spectra and no other isomers were detected. Thus, this route provided a convenient and highly stereoselective synthesis of ω-alkoxy-(2E,4E)-dienoates. By this method, methyl 10-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-decadienoate (**5a**), methyl 8-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-octadienoate (**5b**) and ethyl 10-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-decadienoate (**5d**) were prepared in good overall yield. These compounds were used as the precursors for preparing natural insecticidal lipid isobutylamides such as piprcide,[1a,1b] and for studying intramolecular Diels-Alder reactions[2d]. It is not apparent why the isomerization of 4c gave a polymer under the catalysis of iridium or ruthenium complexes. The failure of this attempt makes us impossible to obtain the useful synthetic intermediate, ethyl 6-[(tetra-hydropyran-2'-yl)oxy]-(2E,4E)-hexadienoate (**5c**).[2f]

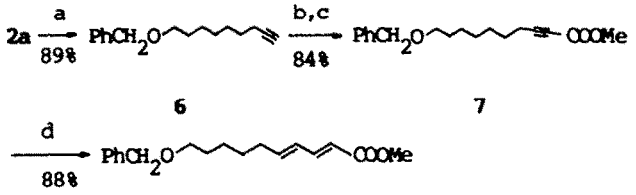
Scheme II



(a) NaH, $NH_2CH_2CH_2NH_2$, 60-65°C, 5h (b) DHP, p-TsOH. (c) n-BuLi, n-hexane, THF, -50—20°C; (d) ClCOOR(R=Me, Et), -20-0°C; (e) 1 mol% $IrH_5(i\text{-}Pr_3P)_2$, 4 mol% n-Bu_3P, toluene, reflux· (f) 1 mol% $RuH_2(Ph_3P)_4$, 6 mol% n-Bu_3P, toluene, reflux.

Methyl 10-benzyloxy-(2E,4E)-decadienoate (**8**) has been used as the starting material to synthesize the degradation product of Chlorothricine.[2a-2c] By the present methodology, this compound could also be obtained in good yield as shown in Scheme III.

Scheme III

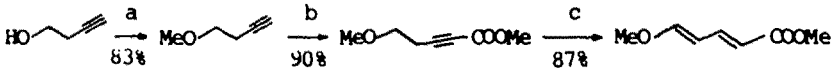


(a) NaH, then $PhCH_2Cl$, THF; (b) n-BuLi, n-hexane, THF, -50—20°C; (c) $ClCOOCH_3$, -20-0°C; (d) 1 mol% $RuH_2(Ph_3P)_4$, 6 mol% $n\text{-}Bu_3P$, toluene, reflux, 30 h.

δ-Alkoxy dienoates:

5-Alkoxy-(2E,4E)-dienoates are a new class of dienes for Diels-Alder reaction bearing an electron withdrawing substitute at position 1 and an electron donating substitute at position 4 of the diene.[9] In addition, it has also been found to be an excellent building block for the synthesis of polyenic ethers.[10] As shown in Scheme IV, the δ-alkoxyl dienoate could be formed by the catalyzed isomerization of a suitable ynoate. Unfortunately, this isomerization gave a mixture of (2E,4E) and (2E,4Z) isomers in a ratio of 1:1. The low stereoselectivity has also been found in the isomerization of alkynyl ethers by Suzuki and Moro-Oka.[11]

Scheme IV



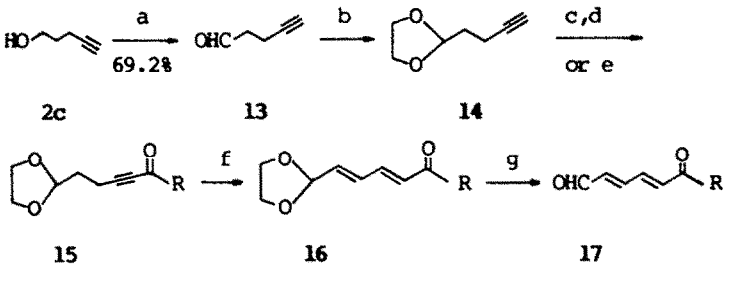
(a) Me_2SO_4, KOH; (b) n-BuLi, n-hexane, THF, -50—20°C, then ClCOOMe, -20-0°C; (c) 1 mol% $IrH_5(i\text{-}Pr_3P)_2$, 4 mol% $n\text{-}Bu_3P$, benzene, reflux, 36 h.

