Elaboration of the ω Chain of 11-Deoxyprostanoid Derivatives through Isoxazole Intermediates

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A new versatile approach to the synthesis of 11-deoxyprostanoic acid derivatives, which entails the use of 3,5-disubstituted isoxazoles as source of the eight carbon atoms of the ω-chain, is described. The key step involves the formation of the C(13)–C(14) bond through a [3 + 2] cycloaddition of the nitrile oxides generated from 3β-(nitromethyl)-2α-substituted-cyclopentanone cycloethylene ketals (**10**, **22**, **31**) to 1-heptyne to give the corresponding isoxazoles (**12**, **24**, **32**), the α-side chain of **24** and **32** being completed through Wittig condensation to give **26** and **36**. Reductive ring opening of the heterocycle under Birch-like conditions gave rise to the β-amino ketones **14**, **27**, and **37**, which underwent a silica gel assisted loss of ammonia to produce the α,β-unsaturated ketones **15**, **28**, and **38**, precursors of the vinylamylcarbinol side chain of prostaglandins (PGs). The alternative reductive ring opening of the isoxazole **12** allowed us to obtain the allylically transposed enone **19**, leading to a new preparation of 13-hydroxyprostanoic acid derivatives **21**.

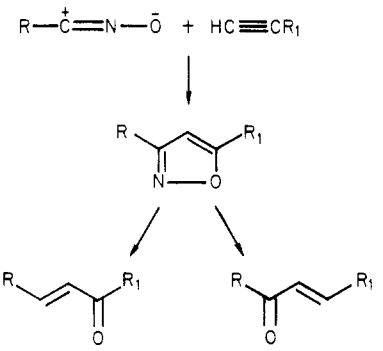
The structural complexities and diverse biological activities of prostaglandins (PGs) make them important and challenging synthetic targets. Since their isolation and characterization in the early 1960's, PGs have elicited a flurry of synthetic activity, culminating in a number of total syntheses.[1] A difficult task in the synthesis of PGs is undoubtedly the construction of the vinylamylcarbinol side chain, and a number of elegant methods have been devised up to date. Herein we describe the details of a new approach to the synthesis of prostanoids, a preliminary account of which has been previously reported,[2] featured by the use of 3,5-disubstituted isoxazoles as templates in forming the proper building block for the eight-carbon chain.

Discussion

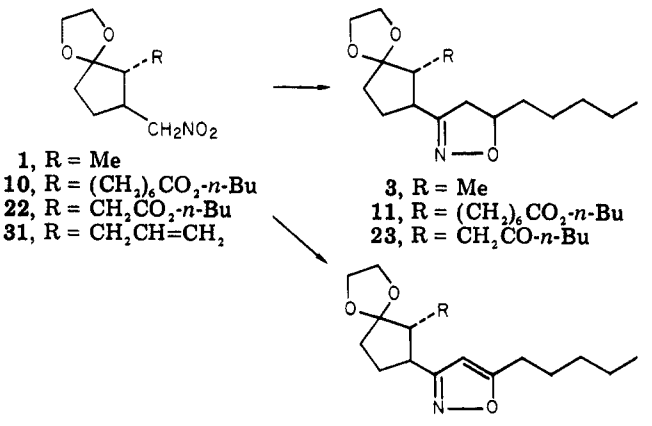
Synthetic Strategy. The central assumption on which this strategy was based was the hypothesis that a 3,5-disubstituted isoxazole can be considered as storage of an α,β-enone moiety and therefore a potential aldol or stabilized Wittig condensation equivalent, releasable at a suitable point of a synthetic project. It was anticipated that these heterocycles could be readily prepared by regiospecific [3 + 2] cycloaddition of nitrile oxides on terminal alkynes[3] and could be regiospecifically opened by suitable reductive treatments to isomeric α,β-enones[4,5] by fission of the labile N–O bond, thus offering the possibility of obtaining two series of prostanoids from a common intermediate (Scheme I).

Model Studies. To test this hypothesis we allowed the nitrile oxide derived from the nitro-compound (**1**), prepared by known procedures (see Experimental Section), to react with 1-heptyne to afford the model isoxazole **2** in 80% yield. However, in view of a possible extension of this strategy to the preparation of prostanoids with modified lower chain, we decided to utilize the more accessible, less expensive, and more reactive 1-alkenes as dipolarophiles, taking advantage of the efficient transformation of the intermediates Δ²-isoxazolines into the corresponding isoxazoles by means of γ-MnO_2,[6] which can tolerate a

Scheme I



Scheme II



1, R = Me
10, R = $(CH_2)_6CO_2$-*n*-Bu
22, R = CH_2CO_2-*n*-Bu
31, R = $CH_2CH{=}CH_2$

3, R = Me
11, R = $(CH_2)_6CO_2$-*n*-Bu
23, R = CH_2CO-*n*-Bu

2, R = Me
12, R = $(CH_2)_6CO_2$-*n*-Bu
24, R = CH_2CO_2-*n*-Bu
32, R = $CH_2CH{=}CH_2$

(1) Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977. Crabbé, P. "Prostaglandin Research"; Academic Press: New York, 1977.
(2) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Simoni, D.; Guarneri, M.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 3141–3142.
(3) Grundman, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971.
(4) Büchi, G.; Vederas, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 9128–9132.
(5) Kashima, C.; Yamamoto, Y.; Tsuda, Y. *J. Org. Chem.* **1975**, *40*, 526–527.
(6) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G. *Synthesis* **1977**, 837.

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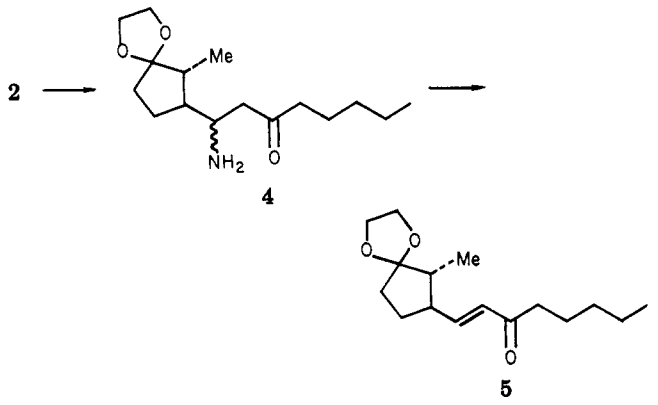
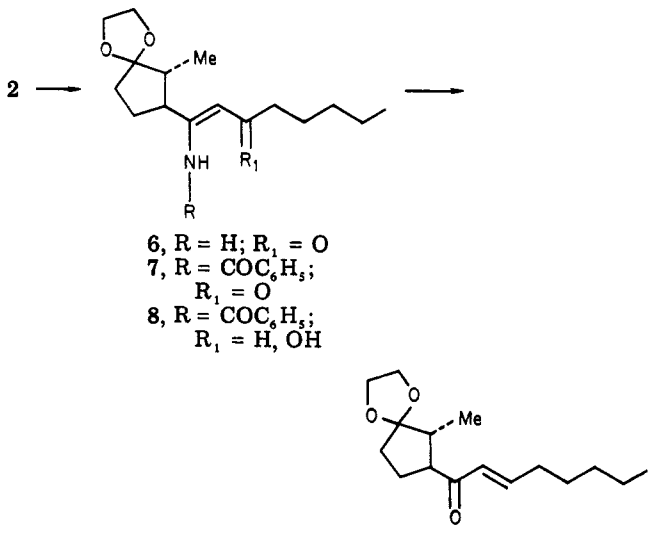
Scheme III



Scheme IV



number of functional and protective groups compared with the previous ones[7] (Scheme II).

