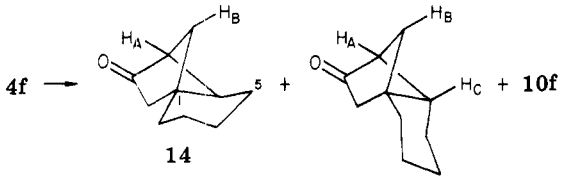
no exact analogy in Beckwith's data (the appropriate radical has not been studied), but predictable from results that are available. The rate of 1,5-cyclization, already reduced by R_3 in **1d**, is further depressed by substituents on the attacking radical center; hence **1e**, with two methyl groups at C(1), undergoes only 1,6-cyclization to give **3e**.[9,16] Therefore it is not unreasonable to expect the radical that corresponds to **11** by having only one substituent at C(1) also to cyclize in this fashion.

In order to test further the predictive value of this analogy, we examined **4f**[17,18] whose corresponding radical **1f** gives nearly equal amounts of **2f** and **3f**.[8] Photolysis of **4f** gave **14** (= **6f**), **15**, and **10f** in a ratio of 12:66:22.[18,19]



14 15

Thus a satisfactory explanation of the divergent photochemistry of **4d**, **4e**,[16] **4g**, and **11** is provided by the chemistry of 5-hexenyl radicals.

In conclusion, we believe that a simple and effective model for understanding and predicting the regiochemistry of a substantial number of photochemical reactions of hexadienones lies in this analogy. It is noteworthy that this model, which treats the β-carbon atom of the enone system simply as a radical center, is so effective, since the actual mechanism of photocycloaddition is known to be complex.[20] There are indications that this correspondence is also valid in other systems where it is appropriate to consider the α-carbon atom of an enone as the radical center. We are continuing to investigate various aspects of this model and its extension to other systems.[21]

Registry No. 1a, 16183-00-9; **1b**, 54389-00-3; **1c**, 38295-12-4; **1d**, 38295-09-9; **1e**, 38295-11-3; **1f**, 19665-04-4; **2a**, 23907-66-6; **2b**, 73926-43-9; **2c**, 73926-44-0; **2d**, 73926-45-1; **3d**, 3170-58-9; **3e**, 73926-46-2; **3f**, 52692-69-0; **4a**, 6857-93-8; **4b**, 33698-69-0; **4c**, 33698-67-8; **4d**, 998-83-4; **4e**, 5837-45-6; **4f**, 73926-47-3; **4g**, 58208-09-6; **5a**, 73926-48-4; **5b**, 73926-49-5; **5c**, 73926-50-8; **5d**, 73926-51-9; **5g**, 73926-52-0; **6a**, 5164-64-7; **6c**, 72904-15-5; **6c** DNP, 73926-53-1; **6d**, 41414-48-6; **7b**, 33698-76-9; **8d**, 73940-59-7; **8g**, 73940-60-0; **10d**, 32853-30-8; **10f**, 2359-69-5; **11**, 41414-31-7; **12**, 73926-54-2; **13** (isomer 1), 41414-45-3; **13** (isomer 2), 41414-44-2; **14**, 73926-55-3; **15**, 73952-55-3.

(16) No reaction was observed when **4e** was photolyzed at 25 °C. Irradiation at elevated temperature led only to the formation of phorone through hydrogen migration. See also ref 11a and Crowley, K. J.; Schneider, R. A.; Meinwald, J. *J. Chem. Soc. C* **1966**, 571; Kropp, P. J.; Gibson, T. W. *Ibid.* **1967**, 143.

(17) Ketone **4f** was prepared by a Mannich reaction on commercially available 1-cyclohexenylacetone.

(18) Spectroscopic data for **4f**, **14**, **15**, and **10f** follow. All new compounds gave satisfactory high-resolution mass spectra. **4f**: IR 2935 (s), 2850 (m), 2838 (m), 1695 (s), 1613 (m), 1390 (m), 975 (m) 940 (m) cm^{-1}; NMR (60 MHz) δ 6.68–6.00 (m, 2 H), 5.83–5.33 (m, 2 H), 3.10 (s, 2 H), 2.33–1.32 (br m, 8 H). **14**: IR 3000 (w), 2932 (s), 2865 (w), 1762 (s), 1438 (m), 1290 (m), 1113 (m), 1010 (m), 980 (m) cm^{-1}; NMR (220 MHz) δ 2.63 (m, 1 H), 2.52 (d, J = 2.6 Hz, 1 H), 2.12 (d, J = 15.3 Hz, 1 H), 1.89–1.03 (m, 11 H). **15**: IR 2935 (s), 2862 (m), 2850 (m), 1762 (s), 1440 (m), 1085 (m), 1018 (m), 980 (m) cm^{-1}; NMR (220 MHz) δ 2.79 (dd, J = 1.9, 1.9 Hz, 1 H), 2.21 (ddd, J = 16.2, 4.8, 1.0 Hz, 1 H), 1.87–1.70 (m, 6 H), 1.64–1.10 (m, 6 H). **10f**: IR 3070 (w), 2935 (s), 2855 (m), 1741 (s), 1160 (m), 880 (m) cm^{-1}; NMR (60 MHz) δ 4.67 (m, 1 H), 4.58 (m, 1 H), 3.63 (s, 3 H), 2.47–1.00 (br m, 13 H).