δ-Oxo-dienones:

Since an aldehyde group can easily react with the transition metal hydrides,[12] the direct isomerization of ω-oxo ynoates or ω-oxo ynones can not be employed in elaboration of the oxo-substituted conjugated diene system. Therefore, a proper protecting group for the aldehyde group is necessary. A practical route to δ-oxo conjugated dienones is shown in Scheme V. Oxidation of 4-pentyn-1-ol (**2c**) with pyridinium chlorochromate gave

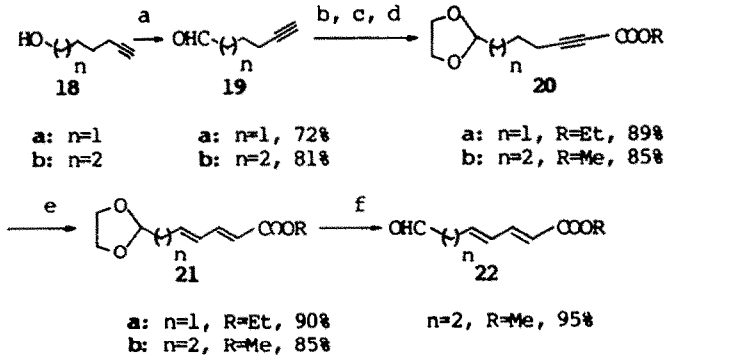
4-pentynal (**13**),[13] which was converted to the corresponding cyclic acetal with ethylene glycol. On treatment of this acetal with n-BuLi and then quenching with a suitable aldehyde to give ynols, the later were oxidized with pyridinium chlorochromate to yield ynones **15** (or more directly, **15b** could be also prepared by the reaction of a lithium alkynylide with N,N-dimethylacetamide[14]), which were isomerized to conjugated dienones **16** under the catalysis of a ruthenium complex.[5b] The product was characterized as a single product with a trans, trans geometry by ^{1}H NMR spectra. The protecting group of **16a** could be cleaved in acidic condition and gave 6-oxo-(2E,4E)-tetradecadienal (**17**), a key precursor for the preparation of Leukotriene B3 and its derivatives.[4a]

Scheme V



(a) PCC, CH_2Cl_2, 25°C; (b) $HOCH_2CH_2OH$, p-TsOH, benzene, reflux; (c) n-BuLi, n-hexane, THF, -50—20°C, then $n\text{-}C_8H_{17}CHO$; (d) PCC, CH_2Cl_2, 25°C; (e) n-BuLi, n-hexane, THF, -50—20°C, then CH_3CONMe_2, -60-10°C; (f) 1 mol% $RuCl_2(Ph_3P)_3$, 8 mol% $n\text{-}Bu_3P$, benzene, reflux; (g) 2.5% HCl, acetone, 0°C.

Scheme VI



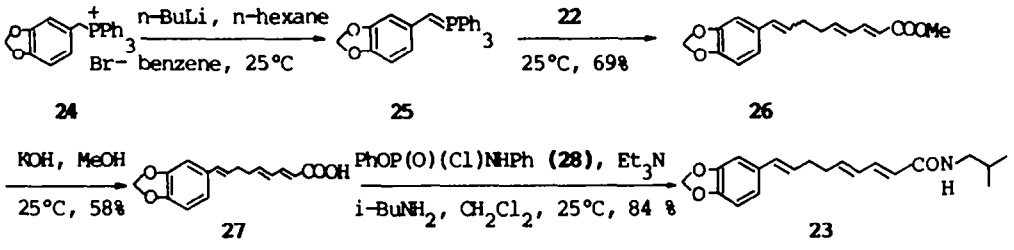
(a) PCC, CH_2Cl_2, 25°C (b) $HOCH_2CH_2OH$, p-TsOH, benzene, reflux; (c) n-BuLi, n-hexane, THF, -50—20°C; (d) $ClCOOR$ (R=Me, Et), -20-0°C; (e) 1 mol% $IrH_5(i\text{-}Pr_3P)_2$, 4 mol% $n\text{-}Bu_3P$, toluene or benzene, reflux; (f) 5% HCl, acetone, reflux.