Thus the isoxazoline **3**, obtained from the nitrile oxide generated in situ from **1** and 1-heptene, underwent easy dehydrogenation by action of γ-MnO_2, affording an alternative and more convenient route to **2**.

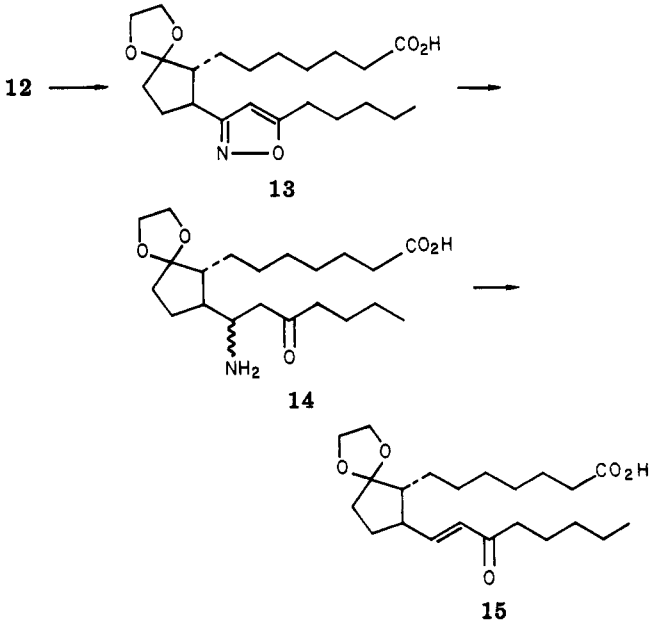
Treatment of **2** with sodium and *tert*-butyl alcohol in liquid ammonia, by following the excellent procedure of Büchi and Vederas,[4] produced the β-amino ketone **4**; the latter, without further purification, was heated for 24 h in toluene solution containing catalytic amounts of *p*-toluenesulfonic acid, giving rise to the expected α,β-unsaturated ketone **5** (Scheme III).

On the other hand, hydrogenolysis of **2** in the presence of PtO_2, prereduced by adding a small amount of Raney Ni, provided a quantitative yield of the vinylogous amide **6**, which was converted to the vinylogous imide **7** by treatment with benzoyl chloride in pyridine.

Reduction of **7** with sodium borohydride and exposure of the crude alcohol **8** to dilute sulfuric acid at room temperature produced the isomeric enone **9** in 50% overall yield (Scheme IV). With the model studies completed, it seemed appropriate to consider the application of these sequences to a cyclopentane ring with the saturated heptanoic or acetic side chain attached.

Synthesis of 11-Deoxy-PGE_1. Compound **10** was an obvious and convenient starting material, being obtainable in 65% overall yield from readily available precursors (see Experimental Section). Cycloaddition of the nitrile oxide, generated in situ from **10** by a conventional procedure, to 1-heptyne proceeded regiospecifically, furnishing the isoxazole **12** in 60% yield. The latter may be alternatively produced in similar yield by dehydrogenation of the Δ^2-isoxazoline **11** in a fashion analogous to that above described for **2**.

Scheme V



Alkaline saponification of the ester function with aqueous methanolic potassium carbonate at room temperature for 12 h provided the acid **13**, which upon reduction with sodium and *tert*-butyl alcohol (3 equiv) in liquid ammonia, followed by careful acidification of the reaction mixture to pH 5, gave the rather sensitive β-amino keto acid **14**. Several attempts to promote loss of ammonia from **14** by heating in refluxing toluene in the presence of toluene-*p*-sulfonic acid were unsuccessful. Only trace amounts of **15** could be isolated by chromatography and identified by spectroscopy from predominant byproducts deriving from extensive decomposition. A more careful examination undertaken in the hope of minimizing the formation of tarry products by performing the deamination stage at as low a temperature as possible led to the discovery that ready and clean removal of ammonia can be achieved simply by heating a chloroform solution of **14** in the presence of suitably activated silica gel.

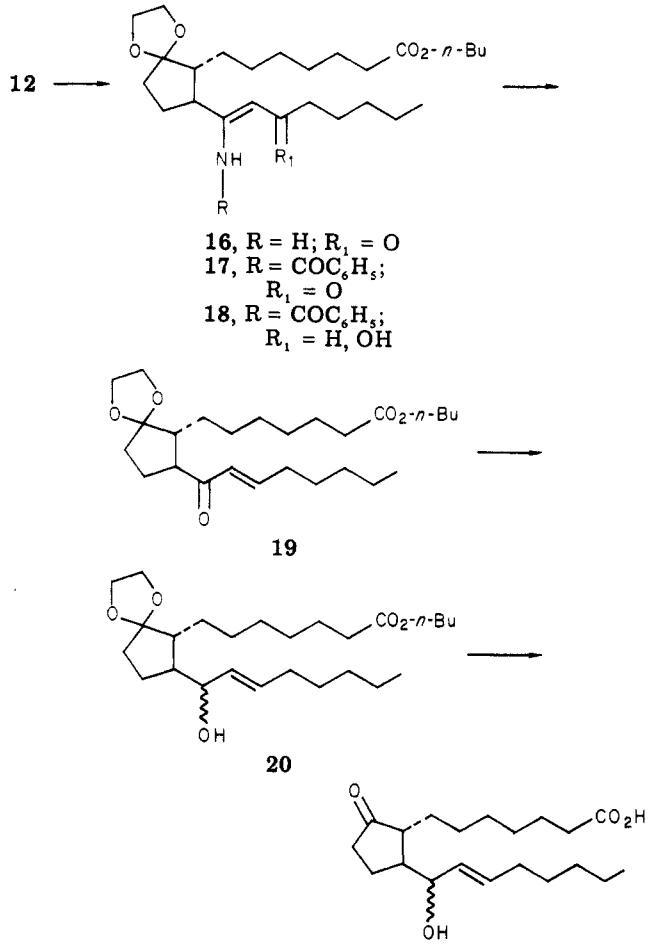
Separation problems as encountered in the previous route were thus avoided by the adoption of this modification, and the enone **15** could be isolated by simple operations in 65% yield (Scheme V). Transformation of **15** in (±)-11-deoxy-PGE_1 and its 15-epimer was carried out by a routine procedure.[1]

Synthesis of 9-Oxo-13-hydroxy-$\Delta^{14,15}$-prostanoic Acid. The application to **12** of the alternative ring opening of the isoxazole nucleus developed by Kashima et al.[5] led to synthesis of the allylically transposed enone **19**, an isomer of **15**, thus offering a new approach to 13-hydroxyprostanoic acid derivatives **21**,[8] obtained as a mixture of inseparable C-13 epimers as outlined in the Scheme IV.

