Tetrahedron Letters,Vol.27,No.20,pp 2199-2202,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

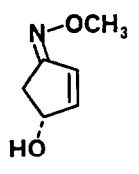
A NEW SYNTHETIC ROUTE TO PROSTAGLANDINS

E. J. Corey, Koichi Niimura, Yoshitaka Konishi, Shinsuke Hashimoto, and Yasumasa Hamada
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

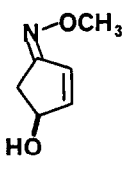
Summary: A short synthetic route to prostaglandins is described which depends on oxime-based methodology and which involves the joining of intermediates **9**, **11**, and **12** in a one-flask operation.

This note describes a new synthetic route to prostaglandins which is based on unique aspects of the chemistry of O-methyloximes (methoximes) and which features the attachment of omega and alpha appendages to a cyclopentyl nucleus in a one-flask operation.[1]

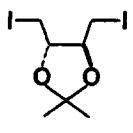
3-Cyclopentenone[2] was transformed into racemic 1-methoxyimino-4-hydroxy-2-cyclopentene (**1** + **2**) by the sequence: (1) oximation with 1.6 equiv of O-methylhydroxylamine hydrochloride and 2.2 equiv of pyridine in methanol at 23° for 30 min to give the corresponding methoxime (81%); (2) epoxidation with 1.3 equiv of m-chloroperbenzoic acid in CH_2Cl_2 at 0° (72%); and (3) syn-β-elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene in benzene at 80° for 8 hr (75%).[3] PMR spectral data indicate that, as expected, the methoxy group in the major product **1** + **2** is syn to the olefinic carbon (syn-deprotonation).[4] Formation of the anti isomer (ca. 3% yield) was observed as a minor event.[4]



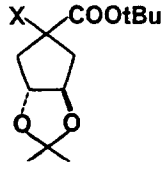
1



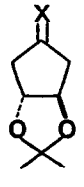
2



3



4 X=CN
5 X=H
6 X=OH



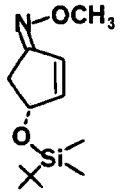
7 X=O
8 X=$NOCH_3$

An effective (but unconventional) process for the separation of the enantiomers **1** and **2** and for the conversion of the S-antipode **2** to the required R-antipode **1** was developed by taking advantage of three findings: (1) α-cyclodextrin selectively precipitates **2** at 23°C from aqueous solutions of the racemate **1** + **2**;[5] (2) partially resolved **1** obtained from the mother liquors of this separation can be purified by conversion to the 3,5-dinitrobenzoate, recrystallization and ester cleavage;[6] and (3) Mitsunobu inversion of **2** using 3,5-dinitrobenzoic acid occurs smoothly to give the 3,5-dinitrobenzoate of **1**.[7] The process based on these operations is convenient and amenable to scale-up. The desired R-antipode **1**, $[\alpha]_D^{23}$ + 193° (c = 1 in $CHCl_3$), can be obtained in >60% weight yield from the racemate **1** + **2**; higher yields are probably achievable. Recovery of α-cyclodextrin is excellent (>95%).

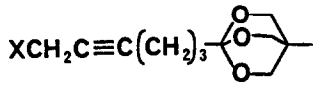
which was decyanated to **5** by treatment in THF solution at –45° with 2.1 equiv of lithium napthalenide for 30 min (77% yield). Exposure of **5** in THF at 0° to 1.6 equiv of lithium diisopropylamide for 30 min followed by oxygenation of the resulting ester enolate with dioxygen at 0° for 20 min produced hydroxy ester **6** (87%). Conversion of **6** to methoxime **8** was accomplished in 60% overall yield by the sequence: (1) saponification with tetrabutylammonium hydroxide at 23° for 2 hr; (2) cleavage of the resulting ammonium salt in dry CH_2Cl_2 solution by reaction with a small excess of lead tetraacetate at –20° for 15 min and 0° for 30 min; and (3) reaction with methoxyamine hydrochloride and pyridine in CH_2Cl_2–pentane at 23° for 2.5 hr. Conversion of **8** to **1** was effected by reaction with a small excess of lithium diisopropylamide in THF at –45° for 20 min (>95%).

The three components required for the assembly of prostaglandin E_2 (PGE_2) were obtained in a straightforward manner. Reaction of the R(+)–hydroxy methoxime **1** with t–butyldimethylsilyl chloride (2 equiv) – imidazole (4 equiv) in dimethylformamide (DMF) at 23° for 1.5 hr[9] afforded the corresponding oily silyl ether **9** (90%), $[\alpha]_D^{23}$ + 157.3° (c = 1.0 in $CHCl_3$). Reaction of the OBO ester of 5–hexynoic acid[10] with n–butyllithium (1 equiv) in THF at –50° followed by dry paraformaldehyde (1.5 equiv, –50° to 23° over 4 hr) gave the propargylic alcohol **10** (94%). Reaction of **10** with 1.2 equiv of iodine, 1.3 equiv of imidazole, and 1.3 equiv of triphenylphosphine at 0° for 30 min produced the iodide **11** as a pale yellow solid. The third component, the E–vinylstannane **12** was obtained from (S)–1–octyn–3–ol[11] by the sequence: (1) silylation[9] with t–butyldimethylsilyl chloride – imidazole – DMF for 18 hr at 23° to give the corresponding silyl ether (94%); and (2) hydrostannation with tributyltin hydride in the presence of bisazoisobutyronitrile (AIBN) at 130° for 2 hr to form **12**, $[\alpha]_D^{23}$ –12.0° (c = 1 in $CHCl_3$), in 89% yield.