ω-Oxo dienoates:

ω-Oxo-(2E,4E)-dienoates were also recognized as precursors to insecticidal lipid isobutylamides by Crombie.[1a] The procedure shown in Scheme VI is an apparent route of choice for assembling this kind of compounds. The iridium complex catalyzed isomerization of ynoates **20** occurred with high stereoselectivity to give ω-ethylenedioxy-(2E,4E)-dienoate (**21**). The protecting group of **21b** was removed by 5% HCl in acetone to yield methyl 8-oxo-(2E,4E)-octadienoate (**22**), which is a convenient building block for many lipid isobutylamides including Tetraene and Achilea millefolium amides.[1a]

Retrofractamide A (**23**) is a new unsaturated isobutylamide which was isolated from Indian Piper retrofractum and characterised as N-isobutyl-(3',4')-methylenedioxyphenyl-(2E,4E,8E)-nonatrienamide.[15] The first synthesis of this amide was reported by Banerji and coworkers,[16] and Wittig-Horner-Wadsworth-Emmons reaction was employed as the key step for the construction of the (2E,4E)-dienoate. However, the overall yield was only 1.3% from a common starting material. With 8-oxo-(2E,4E)-octadienoate (**22**) in hand, we can conveniently obtain retrofractamide A according to the similar method reported by Miyakado and Yoshioka[1b] (Scheme VII). In order to get the piperonyl structural unit, 3,4-methylenedioxybenzyltriphenyl-phosphonium bromide (**24**)[17] was converted with an equimolar amount of n-BuLi to the ylide **25** which was coupled in situ with an equimolar amount of **22** to give the trienoate **26** in 69% yield.[18] ^{1}H NMR showed the E/Z ratio of C-8 double bond was about 3.5/1. After hydrolysis of the E/Z mixture, the pure 9-(3',4'-methylenedioxyphenyl)-(2E,4E,8Z)-nonatrienoic acid (**27**) could be obtained by recrystallizing twice from benzene with a 58% yield. The pure acid was activated with phenyl N-phenylphosphoramidochloridate (**28**) followed by treatment with isobutylamine and triethylamine to give **23**.[19] The overall yield from **18b** was 18.7%.

Scheme VII



In summary, we have demonstrated the synthesis of the useful diene and polyene compounds **5**, **8**, **16**, **17**, **22**, **23** and **27** via an efficient, stereoselective and high yield process under mild conditions. The new methodology may have pratical applications for the synthesis of important polyene natural products as well as intermediates for the synthesis of other complex molecules.

Experimental Section

The melting points and boiling points are uncorrected. All reactions catalyzed by transition metal complexes were carried out under a prepurified nitrogen atmosphere. Benzene and toluene were distilled from sodium and benzophenone under a nitrogen atmosphere. ^{1}H NMR spectra were recorded on an EM-360, JEOL FX-90Q, Bruker MSL-300, or Bruker AM-400 spectrometer. All chemical shifts are reported in δ units downfield from internal Me_4Si, and J values are given in Hertz. Infrared spectra were taken with a IR-440 instrument. Mass spectral data were obtained with electron ionization on a Finnigan 4021 spectrometer. High resolution mass spectral data were determined on Finnigan-MAT 8430 spectrometer. Transition metal catalysts, $IrH_5(i\text{-}Pr_3P)_2$,[22] $RuH_2(Ph_3P)_4$,[23] and $RuCl_2(Ph_3P)_3$[24] were prepared according to the reported method.

2-Ynols were prepared according to the known method.[8] **1a**, bp 101-105°C/7 Torr, yield 78%. **1b**, bp 99-101°C/22.5 Torr (lit.[8] 83°C/12 Torr), yield 87.4%.

8-Nonyn-1-ol (**2a**):[25] A 1-L four-necked flask was equipped with a mechanical stirrer and flushed with nitrogen. NaH (40 g, 80%, 1.33 mol) and ethylenediamine (350 mL, redistilled from NaH) were successively added under cooling with ice. The mixture was cautiously heated to 65°C and kept at this temperature for 2 h. The solution was cooled to 50°C and 2-nonyn-1-ol (0.21 mol) was added dropwise while the temperature was maintained at 50°C. Heating was continued at 60-65°C for 3 h. The solution was allowed to cool to 0°C and H_2O (150 mL) was added. Hydrochloric acid(15%, 100 mL) was added and the solution was extracted with ether. The combined organic layers were washed with hydrochloric acid(15%), saturated NaCl solution, and dried over Na_2SO_4. After removal of the solvent, distillation of the remaining liquid gave 8-nonyn-1-ol (**2a**): 23 g (79%), bp 80-81°C/4 Torr; ^{1}H NMR (CCl_4) 3.6(t, 2H), 2.3(s, 1H, disappearing after adding D_2O), 2.1(m, 2H), 1.8(t, 1H), 1.4(m, 10H).

6-Heptyn-1-ol (**2b**)[26] was prepared by the similar procedure in 64% yield, bp 98-99°C/20 Torr. 4-Pentyn-1-ol (**2c**) was obtained according to the method reported by Jones et al.[25] in 84% yield, bp 154-155°C (lit.[25] bp 154-155°C).