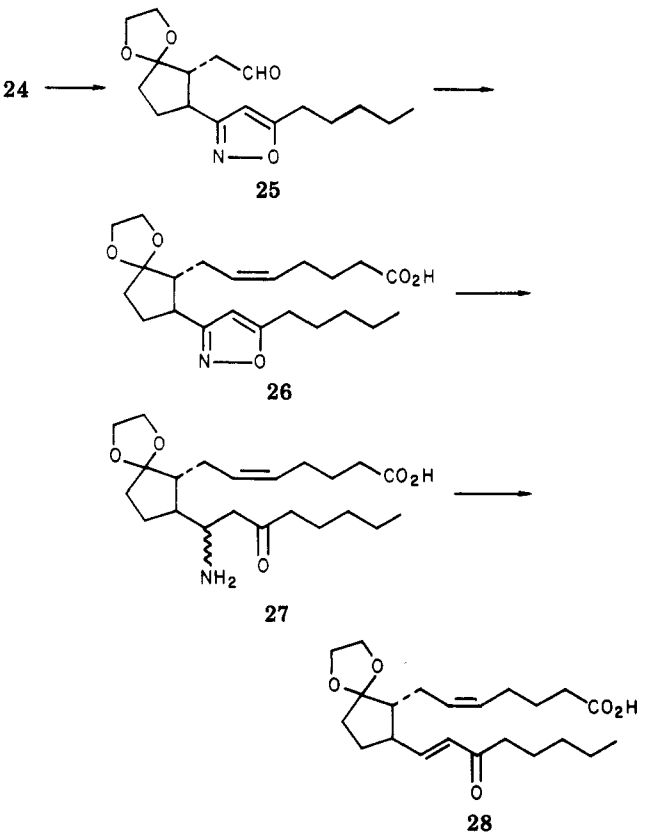
(7) Bianchi, G.; Grünanger, P. *Tetrahedron* **1965**, *21*, 817–822.

(8) For previous syntheses of 13-hydroxyprostanoic acid derivatives, see: Greene, A. F.; Girard, G. R.; Kervin, J. F. *Tetrahedron Lett.* **1975**, 937–938. Noguer, A. J.; Maldonado, L. A., Synth. Commun. **1976**, *6*, 39–45. Bartmann, W.; Beck, G.; Kunstmann, R.; Lerch, U.; Teufel, H. *Tetrahedron Lett.* **1976**, *3879*–3882. Wissner, A. *J. Org. Chem.* **1977**, *42*, 356–358.

Scheme VI



Scheme VII



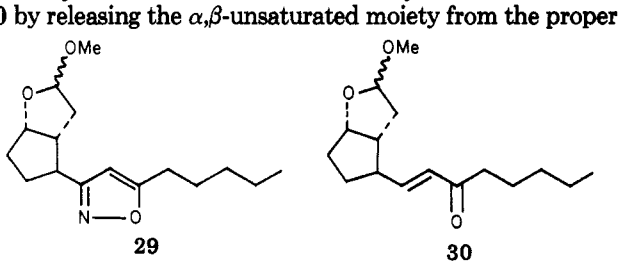
Two steps deserve some comment. First, it is noteworthy to emphasize the fact that the rate of the reductive N–O bond fission of the isoxazole ring, which is known to be generally promoted by a variety of hydrogenation catalysts,[9] was dramatically affected by the use of platinum oxide prereduced by addition of a small quantity of Raney nickel. Presumably a synergic effect drives the reduction to completion faster than with the two separate catalysts.[10] Second, the acid treatment of **18** to give **19**, unlike the model compound **8**, was accompanied by some concomitant cleavage of the ketal. Reketalization of the nonconjugated carbonyl proceeded smoothly by the ketal-exchange technique with 2-methyl-2-ethyl-1,3-dioxolane,[11] affording **19** in good yield (Scheme VI). Alternatively it was determined that totally unprotected **19** may be regioselectively reduced by the action of K-Selectride in THF at −78 °C, affording directly **21**.

Synthesis of 11-Deoxy-PGE$_2$. Having accomplished the synthesis of 11-deoxy-PGE$_1$ derivatives, we next turned our attention to the extension of the method to the preparation of 11-deoxy-PGE$_2$. The key intermediate **22** was obtained in 82% overall yield by the usual two-step sequence using the procedure which we introduced a few years ago. It involves tetramethylguanidine-catalyzed addition of nitromethane to α,β-unsaturated compounds,[12] which proceeded faster than other examined cases, probably with the assistance of the acetate side chain, and was followed by ketalization.[13]

With **22** in hand, the carbon skeleton of the ω chain was constructed, as in the foregoing route, through a cycloaddition of the nitrile oxide generated from **22** to 1-heptyne or 1-heptene, giving rise respectively to the isoxazole **24** or the Δ^2-isoxazoline **23**, the latter being easily converted to **24** by means of γ-MnO_2.[6] With the structure **24** assured, we set out to complete the elaboration of the α-chain.

Accordingly, the carboxy ester group of **24** was reduced at −78 °C with DIBAH in toluene to give an 84% yield of the aldehyde **25**. Wittig reaction of **25** with the potassium salt of (4-carboxybutylidene)triphenylphosphorane in Me_2SO produced a 61% yield of the acid **26**. The latent α,β-unsaturated ketone moiety **28** was unmasked from **26** by the Büchi procedure[4] coupled with the improvement of activated silica gel promoted loss of ammonia from the intermediate β-amino carbonyl compound **27** (Scheme VII). Transformation of **28** into epimeric 11-deoxy-PGE$_2$ derivatives required routine procedures.[1]

Synthesis of 11-Deoxy-PGF$_2$. In a preliminary report[2] we described a demonstrative application of our strategy to the synthesis of the classical 11-deoxy-PGs intermediate **30** by releasing the α,β-unsaturated moiety from the proper



isoxazole derivatives (**29**), while the function on which the

(9) Quilico, A. In "Five and Six-Membered Compounds with Nitrogen and Oxygen"; Interscience: New York, 1962.
(10) Augustine, R. L. "Catalytic Hydrogenation"; Marcel Dekker: New York, 1965.
(11) Bauduin, G.; Petrasanta, J. *Tetrahedron* **1973**, *29*, 4225–4231.
(12) Pollini, G. P.; Barco, A.; De Giuli, G., *Synthesis* **1972**, 44–45.
(13) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.

