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SYNTHESIS OF A PYRAZOLE PROSTACYCLIN[1]

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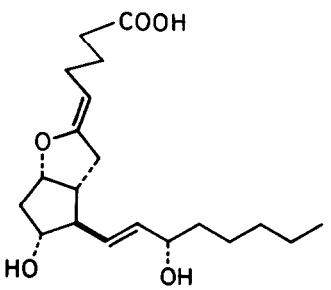
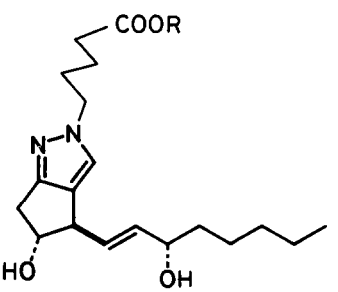
Summary: A highly convergent entry to chiral heteroaromatic prostacyclin analogues is outlined.

Prostacyclin (I) exhibits remarkable biological activities.[2] The clinical use, however, is not viable because of its unstable nature arising from the presence of an exceedingly labile vinyl ether linkage.[3] As such intense efforts have been made to elaborate the structural analogues possessing higher chemical stability.[4] To this end we directed our attention to replacement of the alkylidenetetrahydrofuran skeleton by a five-membered heteroaromatic ring. Disclosed herein is an approach to the pyrazole prostacyclin II, which utilizes the newly developed α-alkoxyalkylation of α,β-unsaturated ketones,[5] efficient organocopper conjugate addition to enones,[6] and highly selective asymmetric reduction of prochiral ketones[7] in the key step.



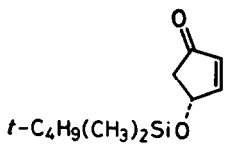
I



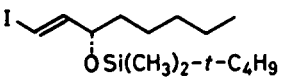
II, R = H
III, R = CH_3

The chiral building blocks IV, $[\alpha]_D^{20}$ +63° (c 1.73, CH_3OH, 94%ee), and V, $[\alpha]_D^{23}$ -37.5° (c 0.973, CH_3OH; derived from the corresponding alcohol, $[\alpha]_D^{22}$ +9.35° (c 1.54, CH_3OH)), which have the "natural" absolute configuration are easily accessible by enantioselective reduction of 4-cyclopentene-1,3-dione[7e] and (E)-1-iodo-1-octen-3-one,[7b] respectively, by a binaphthol-modified lithium aluminum hydride reagent (BINAL-H),[8-12] followed by silylation by the standard procedure.[13] First, the enone IV was converted to the dimethoxymethyl

derivative VI[14] in 79% yield by sequential treatments with (1) phenylselenotrimethylsilane (1 equiv) and trimethylsilyl trifluoromethanesulfonate[15] (0.02 equiv) in dichloromethane (-78 °C, 30 min), (2) trimethyl orthoformate (1 equiv, -78 °C and then -25 °C for 30 min), (3) pyridine (0.08 equiv, -20 °C), and (4) 30% hydrogen peroxide (excess, 0 °C and then up to 40 °C for 10 min).[5] Reaction of VI and an organocopper reagent formed from stoichiometric amounts of copper(I) iodide and lithio derivative of V (generated via metal-halogen exchange with t-butyllithium) and 2 equiv of tributylphosphine (ether, -78 °C/20 min and -30 °C/20 min) afforded the vicinally side-chain incorporated product VII[16] in 48% yield. Subsequent condensation with hydrazine hydrate (37 equiv, CH_3OH, 22 °C, 20 min) produced the pyrazole derivative VIII[17] in 84% yield. Kaliation with excess potassium hydride (THF—HMPA, 20 °C, 40 min) followed by treatment with methyl 5-iodopentanoate (THF—HMPA, 20 °C, 15 min) gave rise to an approximately 1:1 mixture of IX and X (67% yield). Medium-pressure chromatography on a silica gel column (6:1 hexane—ethyl acetate as eluant) furnished pure samples of IX[18] and X.[19] Finally deblocking of X with tetrabutylammonium fluoride (THF, 40 °C, 13 h) completed



IV



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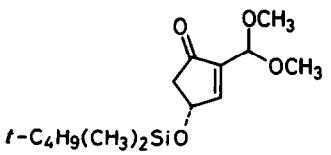

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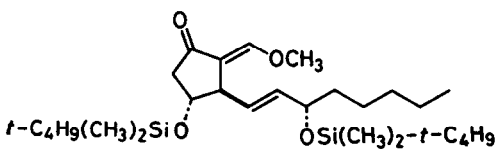
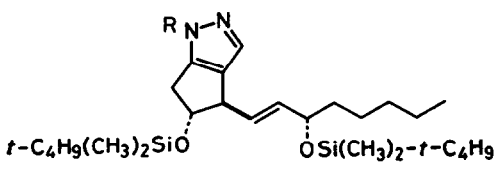
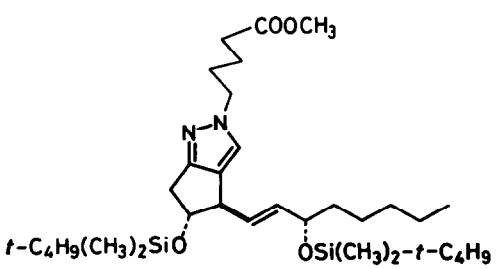


VII



VIII, R = H

IX, R = $(CH_2)_4COOCH_3$



X

the synthesis of III, $^{20}[\alpha]_D^{22}$ -4.3° (c 0.54, CH_3OH) (77%).