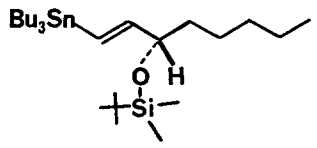
The PG system was assembled from components **9**, **11** and **12** as follows. Stannane **12** (2.6 equiv) was converted to a mixed cyanocuprate reagent by successive reaction in THF with n–butyllithium (2.4 equiv, –42°, 40 min) and cuprous cyanide (1.2 equiv, –78°, 60 min). To this reagent at –78° was added via cannula a freshly prepared solution of a mixture of 1 equiv of silyl ether **9** and 1 equiv of boron trifluoride etherate in toluene at –78°. After 15 min at –78° and 30 min at –50° the mixture was cooled to –78°, treated with 10% v/v of hexamethylphosphoric triamide, 2 equiv of triethylamine and 2.7 equiv of the iodide **11**. The reaction mixture was maintained at –78° for 15 min, –50° for 15 min, –10° for 4 hr, and 23° for 16 hr, quenched with aqueous ammonium chloride and subjected to extractive isolation and silica gel chromatography. Although some starting methoxime **9** (16%) was recovered, the major product was the desired prostanoid **13** (60%, 75% corrected for recovered **9**), $[\alpha]_D^{23}$ –27.5° (c = 1.0 in $CHCl_3$), R_f 0.24 (silica gel tlc using 5:1 hexane–ethyl acetate). OBO ester cleavage (stirring with sodium bisulfate in 5:1 dimethoxyethane – water at 0° for 20 min followed by basification with lithium hydroxide to pH 10.5 and stirring at 23° for 2 hr, then acidification and extractive isolation), esterification (CH_2N_2) and subsequent Lindlar reduction in benzene in the presence of quinoline produced the methoxime methyl ester of PGE_2 bis t–butyldimethylsilyl ether, identical by tlc, PMR, IR, and rotation with a comparison sample prepared from authentic PGE_2. Cleavage of the methoxime function of **14** was surprisingly difficult using aqueous Ti^{+3} at varying pH.[12] Because none of the established methods for deoximation were operable a study of new reagents



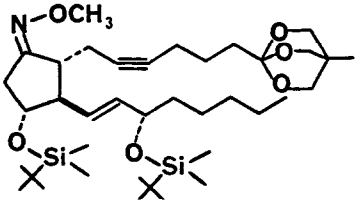
9



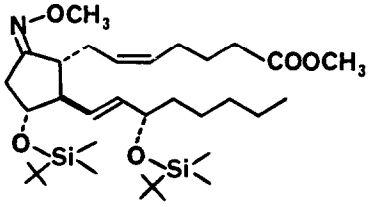
10 X=OH
11 X= I



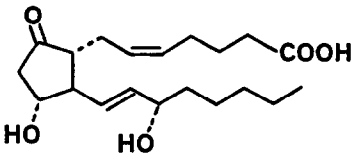
12



13



14



15

was made. Success was realized using a solid reagent made by reduction of $TiCl_3$·3 THF[13] by diisobutylaluminum hydride (DIBAL) in toluene.[14] The carboxylic acid corresponding to **14** (obtained quantitatively from **14** by saponification with 2:1 THF - 0.1 M lithium hydroxide at 23° for 17 hr, followed by acidification and isolation) in toluene was treated with 1 equiv of DIBAL in toluene and then with three portions of the solid Ti reagent[14] each corresponding to 1.2 methoxime reduction equivalents at intervals of 30 min. After a further 40 min the product was isolated by quenching with aqueous sodium acetate, acidification with citric acid, extraction with CH_2Cl_2, and silica gel chromatography to give PGE_2 11,15-bis-t-butyldimethylsilyl ether identical by spectroscopic and tlc comparison with a reference sample (73% yield). Desilylation using 8:1 acetonitrile - 40% aqueous hydrofluoric acid at 23° afforded PGE_2 (**15**) (98%) identical with an authentic sample produced by total synthesis.[15]

In the conversion of **9** to **13** the BF_3 complex of methoxime **9** is doubtless the reactive species since uncomplexed **9** does not react with the mixed cuprate derived from **12** in the absence of BF_3. The alkylation of the cuprate adduct with **9** by iodo acetylene **11** requires that BF_3 be removed from that intermediate; hexamethylphosphoric triamide and triethylamine are used for that purpose, as well as to insure the integrity of the OBO ester group. Although the conditions for the synthesis of **13** were carefully selected it is probable that higher yields are achievable.