α side chain had to be constructed was protected as a lactol methyl ether. Although this route presented the drawback of too many steps, at least at the outset of our investigations, it avoided the difficulties encountered in the deamination step before we succeeded in improving the efficiency of the procedure. For the purpose of demonstrating the viability of this approach, we have developed an alternative route to **30** starting from the nitro derivative **31**, obtained in 60% overall yield by standard methods (see Experimental Section).

The assembly of the ω chain as the 3,5-disubstituted isoxazole **32** was performed through the cycloaddition step which paralleled those carried out above, except a fivefold excess of 1-heptyne was used. Using these conditions, we could detect no products arising from the attack of the 1,3-dipole on the olefinic dipolarophile. Unfortunately the use of 1-heptene to produce the corresponding Δ^2-isoxazoline was precluded as we were unable to effect its transformation into **32** in acceptable yield without affecting the allylic side chain.

Deketalization of **32** was obtained by brief acid treatment, furnishing quantitatively the ketone **33**. While reduction of **33** with $NaBH_4$ at −40 °C gave rise to a mixture of C(9) epimeric alcohols, $LiAlH(O\text{-}T\text{-}Bu)_3$ proved to be more stereoselective, producing the alcohol **34** as the sole product. This result parallels the one previously described[2] by us for a similar reduction with K-Selectride. The alcohol **34** was then subjected to osmium tetraoxide catalyzed periodate oxidation,[14] affording the hydroxy aldehyde **35** as a mixture of open-chain compound and cyclic hemiacetal in 96% yield, which were easily transformed into **30** as previously reported.[2]

At this point it must be emphasized how this scheme may offer the opportunity of completing the α chain before the ω one and vice versa merely by submitting **35** to the Wittig reaction with (4-carboxybutylidene)triphenylphosphorane in Me_2SO to give the acid **36** in 60% yield. Transformation of **36** into the enone **38** followed the usual pathway (Scheme VIII).

Conclusion

The foregoing results further emphasize the usefulness of 3,5-disubstituted isoxazoles as equivalents of sensitive functions and the versatility of cycloaddition reactions as a tool for the formation of a carbon–carbon bond. Although a number of concise and pleasing approaches have already been proposed in this topical area, which have effectively solved the problems associated with the synthesis of PGs, this strategy can offer the advantage of utilizing cheap reagents and high-yield procedures. Moreover, it avoids the need of rather unstable aldehydic intermediates, commonly encountered in PG chemistry, from which the ω chain is elaborated via a suitable Wittig–Emmons reaction. In our hands, the failure of Michael addition of nitromethane to a cyclopent-2-en-1-one when a hydroxylic function was present at C-11 can be considered as the only limitation of this method.

In order to overcome this hurdle, we are currently actively investigating a roundabout route which would allow the introduction of the C(11) hydroxylic function at a later stage, after the isoxazole scaffold destined to become the vinylamylcarbinol side chain has already been constructed.

Experimental Section

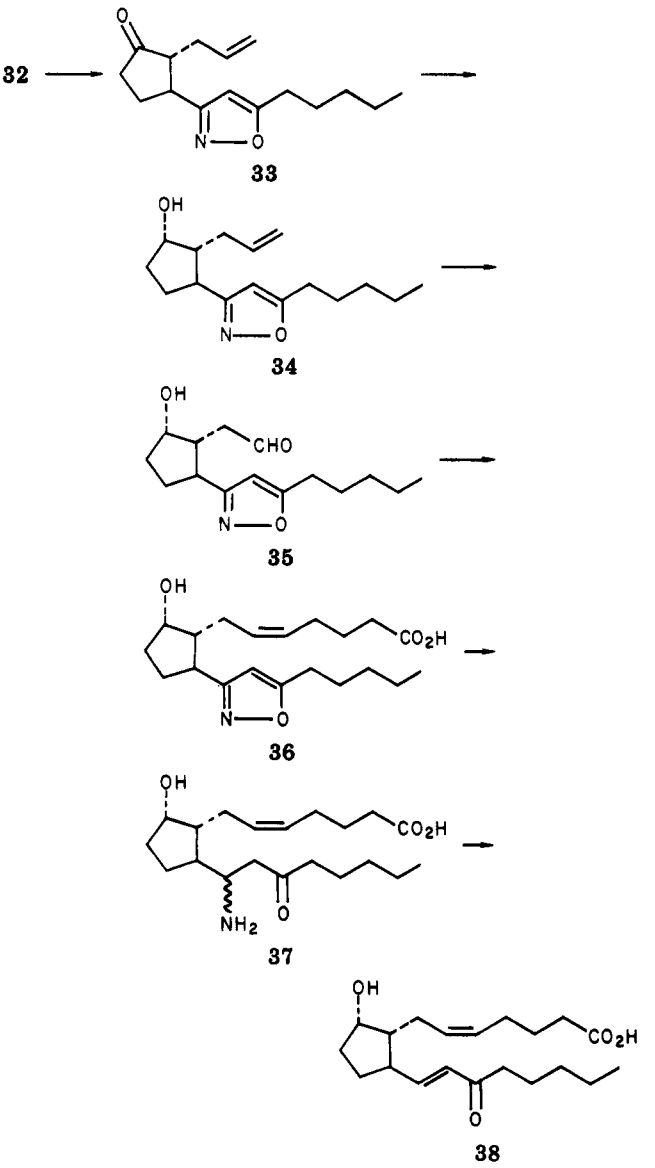
Melting points and boiling points are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated 60 F_{254} Merck plates. Infrared (IR) spectra were measured on a Perkin-Elmer 297 spectrometer. Nuclear magnetic resonance (^1H NMR) spectra were obtained with a Brucker WP80 spectrometer, and peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. All drying operations were performed over anhydrous magnesium sulfate.

Starting Materials. The nitro compounds **1**, **10**, **22**, and **31** were prepared from the corresponding α,β-unsaturated ketones by tetramethylguanidine-catalyzed addition of nitromethane[12] followed by ketalization with ethylene glycol in the presence of pyridinium-*p*-toluenesulfonate.[12]

Spectroscopic Properties of the Starting Materials. 6α-Methyl-7β-(nitromethyl)-1,4-dioxaspiro[4.4]nonane (1) was prepared from 2-methylcyclopent-2-en-1-one[15] in 73% overall yield after chromatographic purification: IR (film) 1545 cm^{-1}; ^1H NMR (CCl_4) δ 1.03 (d, 3 H, J = 5 Hz), 3.9 (s, 4 H), 4.35–4.75 (m, 2 H).

Butyl 7β-(nitromethyl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (10) was prepared from butyl 5-oxocyclopent-1-ene-1-heptanoate[16] in 65% overall yield after chromatographic purification: IR (film) 1730, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9

Scheme VIII



(14) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. V.; Johnson, W. S., *J. Org. Chem.* **1956**, *21*, 478–479.

(15) Traverso, G.; Pollini, G. P.; De Giuli, G.; Barco, A.; Invernizzi Gamba, A., *Gazz. Chim. Ital.* **1971**, *101*, 225–244.