Ethyl 10-[(tetrahydropyran-2'-yl)oxy]-2-decynoate (4d): A solution of n-BuLi(0.04 mol) in n-hexane(40 mL) was added dropwise to a mixture of 9-[(tetrahydropyran-2'-yl)oxy]-1-nonyne(**3b**, 0.036 mol) in THF(40 mL) cooled to -50°C. After addition, the resulting solution was allowed to warm to -20°C and then stand at -50°C.

The above lithiated acetylene was added dropwise in 10 equal portions by a syringe at below -30°C to a three-necked flask containing a solution of ethyl chloroformate (0.072 mol) in THF(60 mL). The temperature was kept between -25 and -35°C during the addition. Stirring at this temperature was continued for another 30 min, then the temperature was allowed to rise to 10°C. The reaction mixture was poured into 10% Na_2CO_3 solution(100 mL) and extracted with ether. The organic layers were washed with saturated NaCl solution to neutral. After removal of solvent, the residual oil was distilled to give **4d**, 9.4 g (84%),

as a colourless liquid. bp 138-140°C/0.01 Torr; IR (neat) 2240, 1720, 1120 cm^{-1}; ^1H NMR(CCl_4) 4.2(m, 5H), 3.8 (m, 2H), 2.2(m, 2H), 1.4-1.2(m, 19H); MS, m/e 296 (M^+), 267, 225, 121, 85, 43; Anal. calcd for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52. Found: C, 68.58; H, 9.48.

The following ω-alkoxy-2-ynoates were synthesized by this procedure:

Methyl 10-[(tetrahydropyran-2'-yl)oxy]-2-decynoate (4a): yield 89%, bp 141-143°C/0.025 Torr; IR(neat) 2240, 1720 cm^{-1}; ^1H NMR(CCl_4) 4.5(m, 1H), 3.8(s, 3H), 3.6(m, 4H), 2.2, (t, 2H), 1.4 (m, 16H); MS, m/e 282(M^+), 267, 121, 85, 41; Anal. calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.29. Found: C, 68.37; H, 9.20.

Methyl 8-[(tetrahydropyran-2'-yl)oxy]-2-octynoate (4b): bp 139-140°C/0.08 Torr; yield 83%; IR(neat): 2240, 1715 cm^{-1}; ^1H NMR(CCl_4) 4.5(s, 1H), 3.8(s, 3H), 3.6(m, 4H), 2.2(t, 2H), 1.4(m, 12H); MS, m/e 254(M^+), 239, 121, 85, 41; Anal. calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.35; H, 8.63.

Ethyl 6-[(tetrahydropyran-2'-yl)oxy]-2-hexynoate (4c): bp 120-121°C/0.1 Torr; yield 85%; IR(neat): 2240, 1720 cm^{-1}; ^1H NMR(CCl_4) 4.5(m, 1H), 4.0(q, 2H), 3.8(m, 4H), 2.2(t, 2H), 1.8(m, 8H), 1.0(t, 3H); MS, m/e 240(M^+), 211, 167, 139, 85, 41; Anal. calcd for $C_{13}H_{20}O_4$: C, 64.98, H, 8.39. Found C: 64.77, H, 8.30.

Methyl 10-benzyloxy-2-decynoate (7): bp 122-124°C/0.02 Torr; yield 90%; IR(neat) 2240, 1720 cm^{-1}; ^1H NMR(CCl_4) 7.2(s, 5H), 4.2(s, 2H), 3.6(s, 3H), 3.4(t, 2H), 2.2(m, 2H), 1.4(m, 10 H); MS,m/e 288(M^+), 257, 81, 43; Anal. calcd for $C_{18}H_{24}O_3$: C, 74.96; H, 8.39. Found: C, 74.79; H, 8.27.

Methyl 5-methoxy-2-pentynoate (11): bp 101-103°C/17 Torr, yield 90%; IR(neat) 2240, 1720 cm^{-1}; ^1H NMR(CCl_4) 3.8(s, 3H), 3.6(t, 2H), 3.4(s, 3H), 2.4(t, 2H); MS, m/e 142(M^+), 111, 75, 65, 45. Anal. calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.16; H, 7.03.

General procedure for the isomerization of alkoxyl substituted 2-ynoates to alkoxyl substituted (2E,4E)-dienoates catalyzed by $IrH_5(i\text{-}Pr_3P)_2$ + 4n-Bu_3P or $RuH_2(Ph_3P)_4$ + 6n-Bu_3P:

A mixture of ω-alkoxy-2-ynoate (2.5 mmol), catalyst (0.025 mmol) and n-Bu_3P (0.1-0.15 mmol) in toluene was heated at reflux for about 30 h (benzene was used as solvent for ynoate 11). After cooling and removal of the solvent, the red residue was either distilled under reduced pressure or passed through a column of silica gel. The dienoate was isolated as a colourless or pale yellow liquid.

