Pergamon

Tetrahedron Letters 40 (1999) 7179–7183

TETRAHEDRON
LETTERS

A convenient strategy for the synthesis of β,γ-unsaturated aldehydes and acids. A construction of skipped dienes

Goutam Saha,[a] Manas K. Basu,[a] Seongjin Kim,[a] Young-Ju Jung,[a] Yurdanur Adiyaman,[a] Mustafa Adiyaman,[b] William S. Powell,[c] Garret A. FitzGerald [d] and Joshua Rokach [a,*]

[a] *Claude Pepper Institute and Department of Chemistry, Florida Institute of Technology, 150 W. University Blvd., Melbourne, FL 32901, USA*

[b] *Abant Izzet Baysal University, Department of Chemistry, 14280 Golkoy, Bolu, Turkey*

[c] *Meakins-Christie Laboratories, 3626 St-Urbain St., Montreal, Quebec H2X 2P2, Canada*

[d] *The Center for Experimental Therapeutics, The University of Pennsylvania, Philadelphia, PA 19104, USA*

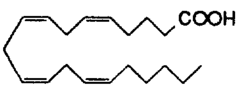
Received 9 July 1999; revised 26 July 1999; accepted 27 July 1999

Abstract

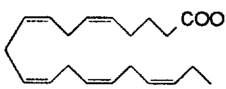
A novel strategy is described for the synthesis of β,γ-unsaturated aldehydes which are the useful synthons for the synthesis of arachidonic acid and other eicosanoid products. These β,γ-unsaturated aldehydes have been used in the total synthesis of arachidonic acid. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: β,γ-unsaturated aldehydes; eicosanoids; $Pb(OAc)_4$; arachidonic acid; isoprostanes; 5-oxo-ETE.

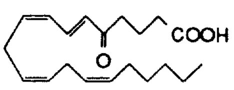
In dealing with the chemistry and synthesis of eicosanoids such as polyunsaturated fatty acids, e.g. arachidonic acid (AA) **1**, eicosapentaenoic acid (EPA) **2**, hydroxyeicosatetraenoic acids (HETEs), leukotrienes (LTs) and the most recent additions to the eicosanoid field, oxoeicosanoids,[1,2] e.g. 5-oxo-ETE **3**, and isoprostanes (iPs),[3,4] e.g. **4**, we are confronted with the construction of several double bonds separated by a methylene group or skipped dienes. We have recently reported on a method for the construction of skipped dienes in which one of the double bonds is primary.[5]



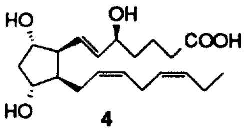
1
Arachidonic Acid



2
Eicosapentaenoic Acid



3
5-oxo-ETE



4
iPF3α -VI

One of the most practical methods we have used in the construction of eicosanoids, is the Wittig reaction, as shown in Scheme 1a.

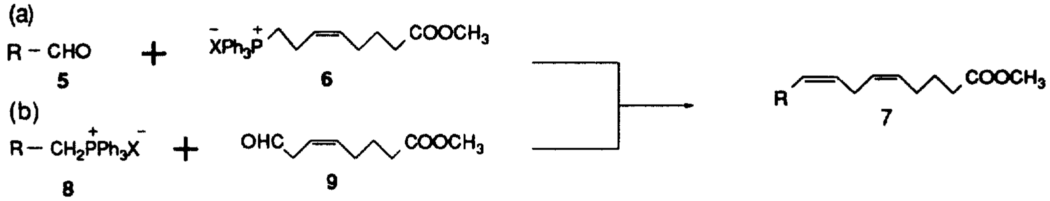
The reverse process, however, (Scheme 1b) is not straightforward due to the great difficulty in obtaining β,γ-unsaturated aldehydes, such as **9**. The reason lies in the tendency of the double bond

---

[*] Corresponding author.