(16) Barco, A.; Benetti, S.; Baraldi, P. G.; Simoni, D. *Synthesis* **1981**, 199–200.

(17) Traverso, G.; Pirillo, D.; Villa, A., *Farmaco Ed. Sci.* **1973**, *28*, 1040–1042.

(t, 3 H, J = 5 Hz), 3.93 (s, 4 H), 4.1 (t, 2 H, J = 6 Hz), 4.5–4.8 (m, 2 H).

Butyl 7β-(nitromethyl)-1,4-dioxaspiro[4.4]nonane-6α-acetate (22) was prepared from butyl 5-oxocyclopent-1-ene-1-acetate[16] in 82% overall yield after chromatographic purification: IR (film) 1740, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 5 Hz), 3.9 (s, 4 H), 4.0 (t, 2 H, J = 7 Hz), 4.4–4.8 (m, 2 H).

6α-Allyl-7β-(nitromethyl)-1,4-dioxaspiro[4.4]nonane (31) was prepared from 2-allylcyclopent-2-en-1-one[17] in 60% overall yield after chromatographic purification: IR (film) 1640, 1545 cm^{-1}; ^1H NMR (CCl_4) δ 3.83 (s, 4 H), 4.5–4.7 (m, 2 H), 4.75–5.2 (m, 2 H), 5.4–5.8 (m, 1 H).

General Procedure for the Preparation of Isoxazoles 2, 12, 24, and 32. To a stirred mixture of the nitro ketal (10 mmol) and 1-heptyne (20 mmol) in benzene (10 mL) containing several drops of Et_3N was add a solution of PhNCO (20 mmol) in benzene (10 mL) dropwise at 25 °C. The mixture was stirred overnight at room temperature and then heated at 50 °C for 1 h. The cooled mixture was filtered, and the filtrate washed with water (2 × 10 mL) and dilute 5% NH_4OH (10 mL), dried, and evaporated under reduced pressure. The residue was chromatographed on silica gel.

General Procedure for the Preparation of Δ^2-Isoxazolines 3, 11, and 23. Δ^2-Isoxazolines are obtained in the same manner as for the isoxazoles when 1-heptene was substituted for 1-heptyne. Transformation into the corresponding isoxazoles was performed by means of γ-MnO_2 by following the previously reported general method.[6]

6α-Methyl-7β-(5-pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane (2). This compound was obtained as an oil in 70% yield, by starting from **1**, according to the general procedure: bp 123–125 °C (0.01 mmHg); IR (film) 1600 cm^{-1}; ^1H NMR (CCl_4) δ 0.6–1.0 (m, 6 H), 3.9 (s, 4 H), 5.8 (s, 1 H). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.95; H, 8.93; N, 5.22.

6α-Methyl-7β-(5-pentyl-4,5-dihydroisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane (3). This compound was prepared, by starting from **1** and following the general procedure, in 82% yield as an oil after column chromatography on silica gel (eluant Et_2O–petroleum ether, 1:7): ^1H NMR (CCl_4) δ 0.7–1.0 (m, 6 H), 3.8 (s, 4 H), 4.3 (m, 1 H). Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.40; H, 9.54; N, 5.08. Oxidation of **3** with γ-MnO_2 gave **2** quantitatively.

6α-Methyl-7β-(3-oxo-*trans*-1-octenyl)-1,4-dioxaspiro[4.4]nonane (5). Sodium (1.2 g) was added to a well-stirred solution of liquid ammonia (200 mL), THF (30 mL), *tert*-butyl alcohol (2.8 g, 37 mmol), and isoxazole **2** (3.53 g, 12.65 mmol) until the solution remained blue. After additional stirring for 15 min, solid NH_4Cl was added until decoloration, and the ammonia was evaporated. The residue was treated with saturated aqueous NH_4Cl (20 mL) and extracted with $CHCl_3$ (3 × 30 mL). The material was dried and concentrated in vacuo, and the residue (**4**) was refluxed in toluene (20 mL) containing few crystals of *p*-toluenesulfonic acid for 24 h. Concentration in vacuo followed by distillation gave 2.01 g (60%) of the enone **5**: bp 106–107 °C (0.01 mmHg); IR (film) 1670, 1625 cm^{-1}; ^1H NMR (CCl_4) δ 0.6–1.0 (m, 6 H), 3.8 (s, 4 H), 5.9 (d, 1 H, J = 16 Hz), 6.6 (dd, 1 H, J = 16, 8 Hz). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.82; H, 9.76.

7β-(1-Amino-3-oxo-*trans*-1-octenyl)-6α-methyl-1,4-dioxaspiro[4.4]nonane (6). A solution of the isoxazole **2** (2.8 g, 10 mmol) in methanol (40 mL) was added to a prehydrogenated mixture of PtO_2 (0.2 g) prereduced by adding a small amount of Raney nickel in methanol (20 mL). After the hydrogenation was complete, the mixture was filtered through Celite and concentrated in vacuo to give **6**, which was used without further purification in the next step: IR (film) 3350, 1600, 1510 cm^{-1}.

7β-(1-Benzamido-3-oxo-*trans*-1-octenyl)-6α-methyl-1,4-dioxaspiro[4.4]nonane (7). To an ice-cooled solution of crude **6** in anhydrous pyridine (35 mL) was added benzoyl chloride (2.4 g, 17 mmol) dropwise. After being allowed to stand overnight at room temperature, the mixture was diluted with water (40 mL) and extracted with CH_2Cl_2 (3 × 25 mL), and the extracts were washed with aqueous saturated $NaHCO_3$ solution, dried, and concentrated in vacuo. Recrystallization of the crude product from *n*-pentane gave **7**: 2.5 g (64.9% from **2**; colorless needles; mp 59–60 °C; IR (Nujol) 1685, 1630, 1590, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 5 Hz), 1.0 (d, 3 H, J = 8 Hz), 3.9 (s, 4 H), 5.66 (s, 1 H), 7.3–8.3 (m, 5 H), 13.63 (s, 1 H). Anal. Calcd for $C_{23}H_{31}NO_4$: C, 72.51; H, 7.86; N, 3.52. Found: C, 72.43; H, 7.83; N, 3.70.

6α-Methyl-7β-(1-oxo-*trans*-2-octenyl)-1,4-dioxaspiro[4.4]nonane (9). To a solution of **7** (1.92 g, 5 mmol) in methanol (15 mL) was added $NaBH_4$ in small portions during 2 h at room temperature. Water (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 25 mL). The dried organic extracts, containing **8**, were concentrated to half of their original volume and stirred for 12 h with dilute 1:1 sulfuric acid (15 mL). The separated organic phase was dried and concentrated in vacuo, and the residue was treated overnight with 2-butanone ethylene ketal in benzene containing 2% of ethylene glycol in the presence of a crystal of *p*-toluenesulfonic acid to ketalize any deprotected compound. The mixture was neutralized with saturated aqueous $NaHCO_3$ solution, and the organic phase was separated, dried, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant Et_2O–petroleum ether, 1:7) to give **9** as an oil: 0.9 g (50%); IR (film) 1665, 1625 cm^{-1}; ^1H NMR (CCl_4) δ 0.7–1.0 (m, 6 H), 3.86 (s, 4 H), 6.1 (dt, 1 H, J = 16, 1.5 Hz), 6.83 (dt, 1 H, J = 7 Hz). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.95; H, 10.01.