Methyl 10-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-decadienoate (5a): IR(neat) 3010, 1720, 1640, 1620 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) 7.38(dd, J_{32}=15.3 Hz, J_{34}=10.8 Hz, 1H), 5.86 (d, J_{23}=15.3 Hz, 1H), 5.84(dd, J_{43}=10.8 Hz, J_{45}=15.1 Hz, 1H), 5.79(dt, J_{54}=15.1 Hz, J_{56}=7.6 Hz, 1H), 4.50(m, 1H), 3.64(m, 2H), 3.50(s, 3H), 3.41(m, 2H), 2.01(m, 2H), 1.52(m, 12H); MS, m/e 282(M^+), 219, 199, 85, 41.

Methyl 8-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-octadienoate (5b): IR(neat) 3010, 1720, 1640, 1620cm $^{-1}$; ^1H NMR(300 MHz, C_6D_6) 7.39(dd, J_{32}=15.3 Hz, J_{34}=10.8 Hz, 1H), 5.85(d, J_{23}= 15.3 Hz, 1H), 5.81(dd, J_{43}=10.8 Hz, J_{45}=15.3 Hz, 1H) 5.67(dt, J_{54}=15.3 Hz, J_{56}=7.8 Hz, 1H), 4.50(m, 1H), 3.66(m, 2H), 3.41 (s, 3H), 3.32(m, 2H), 2.01(m, 2H), 1.5(m, 8H); MS, m/e

254 (M^+), 223, 171, 139, 85.

Ethyl 10-[(tetrahydropyran-2'-yl)oxy]-(2E,4E)-decadienoate (**5d**): IR(neat) 3010, 1720, 1640, 1620 cm^{-1}; ^1H NMR(300 MHz, C_6D_6) 7.48(dd, J_{32}=15.6 Hz, J_{34}=10.8 Hz, 1H), 5.90(d, J_{23}=15.6 Hz, 1H), 5.83(dd, J_{43}=10.8 Hz, J_{45}=15.3 Hz, 1H), 5.65(dt, J_{54}=15.3 Hz, J_{56}=7.1 Hz, 1H), 4.60(m, 1H), 4.02(q, 2H), 3.50(m, 4H), 1.80(m, 2H), 1.6-0.9(m, 12H), 0.9(t, 3H); MS, m/e 296(M^+), 219, 85, 55.

Methyl 10-benzyloxy-(2E,4E)-decadienoate (**8**): IR(neat) 3050, 1720, 1640cm^{-1}; ^1H NMR(300 MHz, C_6D_6) 7.48(dd, J_{32}=15.4 Hz, J_{34}=10.8 Hz, 1H), 7.24(m, 5H), 5.91(d, J_{23}=15.4 Hz, 1H), 5.83(dd, J_{43}=10.8 Hz, J_{45}=15.3 Hz, 1H), 5.67(dt, J_{54}=15.3 Hz, J_{56}=7.2 Hz, 1H), 4.84(s, 2H), 4.21(m, 2H), 4.01(s, 3H), 2.21(m, 2H), 1.48(m, 6H); MS, m/e 288(M^+), 199, 121, 91, 85.

Methyl (2E,4)-pentadienoate (**12**): IR(neat) 1720, 1630 cm^{-1}; ^1H NMR(90 MHz, CDCl3) [7.6(dd, J_{32}=16 Hz, J_{34}=11 Hz, 2E,4Z), 7.2(dd, J_{32}=16 Hz, J_{34}=11 Hz, 2E,4E), 1H], [6.9(d, J_{54}=12 Hz, 2E,4E), 6.2(d, J_{54}=6 Hz, 2E,4Z), 1H], 5.7(d, J_{23}=11 Hz, J_{45}=6 Hz, 2E,4Z), 1H], 3.8(s, 6H); MS, m/e 142(M^+) 111, 95, 53, 45, 41.

5-Hexynal (19a): To a suspension of pyridinium chlorochromate(0.18 mol) in CH_2Cl_2 (200 mL) was added dropwise 5-hexyn-1-ol(0.12 mol) under cooling. The mixture was stirred at 25°C for about 4.5 h and the resulting solution was filtered through a 15 cm alumina column. The precipitate was washed with ether(8x40 mL) and the washing solution was filtered through the same column. The combined ether solution was distilled through a 12 cm Vigreux column keeping the bath temperature below 60°C. Distillation of the residue gave **19a**, 8.4g (72%), bp 90-91°C/80 Torr (lit.[26] 62-64°C/33 Torr); ^1H NMR(CCl_4) 9.6(s, 1H), 2.6-2.2(m, 4H), 1.8(m, 3H).

