Synthesis of 7,13-Bridged Arachidonic Acid Analogues

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cis- and *trans*-7,13-Bridged arachidonic acids (**2** and **3**, R=H) and their 5,6,14,15-tetradehydro-analogues (**4** and **5**, R=H) have been synthesized employing a divinylcyclopropane rearrangement as a key step.

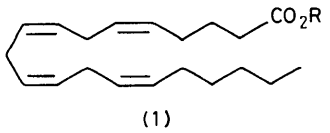
As part of a programme directed towards modulating the arachidonic acid (**1**) system[1] we designed the bridged compounds (**2**)—(**5**) aiming to mimic the suspected bent J or U shape conformation of arachidonic acid[2] and diminish the reactivity of positions 7 and 10. We report here a facile and efficient entry into this class of compounds that involves a novel divinylcyclopropane rearrangement to construct the cycloheptadiene system.

Reduction of the *trans*-diester (**6**) ($LiAlH_4$, Et_2O, 0 °C, 90%) yielded the diol (**7**) which was converted by Swern oxidation [Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, 90%] into the *trans*-dialdehyde (**8**).[3] Condensation of (**8**) with excess of the ylide derived from $Me_3SiC{\equiv}CCH_2PPh_3Br$[4] ($Bu^nLi$, THF,† −78 → −60 °C, then aq. NH_4Cl, 75%) afforded the diacetylene (**9**)† (mixture of isomers), deprotection of which ($AgNO_3$–KCN, EtOH–H_2O, 0 °C, 94%) led to compound (**10**). Sequential alkylation of (**10**) {a, 1.0 equiv. of Bu^nLi, THF, $Me[CH_2]_4I$, HMPA,† −40 → −25 °C, 82%; b,[5] 1.0 equiv. of Bu^nLi, THF, $(MeO)_3C[CH_2]_3I$, HMPA, −40 → −25 °C, mild acid hydrolysis, and flash silica column chromatography, 75% yield based on *ca.* 75% conversion} furnished the desired precursor (**12**).

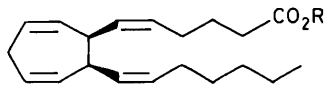
Thermolysis[3] of (**12**) (200 °C, benzene, sealed tube) smoothly gave rise to the two products (**4**; R=Me) and (**5**; R=Me) in essentially quantitative yield [racemic, (**4**) : (**5**) *ca.* 4 : 1], separated by flash silica column chromatography [(**4**; R=Me):† R_f 0.18, 3% ether in light petroleum, four developments; (**5**; R=Me):‡ R_f 0.20, 3% ether in light petroleum, four developments].

† Abbreviations: THF = tetrahydrofuran, HMPA = hexamethylphosphoramide.

‡ All new compounds gave satisfactory spectroscopic and analytical data: ^1H n.m.r., $CDCl_3$, 250 MHz: (**2**; R=Me) δ 0.88 (3H, t, *J* 6.7 Hz 20-H), 1.19—1.42 (6H, m, 17-, 18-, and 19-H), 1.70 (2H, m, 3-H), 1.95—2.18 (4H, m, 4- and 16-H), 2.32 (2H, t, *J* 7.5 Hz, 2-H), 2.66 (1H, dt, *J* 17.5 and 7.0 Hz, 10-H), 3.12 (1H, br. d, *J* 17.5 Hz, 10-H), 3.47 (2H, m, 7- and 13-H), 3.66 (3H, s, CO_2Me), and 5.30—5.72 (8H, m, olefinic); (**3**; R=Me) δ 0.86 (3H, t, *J* 6.7 Hz, 20-H), 1.23—1.39 (6H, m, 17-, 18-, and 19-H), 1.66 (2H, m, 3-H), 1.96—2.12 (4H, m, 4- and 16-H), 2.29 (2H, t, *J* 7.5 Hz, 2-H), 2.85 (2H, m, 10-H), 3.46 (2H, m, 7- and 13-H), 3.64 (3H, s, CO_2Me), and 5.20—5.70 (8H, m, olefinic); (**4**; R=Me), δ 0.87 (3H, t, *J* 6.7 Hz, 20-H), 1.21—1.56 (6H, m, 17-, 18-, and 19-H), 1.79 (2H, m, 3-H), 2.16 (2H, dt, *J* 7.5 and 2.9 Hz, 16-H), 2.24 (2H, dt, *J* 7.0 and 2.0 Hz, 4-H), 2.46 (2H, t, *J* 7.5 Hz, 2-H), 2.10 and 2.93 (each 1H, br. d, *J* 17.5 Hz, 10-H), 3.54 (2H, br. s, 7- and 13-H), 3.64 (3H, s, CO_2Me), and 5.66 (4H, m, 8-, 9-, 11-, and 12-H); (**5**; R=Me) δ 0.88 (3H, t, *J* 6.7 Hz, 20-H), 1.18—1.56 (6H, m, 17-, 18-, and 19-H), 1.8 (2H, m, 3-H), 2.17 (2H, t, *J* 7.5 Hz, 16-H), 2.25 (2H, t, *J* 7.0 Hz, 4-H), 2.84 (2H, br. s, 10-H), 3.45 (2H, br. s, 7- and 13-H), 3.65 (3H, s, CO_2Me), and 5.68 (4H, m, 8-, 9-, 11-, and 12-H).



(1)



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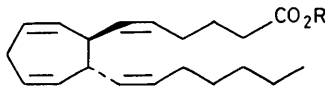

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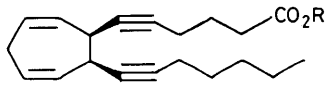

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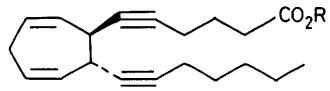
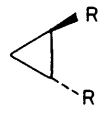


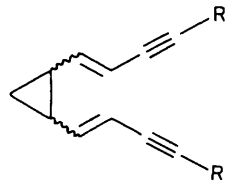
(5)

The stereochemistry of the 7,13 junction in (**4**) and (**5**) was based on the ^{1}H n.m.r. signals for H-10 according to the assignments of Baldwin *et al.*[3] Controlled hydrogenation of the *cis*-isomer (**4**; R=Me) (Lindlar catalyst, hexane, 25 °C) resulted in the formation of (**2**; R=Me)‡ (70%; R_f 0.35, 10% ether in light petroleum), whereas similar treatment of the *trans*-isomer (**5**) furnished (**3**; R=Me)‡ (70%; R_f 0.38, 10% ether in light petroleum, silica). Finally mild alkaline hydrolysis of (**2**)—(**4**) (R=Me) (LiOH–H_2O–THF, 25 °C) led to the arachidonic acids (**2**)—(**4**) (R=H) in almost quantitative yield.

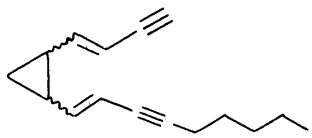
Preliminary biological and chemical investigations with these newly synthesized molecules indicate high stability and potent and selective 5-lipoxygenase inhibitory activity.



(6) R = CO_2Et
(7) R = CH_2OH
(8) R = CHO



(9) R = $SiMe_3$
(10) R = H



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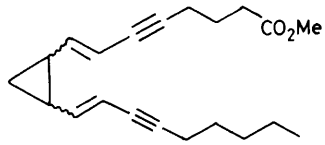

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