Butyl 7β-(5-Pentyl-4,5-dihydroisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (11). This compound was prepared from **10** in 72% yield, by following the general procedure, after chromatographic purification on silica gel with Et_2O–petroleum ether (1:1) as the eluant: IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75–1.0 (m, 6 H), 2.45–3.10 (m, 2 H), 3.93 (s, 4 H), 4.09 (t, 2 H, J = 6 Hz), 4.25–4.7 (m, 1 H). Anal. Calcd for $C_{26}H_{45}NO_5$: C, 69.14; H, 10.04; N, 3.10. Found: C, 69.01; H, 10.21; N, 2.94.

Butyl 7β-(5-Pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (12). This compound was prepared either by γ-MnO_2-promoted oxidation of **11** in 66% yield, as above described, or directly by cycloaddition of the nitrile oxide generated from **10** to 1-heptyne by following the directions above reported, in 60% yield after chromatographic purification on silica gel with Et_2O–petroleum ether (1:9) as the eluant. Compound **12** is a light yellow oil which presents the following spectral data: IR (film) 1730, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75–1.10 (m, 6 H), 3.93 (s, 4 H), 4.1 (t, 2 H, J = 6 Hz), 5.9 (s, (1 H). Anal. Calcd for $C_{26}H_{43}NO_5$: C, 69.45; H, 9.64; N, 3.12. Found: C, 69.61; H, 9.51; N, 3.26.

7β-(5-Pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoic Acid (13). A solution of **12** (2 g, 4.44 mmol) in MeOH (15 mL) was treated with K_2CO_3 (2 g, 15 mmol) in water (15 mL) and allowed to stand at room temperature overnight. Most of the methanol was removed in vacuo, and the solution was acidified at pH 5 with dilute (1:1) HCl. The precipitated oil was extracted with Et_2O, dried, and concentrated in vacuo to afford a quantitative yield (1.75 g) of **13** as an oil: IR (Nujol) 1705, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) 0.9 (t, 3 H, J = 6 Hz), 3.9 (s, 4 H), 5.9 (s, 1 H), 9.3 (br s, 1 H). Anal. Calcd for $C_{22}H_{35}NO_5$: C, 67.14; H, 8.97; N, 3.56. Found: C, 66.99; H, 8.93; N, 3.51.

7β-(3-Oxo-*trans*-1-octenyl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoic Acid (15). A solution of acid **13** (1.96 g, 5 mmol) in THF (15 mL) containing *tert*-butyl alcohol (1.11 g, 15 mmol) was added to liquid ammonia (160 mL). Sodium (0.575 g) was then added portionwise until the solution remained blue. After additional stirring for 15 min, solid NH_4Cl was added until decolorization, and ammonia was allowed to evaporate. The residue was treated with saturated NH_4Cl (15 mL), carefully acidified in an ice-bath to pH 5, and extracted with $CHCl_3$ (3 × 25 mL). The dried extracts, containing **14**, were concentrated in vacuo to half of their volume and preheated at 150 °C overnight, silica gel (5 g) was added, and the mixture was refluxed overnight. The reaction mixture was filtered and the filtrate concentrated in vacuo to leave **15** (1.38 g, 73%) as an homogeneous oil: IR (film) 1710, 1665, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 6 Hz), 3.9 (s, 4 H), 6.17 (d, 1 H, J = 16 Hz), 6.8 (dd, 1 H, J = 16, 7.5 Hz), 9.6 (br s, 1 H). Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.70; H, 9.38.

Butyl 7β-(1-Amino-3-oxo-*trans*-1-octenyl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (16). The isoxazole **12** (2 g, 4.44 mmol) in methanol (40 mL) was reduced at atmospheric pressure over platinum oxide prereduced (0.2 g) in the presence of a small

amount of Raney nickel catalyst. After the theoretical amount of H_2 was consumed, the catalyst was filtered off through Celite. Removal of the solvent under reduced pressure provided vinylogous amide **16** as a clear oil (about 2 g) which was used without further purification: IR ($CHCl_3$) 3470, 3400, 1710, 1610, 1510 cm^{-1}.

Butyl 7β-(1-Benzamido-3-oxo-*trans*-1-octenyl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (17). The procedure was the same as for **7**. The quantities employed were as follows: enamino ketone **16**, about 2 g (crude); pyridine, 11 mL; benzoyl chloride, 1.47 g (10 mmol). The product was purified by chromatography on silica gel with Et_2O–petroleum ether (9:1) as the eluant. The yield was 1.4 g of **17** as a viscous oil: IR (film) 3200, 1720, 1685, 1630, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66–1.00 (m, 6 H), 3.96 (s, 4 H), 4.06 (t, 2 H, J = 6 Hz), 5.8 (s, 1 H), 7.3–8.3 (m, 5 H), 11.7 (s, 1 H). Anal. Calcd for $C_{33}H_{49}NO_6$: C, 71.32; H, 8.89; N, 2.52. Found: C, 71.17; H, 8.73; N, 2.31.

Butyl 7β-(1-Oxo-*trans*-2-octenyl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (19). A solution of **17** (1.4 g, 2.5 mmol) in methanol (15 mL) was treated with solid $NaBH_4$ (0.2 g), which was added portionwise in 15 min until disappearance of the starting material. Stirring was continued for 2 h at room temperature. Water (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 25 mL). Removal of the solvent in vacuo left the alcohol **18**, which, without further purification, was dissolved in CH_2Cl_2 (20 mL) and stirred with dilute (1:1) sulfuric acid (20 mL) overnight at room temperature. The organic phase was separated, washed with saturated $NaHCO_3$ (2 × 10 mL), and dried. Removal of the solvent left **19** accompanied by a small amount of deketalized product. The crude mixture was stirred at room temperature for 12 h with 2-methyl-2-ethyl-1,3-dioxolane (15 mL) containing 2% of ethylene glycol in the presence of a crystal of *p*-toluenesulfonic acid. Benzene (15 mL) and triethylamine (1.5 mL) were added, and the mixture was washed with water (20 mL). Removal of the solvent and column chromatography on silica gel with Et_3O–petroleum ether (2:8) as eluant afforded **19** as a clear oil: 0.54 g (50%); IR (film) 1730, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.1 (m, 6 H), 3.9 (s, 4 H), 4.06 (t, 2 H, J = 7 Hz), 6.13 (dt, 1 H, J = 16, 1.5 Hz), 6.9 (dt, 1 H, J = 16, 8 Hz). Anal. Calcd for $C_{26}H_{44}O_5$: C, 71.52; H, 10.16. Found: C, 71.77; H, 10.02.