The other ynals were prepared by the same procedure: 4-pentynal (**13**)[27]: bp 128°C, yield 69.2%, ^1H NMR(CCl_4) 9.5 (s, 1H), 2.4(m, 4H), 1.8(m, 1H); 6-heptynal (**19b**)[28]: bp 78-80°C/20 Torr; 81%; ^1H NMR(CCl_4) 9.6(s, 1H), 2.2(m, 4H), 1.7(m, 5H).

1-Ethylenedioxy-4-tetradecyn-6-one (15a): A mixture of 4-pentynal(0.207 mol), ethylene glycol(0.26 mol) and p-toluenesulfonic acid(50 mg) in dry benzene was azeotropically distilled until no more aqueous phase separated. Work up gave the acetal as a colourless liquid, 18 g(76%), bp 85-86°C/32 Torr; (lit.[29] 66-68°C/23 Torr); ^1H NMR(CCl_4) 4.8(m, 1H), 3.8(s, 4H), 2.2(m, 2H), 1.8-1.6(m, 3H).

A solution of n-BuLi(0.024 mol) in n-hexane(24 mL) was added dropwise to a mixture of the above acetal(0.024 mol) and absolute ether(200 mL) at -50--20°C to give the lithium alkynylide. 1-Nonanal(0.024 mol) was added at -50°C and the temperature was allowed to rise to 0°C. The resulting solution was poured into water(100 mL) and extracted three times with ether. The combined organic layers were washed with saturated NaCl solution to neutral and dried over Na_2SO_4. The crude ynol, obtained after removal of solvent, was oxidized with PCC (according to the procedure for the preparation of **19a** to give **15a**, 5.4 g(86% from **14**); bp 131-133°C/0.01 Torr; IR(neat) 2240, 1680 cm^{-1}; ^1H NMR(CCl_4) 4.8(t, 1H), 3.8(s, 4H), 2.2(t, 2H), 1.8(m, 2H), 1.4(m, 14H), 1.0(t, 3H); MS, m/e 266(M^+), 223, 125,

73, 45; Anal. Calcd exact mass for $C_{16}H_{26}O_3$, 266.188. Found, 266.187.

7-Ethylenedioxy-3-heptyn-2-one (15b): To the lithium alkynylide(0.034 mol) (prepared as above) was added N,N-dimethylacetamide(0.04 mol) with cooling at -60°C. The temperature was allowed to rise to 10°C and stirring was continued for additional 3 h. The mixture was poured into water (100 mL) and extracted with ether(200 mL). After washing with saturated NaCl solution, drying over Na_2SO_4, and removal of solvent, the residue was distilled to give **15b**, 4.9 g(85.6%), bp 78-80°C/0.7 Torr; IR(neat) 2240, 1680 cm^{-1}; ^1H NMR(CCl_4) 4.8 (t, 1H), 3.8(s, 4H), 2.2(m, 5H), 1.4(m, 2H); MS, m/e 168(M^+), 125, 109, 87, 45; Anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.89; H, 7.24.

Isomerization of 2-ynone 15 under the catalysis of $RuCl_2(Ph_3P)_3$ + $8n\text{-}Bu_3P$: A mixture of 2-ynone(**15**, 5 mmol), $RuCl_2(Ph_3P)_3$ (0.05 mmol) and $n\text{-}Bu_3P$ (0.4 mmol) in benzene (5 mL) was heated at reflux for about 24 h. After cooling and removal of solvent, the resulting oil was distilled at reduced pressure and then purified by filtration through a short column of silica gel to give **16**.

1-Ethylenedioxy-(2E,4E)-tetradecadien-6-one (**16a**): IR(neat) 1680, 1640, 1620 cm^{-1}; ^1H NMR(300 MHz, C_6D_6) 7.02(dd, J_{43}=10.1 Hz, J_{45}=15.5 Hz, 1H), 6.30(dd, J_{32}=15.3 Hz, J_{34}=10.1 Hz, 1H), 5.96(d, J_{54}=15.5 Hz, 1H), 5.86(dd, J_{23}=15.3 Hz, J_{21}=5.1 Hz, 1H), 5.22(d, 1H), 3.45(m, 4H), 2.20(t, 2H), 1.20(m, 12H), 0.93(t, 3H); MS, m/e 266(M^+), 183, 125, 95, 81, 55; Anal. calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found C, 72.14; H, 9.80.