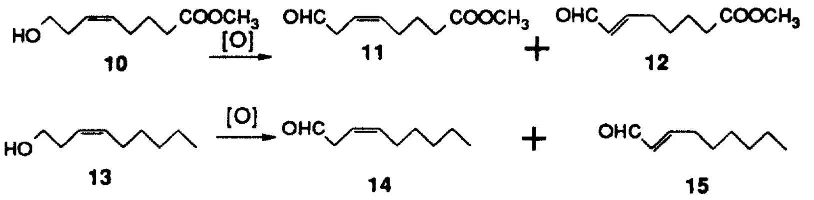
0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.

PII: S0040-4039(99)01498-7



Scheme 1.

to move into conjugation with the carbonyl function during its preparation. For example, in the case of alcohols such as **10** and **13**, attempted oxidations with various oxidizing agents (Scheme 2) gave a modest to low yield of a mixture of β,γ-unsaturated aldehydes and the product of double bond migration, the α,β-unsaturated aldehyde.

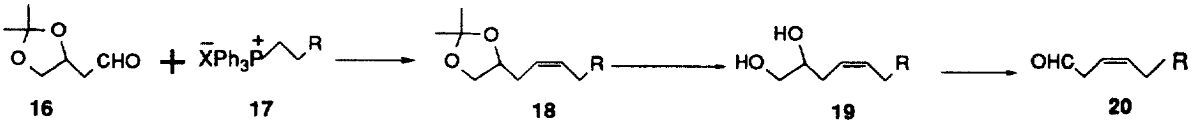


	Yield of aldehydes	Ratio of β,γ / α,β
Jones	45%	10 / 90
Swern	76%	32 / 68
Moffat	48%	50 / 50
Swern	72%	40 / 60
PCC	51%	10 / 90
DMSO/ SO_3.Py/Et_3N	35%	25 / 75

Scheme 2.

The isomers, in addition, are almost superimposed on TLC and impractical to separate in a preparative manner by column chromatography.[6] Preparation of substituted β,γ-unsaturated aldehydes have been reported. High pressure (>100 atm) hydroformylation of substituted butadienes using rhodium catalysts have been reported to yield α-methyl β,γ-unsaturated aldehydes. The stereochemistry of the double bond appears to be predominantly *trans.*[7]

We are reporting here on a new strategy for the synthesis of β,γ-unsaturated aldehydes as presented in Scheme 3 and Table 1. We are predominantly interested in the β,γ-*cis* aldehydes (entries 1–6), but the *trans* can be prepared as well (entry 7). As can be seen, it makes use of a four-carbon synthon which is later shortened by one carbon.



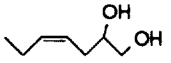
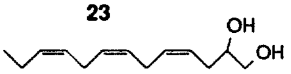
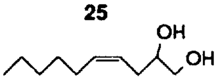
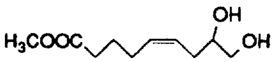
Scheme 3.

The success of this approach was made possible by the very clean cleavage of the diol to the aldehyde by $Pb(OAc)_4$ in high yield.

The fast rate of the diol cleavage to the aldehyde (10–20 min) is almost certainly a factor in the exclusive formation of the β,γ-unsaturated aldehydes.

The preparation of the aldehydes is as follows: To a solution of the diol (1 mmol) in anhydrous CH_2Cl_2 (15.5 ml) was added anhydrous Na_2CO_3 (3.3 mmol) with stirring under argon. The reaction mixture was cooled to –40°C and $Pb(OAc)_4$ (1.2 mmol) was added. The reaction mixture was kept at –40 to –30°C for 20 min and filtered through Celite/fluorisil. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried and concentrated to afford the aldehyde as a colorless oil.[8] All yields are isolated yields. In entry 1, the oxidation is quantitative (as judged by TLC), the product, however, is volatile and resulted in the lower isolated yield shown.

