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A VERSATILE SYNTHON FROM CASTOR OIL: A DIRECT, PRACTICAL AND NOVEL ROUTE TO 9,11-ETHENO-PGH$_1$

S. Ranganathan*, D. Ranganathan and M.M. Mehrotra
Prostaglandins Laboratory, Department of Chemistry,
Indian Institute of Technology, Kanpur 208 016, India

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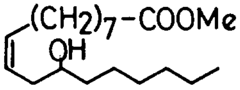
The transformation of castor oil to etheno-PGH$_1$ (10) - a specific inhibitor of PGE$_1$ and belonging to a family of great current interest[1] - and the novel 1a-homo-etheno PGH$_1$ (12), reported below, not only provides a practical and very direct route to prostaglandins, but also highlights the latent possibilities in this abundantly available raw material. Additionally, a noteworthy feature of this work is the key C-10 synthon 7, which, inter alia, is linked to prostaglandins and a host of their analogs and some macrolides.[2]

Methanolysis of castor oil[3] (MeOH, Na(trace), reflux 1 hr) gave methyl ricinoleate[4] [1, 85%, b.p. 130°/0.02 mm, ir: 3571, nmr: 5.42(m,2H)] which on pyrolysis (~600°) yielded methyl-undec-10-enoate [2, 50%, b.p. 81°/0.9 mm, ir: 1653, 910, nmr: 4.95(m,2H), 5.82(m,1H)]. Treatment with phenylmagnesium bromide followed by thermal dehydration, chromic acid oxidation and esterification (PhMgBr, ether; reflux, 2.5 hr; CrO_3-H_2O-AcOH-H_2SO_4; MeOH, H_2SO_4 (trace)) led to methyl-dec-9-enoate [3, overall yield from 2: 49%, b.p. 61°/0.3 mm, ir: 1658, 905, nmr: 4.92(m,2H), 5.8(m,1H)]. Para-toluene sulfonic acid catalysed isomerization in benzene (10 hr, reflux) gave methyl -E-dec-8-enoate [4, 97%, b.p. 61°/0.2 mm, ir: 1639, 966, nmr: 5.4(m,2H)]. Acetoxylation($Hg(OAc)_2$, AcOH, reflux, 15 hr) led cleanly to methyl -10-acetoxy-E-dec-8-enoate [5, 85%, b.p. 115°/0.13 mm, ir: 1733, nmr: 2.0(3H), 4.5(J=5Hz,2H), 5.68(m,2H)] which on hydrolysis (MeOH, Anh.K_2CO_3, rt, 2hr) gave alcohol 6 [94%, b.p. 115°/0.04 mm, ir: 3636, nmr: 4.05(m,2H), 5.62(m,2H)]. Collin's oxidation (CrO_3, py, CH_2Cl_2, rt, 3hr) led to the novel, key C-10 synthon, 9-formyl-methyl-E-dec-8-enoate [7, 80%, overall yield from castor oil: 13%, oil, ir: 1695, 1639, nmr: 5.8(m,1H), 6.75(m,1H), 9.4(J=9Hz,1H), semicarbazone m.p. 130-131°, m/e 255]. 4+2 addition of 7 with cyclopentadiene (diene:olefin::3:1, xylene, reflux under N_2) afforded the desired adduct 8 [73% yield of separable[1a] mixture 2:1 in favour of the desired 8, b.p. 155°/0.2mm, ir: 1715, nmr: 6.1(m,2H), 9.25(J=2.5Hz,1H)]. Reaction of 8 with sodio derivative of dimethyl 2-oxo-heptyl phosphonate gave 9 [61%, ir: 1681,1634, nmr: 6.4(m,4H)] which on $NaBH_4$ reduction (methanol, rt, 1 hr) gave 9,11-etheno PGH$_1$ 10, [99%, overall yield from castor oil: 6%, ir: 3430, nmr: 4.0(m,1H), 5.5(m,2H), 6.06(m,2H)].

An identical series of transformations with methyl-undec-10-enoate gave via the key, novel C-11 synthon, 10-formyl-methyl-E-undec-9-enoate [11, overall yield from castor oil 27%, b.p. 110°/0.06 mm, ir: 1695, 1639, nmr: 5.9(m,1H), 6.65(m,1H), 9.3(J=9Hz,1H), semicarbazone m.p. 139-140°] the novel and potentially active 1a-homo-9,11-etheno PGH$_1$ [12, overall yield from 11: 45%, from castor oil: 12%, ir: 3430, nmr: 4.0(m,1H), 5.5(m,2H), 6.02(m,2H)].



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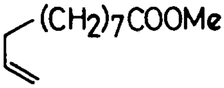

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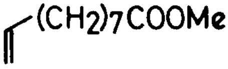

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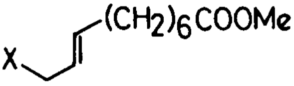
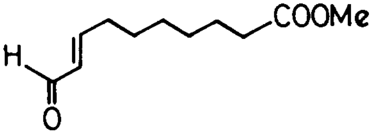


4: X = H ; 5: X = OAc ; 6 X = OH



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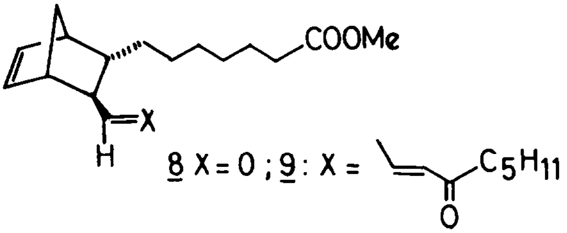
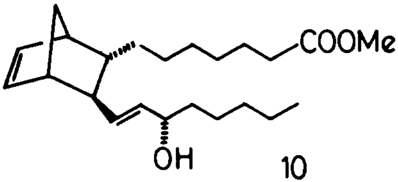


8 X = O ; 9: X =



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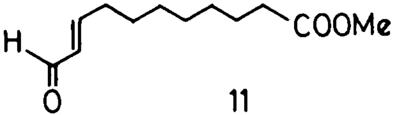

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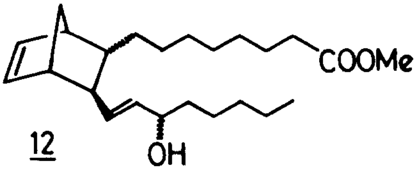

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4. Satisfactory analytical results have been obtained for all compounds; ir as cm^{-1} neat; nmr as δ in CDCl$_3$; the common ester function is characterized by ν_{max} 1740 and δ 3.66.