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STEREOSELECTIVE SYNTHESIS OF 11-DEOXYPROSTAGLANDIN E_1[1]

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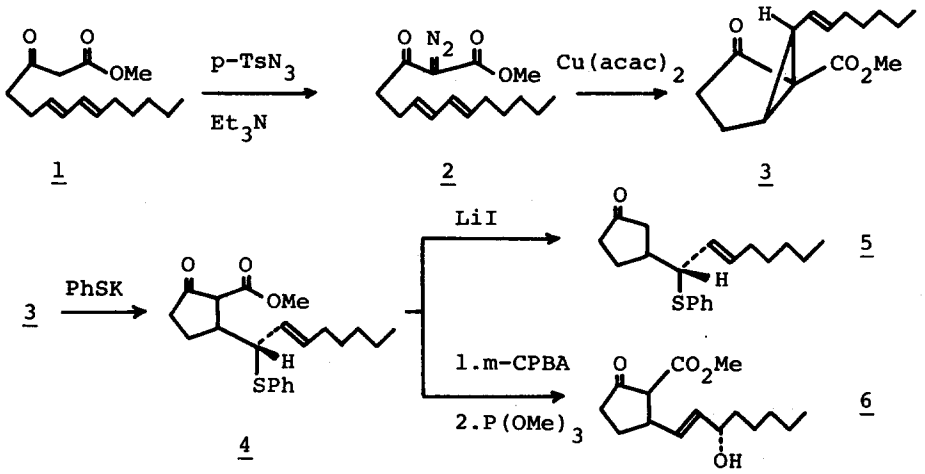
The control of stereochemistry at C-15[2] in the synthesis of prostaglandins has long been an interesting and challenging problem.[3] Corey and his associates[3a] have successfully solved this problem by introducing the p-phenylphenylurethane group on the C-11[2] of prostaglandin skelton as an exogenous directing group for the stereoselective reduction of 15-keto intermediates. Untch and his collaborators[3c] have developed a stereoselective method for the conversion of 13-cis-15β-prostanoids to the 13-trans-15α-isomers of natural configuration by utilizing the sulfenate-sulfoxide rearrangement. We were interested in the latter results. If a more efficient route to the 13α-sulfinyl-14-trans-prostanoids, a key intermediate in Untch's report, could be devised, the generality of the synthetic sequence would be broaden. As reported in the accompanying communication,[4] the 6-substituted 2-oxobicyclo[3.1.0]hexane-1-carboxylates suffered the nucleophilic attack by thiophenol to afford 3-substituted cyclopentanones, in which the phenylthio group was conveniently located on the α-position in the side chain and furthermore had the desired configuration. In this paper, we wish to report an application of these stereospecific ring-forming and ring-opening reactions to the synthesis of 11-deoxyprostaglanin E_1.[5]

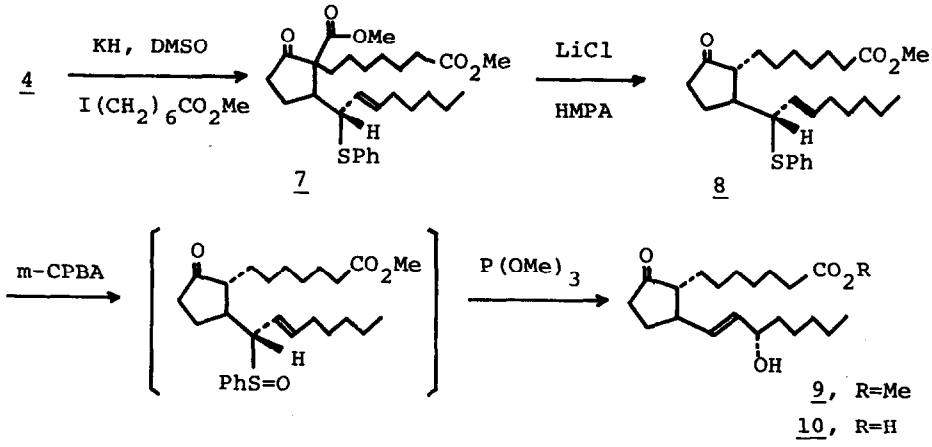
The necessary starting material, i.e., trans, trans-2,4-decadienyl bromide, was prepared from decadienal[6] by reduction with LAH followed by bromination with PBr_3. The bromide was allowed to react with the dianion derived from methyl acetoacetate[7] to give methyl 3-oxo-trans, trans-6,8-tetradecadienoate (1) (bp 136-142°/0.3 mmHg) in 68% yield. The β-keto ester 1 was converted quantitatively to the diazo ester 2 by treatment with p-TsN_3 in MeCN at room