Butyl 7β-(1-Hydroxy-*trans*-2-octenyl)-1,4-dioxaspiro[4.4]nonane-6α-heptanoate (20). To an ice-cooled solution of **19** (2 g, 4.5 mmol) in methanol (50 mL) was added solid sodium borohydride (0.3 g) gradually until no more starting material could be observed by TLC analysis (Et_2O–petroleum ether, 8:2). The reaction mixture was poured into water and extracted with CH_2Cl_2 (3 × 25 mL). The extracts were washed with water and brine, dried, and evaporated to give quantitatively (2.01 g) a mixture of epimeric alcohols **20**: IR ($CHCl_3$) 3450, 1725, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.1 (m, 6 H), 3.9 (s, 4 H), 4.08 (t, 2 H, J = 6 Hz), 5.45 (dd, 1 H, J = 16, 6 Hz), 5.8 (dt, 1 H, J = 16, 6 Hz).

13-Hydroxy-9-oxo-$\Delta^{14,15}$-prostanoic Acid (21). A solution of alcohol **20** (2 g, 4.5 mmol) in methanol (10 mL) was treated with potassium carbonate (2 g) in water (10 mL) and stirred overnight. Most of methanol was eliminated in vacuo, and then the mixture was acidified with 0.5 N HCl, stirred for 30 min, and extracted with Et_2O (3 × 25 mL). Evaporation of the dried extracts left **21** as an oil: 1.4 g (93.3%); IR ($CHCl_3$) 3300, 1720, 970; ^1H NMR ($CDCl_3$) δ 0.7–1.00 (t, 3 H, J = 6 Hz), 3.6 (br s, 2 H), 4.13 (m, 1 H), 5.5 (dd, 1 H, J = 16, 6 Hz), 5.8 (dt, 1 H, J = 16, 6 Hz). Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.25; H, 9.98.

Butyl 7β-(5-Pentyl-4,5-dihydroisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-acetate (23). This compound was prepared by starting from **22** and following the general procedure and was purified chromatographically on silica gel by elution with Et_2O–petroleum ether (1:1). The isoxazoline **23** was obtained as an oil: 70% yield; IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.0 (m, 6 H), 2.45–3.1 (m, 2 H), 3.95 (s, 4 H), 4.09 (t, 2 H, J = 6 Hz), 4.25–4.7 (m, 1 H). Oxidation of **23** with γ-MnO_2 gave **24** in 90% yield.

Butyl 7β-(5-Pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-acetate (24). This compound was prepared by following feneral procedure and starting from **22**. The crude product was purified by column chromatography on silica gel with Et_2O–petroleum ether (1:1) as eluant to give **24** as an oil: 70% yield; IR (film) 1740, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.1 (m, 6 H), 3.9 (s, 4 H), 4.0 (t, 2 H, J = 7 Hz), 5.91 (s, 1 H). Anal. Calcd for $C_{21}H_{33}NO_5$: C, 66.46; H, 8.77; N, 3.69. Found: C, 66.59; H, 8.85; N, 3.56.

7β-(5-Pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-acetaldehyde (25). To a stirred solution of **24** (1.9 g, 5.3 mmol) in toluene (40 mL) cooled at −78 °C under an atmosphere of nitrogen was added diisobutylaluminum hydride (0.85 g (neat), 10 mmol) dropwise, while stirring was continued for 2 h at the same temperature. When the reaction was complete as judged by TLC, methanol (0.2 mL) and water (0.6 mL) were added cautiously, and the mixture was stirred for 30 min. Anhydrous $MgSO_4$ was added and the mixture filtered through Celite. Evaporation of the solvents in vacuo provided the aldehyde **25** (1.3 g, 84%) as a homogeneous oil: IR ($CHCl_3$) 2720, 1730, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 3.95 (s, 4 H), 5.95 (s, 1 H), 9.7 (t, 1 H, J = 1.2 Hz).

7β-(5-Pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane-6α-*cis*-hept-2-enoic Acid (26). To a solution of potassium *tert*-butoxide (6.72 g, 60 mmol) in dry Me_2SO (15 mL) was added (4-carboxybutylidene)triphenylphosphonium bromide (13.29 g, 30 mmol) all at once. To the resultant red solution of the ylide was added dropwise a solution of the aldehyde **25** (1.55 g, 5 mmol) in Me_2SO (5 mL), and the mixture was stirred until the reaction was complete (TLC). Water (40 mL) was added, and the cooled mixture was acidified at pH 5.5 with saturated 30% aqueous sodium dihydrogen phosphate and extracted with Et_2O (2 × 30 mL). The dried extracts were evaporated to give **26** (1.2 g, 61.5%) as an oil after chromatography on silica gel with Et_2O containing 0.2% of methanol as the eluant: IR (film) 1710, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 5 Hz), 3.95 (s, 4 H), 5.35 (m, 2 H), 5.9 (s, 1 H), 8.7–9.1 (br s, 1 H). Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50; N, 3.58. Found: C, 67.76; H, 8.37; N, 3.70.

7β-(3-Oxo-*trans*-1-octenyl)-1,4-dioxaspiro[4.4]nonane-6α-*cis*-hept-2-enoic Acid (28). By use of the procedure outlined for the synthesis of **15**, the acid **28** was obtained as an oil in 78.5% overall yield by starting from **26**: IR ($CHCl_3$) 1710, 1670, 1630, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 5 Hz), 3.9 (s, 4 H), 5.5 (m, 2 H), 6.1 (d, 1 H, J = 16 Hz), 6.8 (dd, 1 H, J = 16, 7 Hz), 7.5 (br s, 1 H). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.95; H, 8.97.

6α-Allyl-7β-(5-pentylisoxazol-3-yl)-1,4-dioxaspiro[4.4]nonane (32). This compound was prepared by following general procedure and starting from **31** (20 mmol) and 100 mmol of 1-heptyne. Column chromatography (silica gel, 1:1 Et_2O–petroleum ether) gave **32** as an oil: 41% yield; IR (film) 3080, 1640, 1605 cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (t, 3 H, J = 5 Hz), 3.86 (s, 4 H), 4.7–5.1 (m, 2 H), 5.4–5.9 (m, 1 H), 5.8 (s, 1 H). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N 4.59. Foundb C, 70.71; H, 8.82; N, 4.70.

2α-Allyl-3β-(5-pentylisoxazol-3-yl)cyclopentan-1-one (33). Exposure of **32** (1.5 g, 5 mmol) to dilute (1:1) sulfuric acid (15 mL) in THF (15 mL) for 30 min followed by dilution with water, extraction with Et_2O (3 × 25 mL), and evaporation gave **33** (1.28 g) quantitatively as an oil: IR (film) 1745, 1640, 1605 cm^{-1}; ^1H NMR δ 0.9 (t, 3 H, J = 5 Hz), 4.73–5.2 (m, 2 H), 5.33–5.7 (m, 1 H), 5.93 (s, 1 H). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.87; N, 5.36. Found: C, 73.41; H, 8.82; H, 5.21.