7-Ethylenedioxy-(3E,5E)-heptadien-2-one (**16b**): IR(neat) 1690, 1640, 1620 cm^{-1}; ^1H NMR(300 MHz, C_6D_6) 7.05(dd, J_{43}=15.4 Hz, J_{45}=10.8 Hz, 1H), 6.32(dd, J_{54}=10.8 Hz, J_{56}=15.2 Hz, 1H), 5.98(d, J_{34}=15.4 Hz, 1H), 5.88(dd, J_{65}=15.2 Hz, J_{67}=7.1 Hz, 1H), 5.22(d, 1H), 3.45(m, 4H), 2.20(s, 3H); MS, m/e 168(M^+), 153, 95, 81, 43; Calcd exact mass for $C_9H_{12}O_3$: 168.078. Found: 168.078.

6-Oxo-(2E,4E)-tetradecadienal (17): A solution of **16a** (2.93 mmol), hydrochloric acid (2.5%, 1 mL) and acetone (5 mL) was stirred at 5°C for 4 h. Work up gave **17**, 0.585 g (90%). IR(KBr) 3010, 2710, 1680, 1640, 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) 9.7(d, J_{12}=8 Hz, 1H), 7.3(dd, J_{32}=15.4 Hz, J_{34}=11 Hz, 1H), 7.2(dd, J_{43}=11 Hz, J_{45}=15.4 Hz, 1H), 6.5(d, J_{54}=15.4 Hz, 1H), 6.4(dd, J_{21}=8 Hz, J_{23}=15.4 Hz, 1H) 2.4(t, 2H), 1.4(m, 12H), 1.0(t, 3H); MS, m/e 222(M^+), 151, 141, 124, 83, 43.

Ethyl 7-ethylenedioxy-2-heptynoate (20a): A solution of 5-hexynal (0.086 mol), ethylene glycol (0.112 mol) and p-toluenesulfonic acid (20 mg) in dry benzene (30 mL) was distilled azeotropically to give the acetal[29], 10.8 g(92%). bp 99-100°C/24 Torr; ^1H NMR(CCl_4) 4.8(m, 1H), 3.8(s, 4H), 2.2 (m, 2H), 1.8-1.6(m, 5H). This acetal was coupled with ethyl chloroformate by a procedure similar to that used for the preparation of **4d** to give **20a**, yield: 89%; bp 114-115°C/0.4 Torr; IR(neat) 2240, 1720 cm^{-1}; ^1H NMR(CCl_4) 4.8(m, 1H), 4.0(q, 2H), 3.8(s, 4H), 2.3(t, 2H), 1.5(m, 4H), 1.0(t, 3H); MS, m/e 212(M^+), 167, 123, 99, 75; Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.01, H, 7.58.

By the similar procedure, methyl 8-ethylenedioxy-2-octynoate (**20b**) was prepared as a colourless liquid. bp: 98-99°C/0.1 Torr; yield: 85.5%; IR(neat) 2240, 1710 cm^{-1}; ^1H NMR

(CCl_4) 4,8(m, 1H), 4.0(s, 3H), 3.8(s, 4H), 2.3(t, 2H), 1.5 (m, 6H); MS, m/e 212(M^+), 167, 123, 99, 75, 45; Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C,62.01; H, 7.58.

General procedure for the isomerization of ethylenedioxy-2-ynoates (20) with $IrH_5(i\text{-}Pr_3P)_2$ + 4n-Bu_3P:

A mixture of **20a** (5 mmol), $IrH_5(i\text{-}Pr_3P)_2$ (0.05 mmol), n-Bu_3P (0.2 mmol) and toluene (5 mL, for **20b**, benzene was employed as solvent) was heated at reflux for 24-36 h. After cooling, the solvent was removed and the resulting oil was distilled at reduced pressure to give **21**.

Ethyl 7-ethylenedioxy-(2E,4E)-heptadienoate (**21a**): IR(neat) 1720, 1645, 1620 cm^{-1}; ^1H NMR(300 MHz, C_6D_6) 7.40 (dd, J_{32}=15.3 Hz, J_{34}=10.2 Hz, 1H), 5.95(d, J_{23}=15.3 Hz, 1H), 5.90(dd, J_{43}=10.2 Hz, J_{45}=15.6 Hz, 1H), 5.84(dt, J_{54}=15.6 Hz, J_{56}=6.3 Hz, 1H), 4.70(t, 1H), 4.05(q, 2H), 3.40(m, 4H), 2.31(dd, 2H), 1.01(t, 3H); MS, m/e 212(M^+), 167, 73, 45; Calcd exact mass for $C_{11}H_{16}O_4$: 212.104. Found: 212.106.