(19) The stereochemical assignments for **14** and **15** are based on the chemical shift and multiplicity of the methine protons α to the carbonyl group. In **14**, this proton (H_A) appears as a doublet, coupled only to H_B, and is shielded by the C(5) methylene group. This methylene group also shifts H_B downfield to 2.63 ppm. In **15**, H_A is now observed as a doublet of doublets, being coupled to both H_B and H_C. Neither H_B nor H_C appear below 1.87 ppm. The magnitude of the coupling constants and the variation in the chemical shifts are in accord with expectation. For a further discussion of the NMR spectra of bicyclo[2.1.1]hexanes, see: Meinwald, J.; Lewis, A. *J. Am. Chem. Soc.* **1961**, *83*, 2769; Wiberg, K. B.; Lowry, B. R.; Nist, B. J. *Ibid.* **1962**, *84*, 1594; Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1980**, *45*, 1332.

(20) For a recent mechanistic study on [2 + 2] photocyclizations, see: Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559.

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Use of [3 + 2] Cycloaddition in Elaboration of the ω Chain of Prostaglandins

Summary: The use of 3,5-disubstituted isoxazoles as an aldol or stabilized Wittig condensation equivalent is applied to the construction of the ω chain of prostaglandins.

Sir: Isoxazoles,[1] isoxazolines,[2] and isoxazolidines[3] have enjoyed an increasing use as key intermediates in the synthesis of naturally occurring substances.

We report here a novel approach to the synthesis of the 11-deoxy derivative **9** of a popular prostaglandins synthon,[4,5] featured by the use in a key stage of [3 + 2] regiospecific cycloaddition which allows the arrangement in masked form of the C(13)–C(20) fragment of prostanoids.

Our synthetic strategy, outlined in Scheme I, starts from the known[6] methyl 2-oxocyclopent-5-enyl-1-acetate (**1**), which underwent an easy 1,1,3,3-tetramethylguanidine catalyzed[7] Michael addition of nitromethane to give an 82% yield of the crucial nitro ketone **2**.[8]

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(8) This intermediate and all others reported in this communication have the expected spectral and analytical properties. **2**: ^1H NMR ($CDCl_3$) δ 4.4–4.8 (m, 2 H), 3.7 (s, 3 H); IR (film) 1740, 1550 cm^{-1}. **3**: ^1H NMR ($CDCl_3$) δ 5.9 (s, 1 H), 3.7 (s, 3 H), 0.95 (t, 3 H, J = 5 Hz); IR (film) 1740, 1600 cm^{-1}. **4**: ^1H NMR ($CDCl_3$) δ 9.25 (br s, 1 H), 5.95 (s, 1 H), 0.95 (t, 3 H, J = 5 Hz); IR ($CHCl_3$) 1740, 1715, 1600 cm^{-1}. **5**: ^1H NMR ($CDCl_3$) δ 5.9 (s, 1 H), 5.5–6.0 (br s, 2 H), 4.5 (m, 1 H), 0.95 (t, 3 H, J = 5 Hz); IR (Nujol) 1680, 1600 cm^{-1}. **6**: ^1H NMR ($CDCl_3$) δ 5.95 (s, 1 H), 5.1 (m, 1 H), 0.95 (t, 3 H, J = 5 Hz); IR (film) 1770, 1600 cm^{-1}. **7**: ^1H NMR ($CDCl_3$) δ 5.90 (s, 1 H), 5.65 (m, 1 H), 4.90 (m, 1 H), 0.95 (t, 3 H, J = 5 Hz); IR (film) 3500–3000, 1600 cm^{-1}. **8**: ^1H NMR ($CDCl_3$) δ 5.90 (s, 1 H), 5.1 (m, 1 H), 4.75 (m, 1 H), 3.30 (s, 3 H), 0.95 (t, 3 H, J = 5 Hz); IR (film) 1600 cm^{-1}. **9**: ^1H NMR ($CDCl_3$) δ 6.75 (m, 1 H, J = 16 Hz), 6.15 (dd, 1 H, J = 16 and J = 7 Hz), 5.1 (m, 1 H), 4.7 (m, 1 H), 3.3 (s, 3 H), 0.90 (t, 3 H, J = 7 Hz); IR (film) 1670, 1630, 970 cm^{-1}.