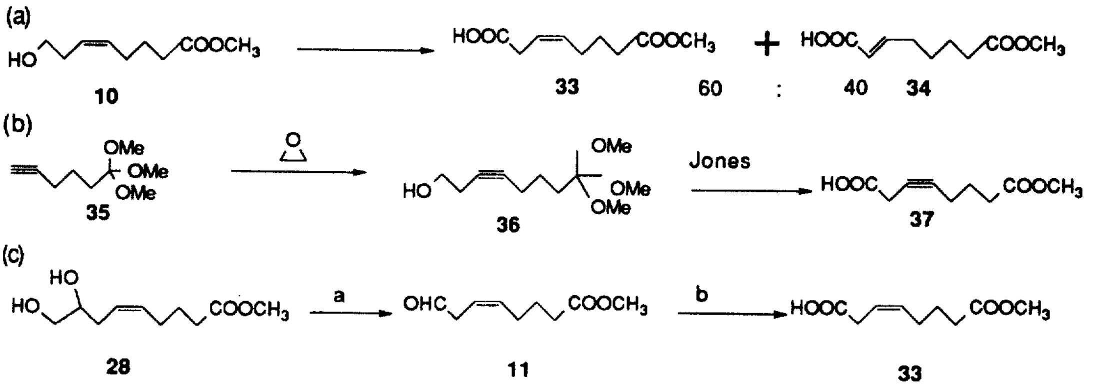
Table 1

Entry	Diol	β,γ-Unsaturated aldehyde	% Yield
1	 **21**	 **22**	84
2	 **23**	 **24**	98
3	 **25**	 **26**	96
4	 **27**	 **14**	98
5	 **28**	 **11**	98
6	 **29**	 **30**	83
7	 **31**	 **32**	83

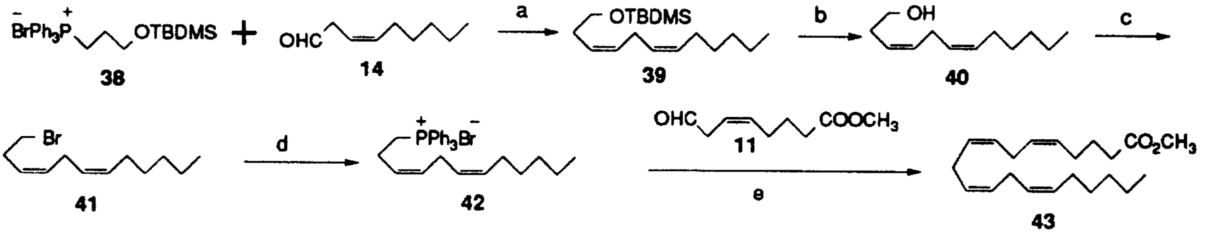
In entries 1, 2 and 3, aldehydes **22**, **24** and **26** can be useful for the synthesis of EPA (C-20 ω3 *n*-5), and docosahexanoic acid (DHA) (C-22 ω3 *n*-6) and derived eicosanoids. C-22 represents the carbon skeleton, ω3 represents the position of the first double bond from the ω end of the molecule, and *n*-6 represents the total number of double bonds in the molecule.[9] In entry 4, synthon **14** can be used in AA-derived product and eicosanoids. AA (C-20 ω6 n-4) is an ω6 fatty acid. In entry 5, aldehyde ester **11** represents the first eight carbons of AA and other similar polyunsaturated fatty acids and eicosanoids derived from AA, EPA and DHA, and iPs of types I, II, IV and VI.[9,10] In entry 6, aldehyde **30** contains an extended chain, the purpose of which is to attach affinity labels in some of the eicosanoid derivatives. Entry 7 represents the formation of a *trans* β,γ-unsaturated aldehyde. In this case too, the formation of aldehyde **32** is not contaminated with the α,β-unsaturated isomer. However, the propensity of **32** to undergo conjugation with the aldehyde is much more pronounced than with all the other *cis*-double bond cases (entries 1 to 6). The cleavage reaction should be stopped as soon as the starting material has reacted, usually 10 min. Aldehyde **32** can be stored in solution for a week, and maybe longer, at −20°C.

In another related process, alcohols such as **10** on oxidation to acids also undergo migration of the double bond into conjugation with the ester group (Scheme 4a). In the past[11] when the acid **33** was the desired product we used a strategy based on an acetylenic group as the olefinic precursor **37** (Scheme 4b). Although the Jones oxidation yield was an acceptable 60%, the synthesis of acetylene **35** is a tedious and time-consuming process.[11] Scheme 4c shows the much improved high-yield two-step synthesis of **33** with no double bond migration in either step.