This result indicates that the conjugate addition route is highly convergent and flexible and holds attractiveness as direct entry to a number of heteroaromatic prostacyclin analogues in optical active form. Molecular design of effective biological mimics as well as improvement of the synthetic sequence is under study.

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16. A single isomer. $[\alpha]_D^{22}$ +40.6° (c 0.65, CH_3OH); IR (neat) 1720, 1635, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 12, $(CH_3)_2Si$ x 2), 0.8—1.0 (br s, 21, CH_3 and $(CH_3)_3C$ x 2), 1.1—1.6 (m, 8, CH_2 x 4), 2.18 (dd, 1, J = 16.5 and 2 Hz, CHCO), 2.54 (dd, 1, J = 16.5 and 2.8 Hz, CHCO), 3.48 (m, 1, CH), 3.78 (s, 3, OCH_3), 4.0—4.2 (m, 2, CHO x 2), 5.50 (m, 2, CH=CH), 7.35 (d, 1, J = 2 Hz, =CHO); Mass (m/z) 496.3385 (M^+). In addition, the corresponding 2-dimethoxymethylcyclopentanone was formed in 23% yield.[5]
17. Initially a mixture of VIII and its 2H-tautomer was formed, $[\alpha]_D^{22}$ -73.6° (c 0.81, CH_3OH). On standing the latter isomerized to the more stable VIII. Separation is not necessary.
18. $[\alpha]_D^{22}$ -43.9° (c 0.38, CH_3OH); IR (neat) 1742, 1550 (shoulder), 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6, $(CH_3)_2Si$), 0.09 (s, 6, $(CH_3)_2Si$), 0.8—1.1 (br s, 21, CH_3 and $(CH_3)_3C$ x 2), 1.1—2.0 (m, 12, CH_2 x 6), 2.33 (t, 2, J = 6.5 Hz, CH_2CO), 2.58 (dd, 1, J = 14.5 and 6 Hz, a proton of CH_2 of the cyclopentane ring), 3.04 (dd, 1, J = 14.5 and 6.5 Hz, a proton of CH_2 of the cyclopentane ring), 3.46 (t, 1, J = 6 Hz, CH), 3.67 (s, 3, OCH_3), 4.00 (t, 2, J = 6 Hz, CH_2N), 4.05 (br, 1, CHO), 4.54 (q, 1, J = 6 Hz, CHO), 5.64 (m, 2, vinyl), 7.14 (s, 1, pyrazole); Mass (m/z) 592.4075 (M^+).
19. $[\alpha]_D^{22}$ -29.4° (c 0.46, CH_3OH); IR (neat) 1740, 1572 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6, $(CH_3)_2Si$), 0.09 (s, 6, $(CH_3)_2Si$), 0.8—1.1 (br s, 21, CH_3 and $(CH_3)_3C$ x 2), 1.1—2.0 (m, 12, CH_2 x 6), 2.28 (dt, 2, J = 5 and 2 Hz, CH_2CO), 2.54 (dd, 1, J = 15.5 and 7 Hz, a proton of CH_2 of the cyclopentane ring), 2.98 (dd, 1, J = 15.5 and 7 Hz, a proton of CH_2 of the cyclopentane ring), 3.38 (t, 1, J = 6 Hz, CH), 3.58 (s, 3, OCH_3), 3.98 (t, 2, J = 6 Hz, CH_2N), 4.0 (br, 1, CHO), 4.35 (q, 1, J = 6.5 Hz, CHO), 5.56 (m, 2, vinyl), 6.87 (s, 1, pyrazole); Mass (m/z) 592.4103 (M^+).
20. IR (neat) 3680—3040, 1740, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3, J = 6 Hz, CH_3), 1.2—2.1 (m, 12, CH_2 x 6), 2.34 (t, 2, J = 6.5 Hz, CH_2CO), 2.68 (dd, 1, J = 15 and 7.5 Hz, a proton of CH_2 of the cyclopentane ring), 2.2—2.9 (br, 2, OH x 2), 3.14 (dd, 1, J = 15 and 7.5 Hz, a proton of CH_2 of the cyclopentane ring), 3.47 (t, 1, J = 6 Hz, CH), 3.66 (s, 3, OCH_3), 4.06 (t, 2, J = 7 Hz, CH_2N), 4.10 (br, 1, CHO), 4.46 (q, 1, J = 6 Hz, CHO), 5.66 (m, 2, vinyl), 7.02 (s, 1, pyrazole); Mass (m/z) 364.2338 (M^+).

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