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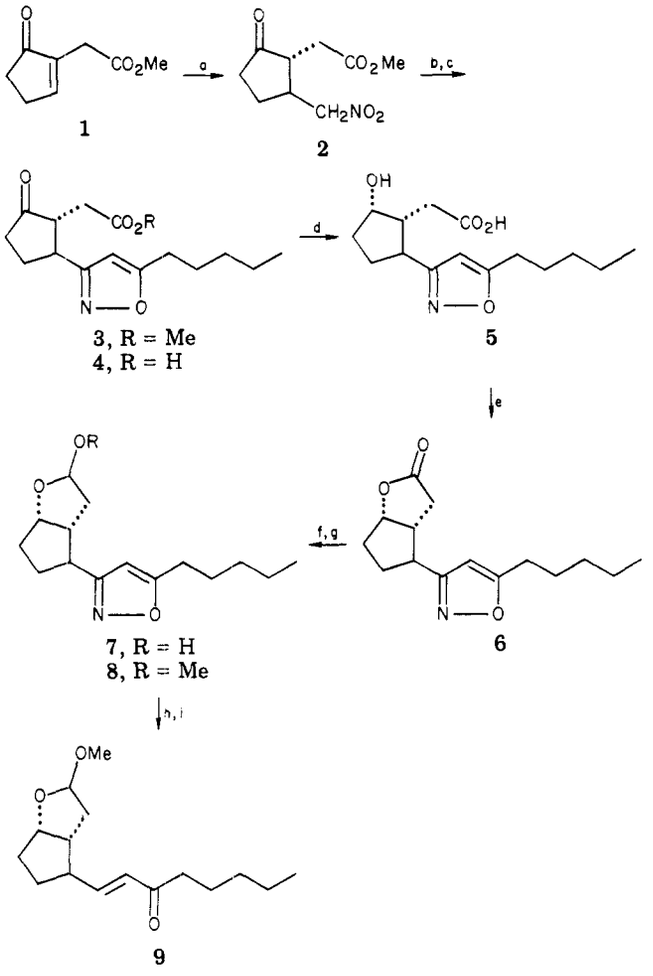
Scheme I[a]



[a] a, $MeNO_2$, 1,1,3,3-TMG, 25 °C, 2 h; b, $HC{\equiv}CC_5H_{11}$, PhNCO, PhH, Et_3N (cat.), 25 °C, 24 h; c, 10% K_2CO_3, H_2O-MeOH (1:1), 25 °C, 12 h; d, K-Selectride, THF, −78 °C, 30 min, 25 °C, 3 h; e, *p*-TsOH (cat.), PhH, reflux, 2.5 h; f, *i*-Bu_2AlH (1.1 equiv), toluene, −78 °C, 1 h; g, MeOH, BF_3 etherate (cat.), −20 °C, 2 h, 0 °C, 1 h; h, *t*-BuOH (3 equiv), NH_3 (liq), Na; i, *p*-TsOH (cat.), toluene, reflux, 24 h.

Cycloaddition of the nitrile oxide, generated in situ from **2** under standard conditions,[9] to 1-heptyne[10] proceeded smoothly, affording a 70% yield of the isoxazole **3**, thus enabling the formation of the carbon framework of the lower C_8 side chain of prostaglandins through C(13)–C(14) bond formation.[11]

Mild saponification of **3** furnished a quantitative yield of the keto acid **4** as a white solid, mp 99–100 °C, which was stereoselectively reduced with K-Selectride to the hydroxy acid **5**, mp 101 °C.

Treatment of **5** with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene easily and quantitatively converted it to the lactone **6**. Reduction of **6** with diisobutylaluminum hydride yielded the lactol **7**, which was protected as the methyl ether **8** by treatment with methanol containing a catalytic amount of boron trifluoride etherate.

Reductive cleavage[12] of the N–O bond in **8**, followed by acid-catalyzed loss of ammonia from the derived crude β-amino ketone, gave a 66% overall yield of the α,β-enone **9**, the required *E* stereochemistry being defined by the 16 Hz coupling constant of the vinylic protons. The latter may be further converted to 11-deoxy analogues of the $F_{2\alpha}$ and E_2 primary prostaglandins by well-established pathways.[13]

This new application further demonstrates the enormous potential provided by these heterocycles as sources of masked functionality, releasable at a suitable point of a synthetic project. Finally, we are now investigating further developments of this approach in two directions, namely, (a) adaptation of this sequence with obvious abbreviations to provide a new efficient route to prostaglandins and closely related analogues and (b) application of similar schemes to the synthesis of other natural compounds having an α,β-enone moiety as a common structural feature.

Registry No. **1**, 57026-61-6; **2**, 73908-66-4; **3**, 73908-67-5; **4**, 73908-68-6; **5**, 73908-69-7; **6**, 73908-70-0; **7**, 73908-71-1; **8**, 73908-72-2; **9**, 73908-73-3; nitromethane, 75-52-5; 1-heptyne, 628-71-7; 1-heptene, 592-76-7.

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(10) The same isoxazole **3** may also be obtained in similar overall yield in two steps from **2**, utilizing the less expensive 1-heptene as dipolarophile, followed by oxidation of the resulting isoxazoline with γ-MnO_2 (Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G. *Synthesis* **1977**, 837).

(11) The nitromethyl moiety has already been utilized in C(13)–C(14) bond-forming reactions as an aldehyde precursor; however, it is noteworthy that it takes part directly in this case, without the involvement of rather unstable aldehydic intermediates (Bagli, J.; Bogri, T. *Tetrahedron Lett.* **1972**, 3815–3817; Alvarez, F.; Wren, D. *Ibid.* **1973**, 569–572).

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