Methyl 8-ethylenedioxy-(2E,4E)-octadienoate (**21b**): IR(neat) 3050, 1720, 1640 cm^{-1}; ^1H NMR(300 MHz, C_6D_6) 7.40 (dd, J_{32}=15.3 Hz, J_{34}=10.8 Hz, 1H), 5.85(d, J_{23}=15.3 Hz, 1H), 5.80(dd, J_{43}=10.8 Hz, J_{45}=15.2 Hz, 1H), 5.67(dt, J_{54}=15.2 Hz, J_{56}=7.1 Hz, 1H), 4.69(t, 1H), 3.41(s, 3H), 3.38(m, 4H), 2.01 (m, 2H), 1.48(m, 2H); MS, m/e 212(M^+), 143, 73, 45; Calcd exact mass for $C_{11}H_{16}O_4$: 212.104. Found: 212.106.

Methyl 8-oxo-(2E,4E)-octadienoate (22): A solution of **21b** (9.4 mmol), hydrochloric acid (5%, 1 mL) and acetone (10 mL) was heated at reflux for 4 h. The reaction mixture was treated with ether (50 mL) and the organic layer was washed with 5% Na_2CO_3 and saturated NaCl solution successively, and then dried over Na_2SO_4. After removal of solvent, distillation of the residue gave **22**, 1.5 g(95%); IR(neat) 2710, 1720, 1640, 1620 cm^{-1}; ^1H NMR(CCl_4) 9.3(s, 1H), 7.0(dd, J_{32}=16 Hz, 1H), 6.0(m, 3H), 4.0(s, 3H), 2.2(m, 4H); MS, m/e 168(M^+), 137, 111, 79, 55.

(3',4'-Methylenedioxyphenyl)-(2E,4E,8E)-nonatrienoic acid (26): Under a nitrogen atmosphere, n-BuLi (8.2 mmol) in n-hexane (5mL) was added dropwise to a solution of 3,4-methylenedioxybenzyltriphenylphosphonium bromide (**24**)[17] in benzene (20 mL) with cooling to 0°C. The suspension was warmed to room temperature and then stirred for another 15 min. The resulting red mixture was cooled to 0°C and a solution of **22** (6 mmol) in benzene (10 mL) was added dropwise. After addition, the mixture was stirred for 30 min at 25°C, and then filtered to remove the insoluble materials. The filtrate was concentrated and the residue was purified by column chromatography (silica gel) to give **26**, 1.17g(69%). ^1H NMR (400 MHz, $CDCl_3$) showed the ratio of two isomers is 8E:8Z=3.5:1. This mixture was hydrolyzed by treatment with 5% KOH methanol solution at 25°C for 4h to give the crude acid. Crystallization twice from benzene gave **27** in 58% yield. mp 144-145°C; IR(KBr) 3300-2500 (br), 1680, 1640, 1620 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) 11.54(s, 1H), 7.32(dd, J_{32}=15.1 Hz, J_{34}=10.0 Hz, 1H), 6.88(s, br, 1H), 6.72(s, br, 2H), 6.30(d, J_{23}=15.1 Hz, 1H), 6.19(m, 2H), 6.01(dt, J_{87}=6.7 Hz, J_{89}=15.4 Hz, 1H), 5.91(s, 2H), 5.78(d, J_{98}=15.4 Hz, 1H), 2.32(m, 4H); MS, m/e 272(M^+), 161, 103, 77.

Retrofractamide A (23): To a mixture of **27** (0.37 mmol), isobutylamine(0.37 mmol), triethylamine(0.5 mmol) and CH_2Cl_2 (5 mL) was added phenyl N-phenylphosphoramidochloridate (**28**, 0.38 mmol)[19] at 0°C, and the solution was stirred at 25°C for 1.5 h. The resulting solution was extracted with ether (100 mL) and the organic layer was washed with water and saturated NaCl solution, and dried over Na_2SO_4. After removal of solvent, the crude product was recrystallized from methanol to give **23** as a pale yellow crystal, mp 126-127°C (lit.[15] 129°C), yield: 84%. IR(KBr) 1665, 1620 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) 7.20 (dd, J_{32}=15.2 Hz, J_{34}=10.8 Hz, 1H), 6.89(s, 1H), 6.65(s, br, 2H), 6.32-5.80(m, 6H), 5.93(s, 2H), 3.12(d-d, 2H), 2.24(m, 4H), 1.83(m, 1H), 0.95(d, 6H); MS, m/e 327(M^+), 161, 131, 103, 94, 77.

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