We have also applied this strategy to the synthesis of the natural product AA (Scheme 5). We were surprised to find that except for one report,[12] AA is isolated from soya bean and vegetal sources.

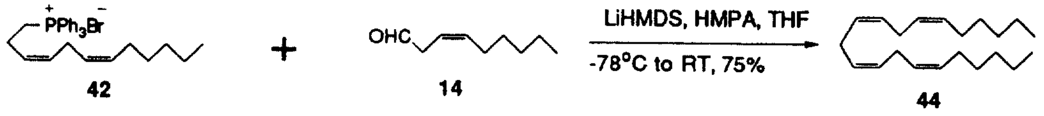


Scheme 4. Reaction conditions: (a) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, –40 to –30°C, 20 min, 98%; (b) $NaClO_2$, KH_2PO_4, *t*-BuOH, 2-methyl-2-butene, H_2O, 91%



Scheme 5. Reaction conditions: (a) LiHMDS, THF, –78°C to rt, 85%; (b) TBAF, THF, 81%; (c) CBr_4, DIPHOS, 92%; (d) Ph_3P, CH_3CN, 96%; (e) LiHDMS, THF, –78°C to rt, 70%

The symmetrical compound **44** has been made in order to study the substrate specificity with the various lipoxygenases (Scheme 6).



Scheme 6.

Acknowledgements

We wish to acknowledge NIH support under Grants DK-44730 (JR), HL-54500 and HL 62250 (GAF); NSF for an AMX-360 NMR instrument (Grant CHE-90-13145); and MRC of Canada under Grant MT-6254 (WSP).

References

1. Berhane, K.; Ray, A. A.; Khanapure, S. P.; Rokach, J.; Powell, W. S. *J. Biol. Chem.* **1998**, *273*, 20951–20959.
2. Khanapure, S. P.; Powell, W. S.; Rokach, J. *J. Org. Chem.* **1998**, *63*, 8976–8982.
3. Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 823–851.
4. Pratico, D.; Tangirala, R. K.; Rader, D. J.; Rokach, J.; FitzGerald, G. A. *Nature Med.* **1998**, *4*, 1189–1192.
5. Adiyaman, M.; Jung, Y.; Kim, S.; Saha, G.; Powell, W. S.; FitzGerald, G.; Rokach, J. *Tetrahedron Lett.* **1999**, *40*, 4019–4022.

6. In all cases, the double bond migration is easy to recognize as the signal for the two aldehydic protons separate well in the ^{1}H NMR of the mixtures of isomers. The aldehydic proton of the desired β,γ-unsaturated compounds appears at δ 9.64–9.67 as a broad triplet and the aldehydic proton of the α,β-unsaturated isomers appears as expected upfield at δ 9.52–9.55 as a doublet. The ratio of these two protons gives an accurate indication of the isomerization process.
7. (a) Bertozzi, S.; Campigli, N.; Vitulli, A.; Lazzaroni, R.; Salvadori, P. *J. Organomet. Chem.* **1995**, *487*, 41–45. (b) Horiuchi, T.; Ohta, T.; Nozaki, K.; Takaya, H. *Chem. Commun.* **1996**, 155–156.
8. A typical ^{1}H NMR is shown for **14**: ($CDCl_3$) δ 9.66 (br t, *J*=1.5 Hz, 1H), 5.70 (m, 1H), 5.54 (m, 1H), 3.19 (d br, *J*=7.1 Hz, 2H), 2.03 (q, *J*=7.16 Hz, 2H), 1.29 (m, 6H), 0.89 (t, *J*=6.92 Hz, 3H).
9. Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Lawson, J. A.; FitzGerald, G. A. *Prostaglandins* **1997**, *54*, 853–873.
10. Rokach, J.; Khanapure, S. P.; Hwang, S. W.; Adiyaman, M.; Schio, L.; FitzGerald, G. A. *Synthesis, First Special Issue, Natural Products Synthesis* **1998**, 569–580.
11. Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 35–38.
12. Viala, J.; Santelli, M. *J. Org. Chem.* **1988**, *53*, 6121–6123.