temp for 3 hrs.[8] Thermolysis of 2 in refluxing PhH in the presence of Cu-(acac)$_2$ for 24 hrs afforded methyl exo-6-(trans-1-heptenyl)-2-oxobicyclo-[3.1.0]hexane-1-carboxylate (3) in 63% yield: bp 135-140°/0.5 mm; ν_{max} 1750, 1730, 990, 970 cm^{-1}; nmr(CCl_4) δ0.87(t, J=6Hz, 3H), 1.08-1.53(m, 6H), 1.80-2.56 (m, 8H), 3.64(s, 3H), 5.11(dd, J=8 and 15Hz, 1H), 5.61(dt, J=7 and 15Hz, 1H). As it was predicted from the previous results,[4] the bicyclohexane 3 was obtained stereospecifically as the sole product. The ring-opening reaction of 3 with 1.1 equiv. of PhSK in t-BuOH at room temp produced the 2,3-disubstituted cyclopentanone 4 in 89% yield: ν_{max} 1765, 1735, 1665, 1625, 975 cm^{-1}; nmr(CCl_4) δ0.82(t, J=6Hz, 3H), 0.94-3.10(m, 14H), 3.32-3.52(m, 1H), 3.58(s, 3H), 4.95-5.42(m, 2H), 6.96-7.40(m, 5H). The cyclopentanone structure as well as the configurational homogeneity of 4 was confirmed by converting it to the 3-substituted cyclopentanone 5. Thus treatment of 4 with LiI in DMSO afforded 5 in 61% yield: ν_{max} 1743, 965 cm^{-1}; nmr(CCl_4) δ0.83(t, J=5Hz, 3H), 0.96-2.56(m, 15H), 3.13-3.51(m, 1H), 4.94-5.36(m, 2H), 6.95-7.41(m, 5H). The methine proton α to phenylthio group was observed as a broad doublet (J=7Hz) in the nmr spectrum when it was decoupled by irradiation to the adjacent olefinic proton. This observation supported the prediction on the attaching position of phenylthio group in 5, and hence 4. In the ^{13}C nmr spectrum of 5, there were observed eleven sharp peaks besides ones attributable to olefinic and aromatic carbons. Each of them could be assigned to the carbon constituting the frame-

work of 5 and thus 5 was configurationally homogeneous. Oxidation of 4 with m-CPBA in CH_2Cl_2 followed by treatment of the resulting sulfoxide with an excess of $P(OMe)_3$[3c,9] in MeOH at 0° gave the allylic alcohol 6 in 70% overall yield: ν_{max} 3440, 1760, 975 cm^{-1}; nmr(CCl_4) δ0.86(t, J=6Hz, 3H), 1.04-2.66(m, 14H), 2.84-3.43(m, 1H), 3.69(s, 3H), 3.89-4.14(m, 1H), 5.34-5.80(m, 2H). The corresponding ethyl ester of 6 has already been used as a precursor to prostanoids.[3b]

The synthesis of 11-deoxyprostaglandin E_1 (10) using the key intermediate 4 was achieved according to the following scheme.



The keto ester 4 was transformed into the anion by treatment with KH in DMSO[10] and then allowed to react with methyl 7-iodoheptanoate to provide the diester 7 in 71% yield: ν_{max} 1738, 1623, 970 cm^{-1}; nmr(CCl_4) δ0.82(t, J=6Hz, 3H), 0.98-2.62(m, 25H), 3.36-3.66(m, 1H), 3.53 and 3.56(two s, 6H), 4.65-5.36(m, 2H), 6.98-7.44(m, 5H). Decarboxylation of 7 by heating at 100° in HMPA in the presence of LiCl[11] for 6 hrs gave the ester 8 in 92% yield: ν_{max} 1740, 1720, 970 cm^{-1}; nmr(CCl_4) δ0.83(t, J=6Hz, 3H), 0.98-2.40(m, 26H), 3.40-3.70(m, 1H), 3.54 (s, 3H), 5.08-5.38(m, 2H), 6.96-7.50(m, 5H).[12] Conversion of 8 to 11-deoxyprostaglandin E_1 methyl ester (9) was effected by successive treatments of 8 with m-CPBA (-20°, 2 hr) and $P(OMe)_3$ (0°, 12 hr) in MeOH. Purification of the crude product by column chromatography afforded 9 in 70% overall yield.[13] The ir and nmr spectra of 9 were identical with those described in literatures.[5a,c] The ester 9 was further hydrolysed[5a] to yield the crystalline 11-deoxyprostaglandin E_1 10 (mp 83-88°).[14]

It is the noteworthy feature of our method that the necessary stereochemical controls at C-8, C-12, C-13, and C-15 were attained during the course of synthetic operations. Consequently, there was no need to use special compound having prerequisite configuration or geometry as a starting material.[6]

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13. There has been obtained another isomer (9% yield based on 8) which was less polar than 9 on TLC and column chromatography. The spectra of this by-product were essentially identical with those of 9. The exact assignment of its structure is now underway.
14. The reported melting points of 15-α and 15-β isomers of 11-deoxyprostaglandin E_1 were as follows: 82.5-85°(α) and 53-56°(β) in ref. 5a; 80-82° (α) in ref. 5b; 85-86°(α) and oil(β) in ref. 5c.