2α-Allyl-3β-(5-pentylisoxazol-3-yl)cyclopentan-1α-ol (34). To a suspension of $LiAlH(O\text{-}t\text{-}Bu)_3$ (2 g, 7.87 mmol) in THF (20 mL) at 0 °C was added dropwise a solution of **33** (1.4 g, 5.36 mmol) in THF (5 mL). When the stirred reaction was complete as judged by TLC (Et_2O–petroleum ether, 2:1), the mixture was poured into water, acidified with 10% HCl, and extracted several times with Et_2O. The organic extracts were dried and evaporated to give alcohol **34**: 1.34 g (95%); oil; IR (film) 3370, 1640, 1600 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (t, 3 H, J = 5 Hz), 4.73–5.2 (m, 2 H), 5.33–5.7 (m, 1 H), 5.93 (s, 1 H). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.12; H, 9.49; N, 5.19.

5α-Hydroxy-2β-(5-pentylisoxazol-3-yl)-cyclopentane-1α-acetaldehyde (35). To a stirred solution of **34** (1.34 g, 5.1 mmol) in dioxane (65 mL) and water (21 mL) was added a small crystal of OsO_4. When the solution turned brownish (ca. 10 min), sodium metaperiodate (2.76 g, 12.3 mmol) was added at 24–26 °C. The reaction mixture was stirred for 4 h at room temperature, the precipitated solid was filtered, and the filtrate was extracted with Et_2O, dried, and evaporated in vacuo to leave 1.3 g (96%) of **35**

as an oil (this compound contains a 30% amount of the lactol form): IR (film) 3380, 1725, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 5 Hz), 5.93 (s, 1 H), 9.76 (t, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.01; H, 8.70; N, 5.19.

5α-Hydroxy-2β-(5-pentylisoxazol-3-yl)cyclopentane-1α-*cis*-hept-2-enoic Acid (36). By use of the procedure outlined for the synthesis of **26**, the acid **36** was obtained as an oil in 60% yield by starting from **35**: IR (film) 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 5 Hz), 4.5 (m, 1 H), 5.5 (m, 2 H), 5.9 (s, 1 H), 6 (br s, 2 H). Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.68; H, 8.99; N, 3.92.

5α-Hydroxy-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-*cis*-hept-2-enoic Acid (38). By use of the procedure outlined for the synthesis of **15**, the acid **38** was obtained as an oil in 70% yield by starting from **36**: IR (film) 1705, 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 5 Hz), 4.5 (m, 1 H), 5.5 (m, 2 H), 6 (br s, 2 H), 6.2 (d, 1 H, J = 16 Hz), 6.8 (dd, 1 H, J = 16, 7.5 Hz). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.65.

Registry No. 1, 78199-90-3; 2, 78199-91-4; 3, 78199-92-5; 4, 78217-49-9; 5, 78199-93-6; 6, 78199-94-7; 7, 78199-95-8; 8, 78199-96-9; 9, 78199-97-0; 10, 78199-98-1; 11, 78199-99-2; 12, 78200-00-7; 13, 78200-01-8; 14, 78200-02-9; 15, 41692-81-3; 16, 78200-03-0; 17, 78200-04-1; 18, 78200-05-2; 19, 78200-06-3; 20 (epimer 1), 78200-07-4; 20 (epimer 2), 78200-08-5; 21 (epimer 1), 78246-84-1; 21 (epimer 2), 78246-85-2; 22, 78200-09-6; 23, 78200-10-9; 24, 78200-11-0; 25, 78200-12-1; 26, 78200-13-2; 28, 78200-14-3; 31, 78200-15-4; 32, 78200-16-5; 33, 78200-17-6; 34 (epimer 1), 78200-18-7; 34 (epimer 2), 78246-86-3; 35, 78200-19-8; 36, 78200-20-1; 38, 78200-21-2; 2-methylcyclopent-2-en-1-one, 1120-73-6; butyl 5-oxocyclopent-1-ene-1-heptanoate, 52477-97-1; butyl 5-oxocyclopent-1-ene-1-acetate, 78200-22-3; 2-allylcyclopent-2-en-1-one, 51557-85-8; 1-heptyne, 628-71-7; 1-heptene, 592-76-7.

Flexible Synthesis of Polyamine Catecholamides

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A scheme is developed for the high-yield synthesis of polyamine catecholamides from the secondary *N*-benzylamines N^5-benzylhomospermidine, N^4-benzylspermidine, and *N*,*N*-bis(3-aminopropyl)benzylamine. These amines are first selectively acylated at the N-terminal positions with 2,3-dimethoxybenzoyl chloride, and the benzyl groups are removed by hydrogenolysis. The resulting diamides are then either demethylated to produce the corresponding bis(catecholamides) or secondary N-acylated and then demethylated. The secondary N-acylations were effected with either 2-hydroxyhippuric acid, *N*-(2,3-dimethoxybenzoyl)glycine, *N*-(2,3-dimethoxybenzoyl)-4-aminobutyric acid, or *N*-(2,3-dimethoxybenzoyl)-β-alanine. Six hexacoordinate and three tetracoordinate catecholamide iron ligands with polyamine backbones of differing lengths were generated by using this procedure. The approach offers a flexible method for optimizing the chelate effect in polyamine catecholamide ligands.

In recent years, a great deal of attention has been focused on the development of new iron chelators.[1-4] The reason for this is probably closely related to the absence of a suitable therapeutic device for the removal of iron from patients suffering toxic iron overload.[5,6] Both natural and synthetic chelators have been considered with most of the synthetic sequestering agents closely modeled after natural products.[7,8] However, a satisfactory drug still has not been developed.[9]

In 1975, Tait reported the isolation of a siderophore, N^4-[*N*-(2-hydroxybenzoyl)threonyl]-N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (I), and its precursor, N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (II), from *Paracoccus denitrificans*[10] (Chart I), both of which showed potential as therapeutic iron-clearing devices.[10,11] These compounds were shown to remove iron from transferrin, the body's serum iron binding protein, as well as from cultured fibroblasts, Chang cells.[11] However, because of the difficulty in isolating these amides, workers were unable to run even the simplest animal studies, i.e., toxicity and iron-clearing experiments.

In an earlier paper, we reported on a high-yield synthesis of compound II and demonstrated it to be less toxic than aspirin and to be absorbed across intestinal walls, i.e., a potential orally effective chelator.[7] We have since shown it to be more effective than deferrioxamine at clearing iron from iron overloaded rats.[12] These results encouraged us to consider the development of a general synthesis of both compound I and II analogues.

It is now clear from Neilands' work[13] that in Tait's original isolation procedure, he hydrolyzed the oxazoline ring of compound III, (*N*-[3-(2,3-dihydroxybenzamido)propyl)]-*N*-[4-(2,3-dihydroxybenzamido)butyl]-2-(2-hydroxyphenyl)-5-methyloxazoline-4-carboxamide to pro-

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