The above reported synthesis of prostaglandins contains a number of noteworthy methodological elements including: (1) the novel syntheses of **1**, (2) the reductive decyanation 4→5, (3) the one-flask process for the attachment of alpha and omega chains to the cyclopentyl unit, and (4) the novel deoximation of methoximes by a solid, lower valent (<3) titanium reagent.[16]

References and Notes

1. For other routes to prostaglandins which involve the same general strategy but which are based on enone–enolate chemistry see (a) M. P. L. Caton in "New Synthetic Routes to Prostaglandins," S. M. Roberts and F. Scheinmann, Academic Press, New York, 1982, pp. 105–134; (b) M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, **107**, 3348 (1985) and refs. cited therein.

2. M. Suzuki, Y. Oda and R. Noyori, *J. Am. Chem. Soc.*, **101**, 1623 (1979).

3. Satisfactory PMR, IR, UV and mass spectral data were obtained for each synthetic intermediate.

4. For preferential syn α–deprotonation see E. J. Corey and D. Enders, *Tetrahedron Letters*, 3 (1976); *Chem. Ber.*, **111**, 1337 (1978). The syn–methoxime (**1**) and the minor anti isomer were distinguished by different PMR chemical shifts for the C(2) proton (6.74 and 6.32δ resp.) and by tlc R_f value (1:1 ethyl acetate – hexane, 0.22 and 0.26 resp.). The C(2) proton in **1** is deshielded by the syn methoxy group in accordance with much past precedent.

5. The use of α–cyclodextrin for this separation was suggested by the close fit between **1** or **2** and the cavity of α–cyclodextrin; see M. L. Bender and M. Komigawa, "Cyclodextrin Chemistry," Springer Verlag, New York, 1978, p. 61. In practice a concentrated solution of the racemate **1** + **2** in water was added to just sufficient α–cyclodextrin (16% solution in water) to complex **2**. The solution was seeded with pure **2**–α–CD complex. After 48 hr at 23° the precipitate was collected. Concentration of the aqueous filtrate in vacuo at 30° afforded a second crop. The two crops were combined and recrystallized (55°→0°) from water. Methoxime **2** was obtained by dissolving in water at 50–53°, cooling and extracting with 1:1 ether – ethyl acetate; α–CD was recovered by evaporation of the aqueous phase in vacuo.

6. The aqueous solutions from the separation of 2–α–CD complex were extracted with ether – ethyl acetate (1:1) to give 1 (ca. 70% ee) which was converted to the 3,5–dinitrobenzoate (3,5–dinitrobenzoyl chloride – pyridine – CH_2Cl_2, 0°, 2 hr), obtained after recrystallization from ethyl acetate – hexane as needles, mp 112°, $[\alpha]_D^{23}$ + 217° (c = 1 in $CHCl_3$) (73% yield). Cleavage of this ester was effected by 2 equiv of potassium carbonate in methanol at 23° for 1.5 hr to give pure 1 in 98% yield.

7. Conversion of **2** to the 3,5–dinitrobenzoate of **1** was accomplished efficiently (91%) by treatment with 1.5 equiv of triphenylphosphine, 1.5 equiv of 3,5–dinitrobenzoic acid and 1.5 equiv of diethyl azodicarboxylate at 0° for 2.5 hr (see O. Mitsunobu, *Synthesis*, 1 (1981)).

8. (a) L. J. Rubin, H. A. Lardy and H. O. L. Fischer, *J. Am. Chem. Soc.*, **74**, 425 (1952); (b) M. Carmack and C. J. Kelley, *J. Org. Chem.*, **33**, 2171 (1968); (c) K. Ogura, M. Yamashita and G. Tsuchihashi, *Tetrahedron Letters*, 759 (1976).

9. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

10. E. J. Corey and N. Raju, *Tetrahedron Letters*, **24**, 5571 (1983).

11. J. Fried, M. Mehra, C. Lin, W. Kao, and P. Dalven, *Annal. N. Y. Acad. Sci.*, **180**, 38 (1971).

12. Cf. however, R. Pappo, P. Collins and C. Jung, *Tetrahedron Letters*, 943 (1973), and R. E. Donaldson, J. C. Saddler, S. Byrn, A. T. McKenzie and P. L. Fuchs, *J. Org. Chem.*, **48**, 2167 (1983).

13. L. E. Manzer, *Inorg. Synth.*, **21**, 135 (1982).

14. This reagent was prepared freshly in the following way. $TiCl_3 \cdot 3\ THF$[13] (810 mg, blue crystals) was added to 7.5 ml of toluene under argon to give a dark green suspension. After cooling to 10° 1.6 ml of a 1.5 M solution of DIBAL in toluene was added over 10 min to give a fine black suspension. After 20 min at 10° and 23° for 2 hr the mixture was centrifuged at 1500 rpm under argon, the dark brown supernatant was removed and the residual black pasty solid (ca. 1g) was suspended in toluene. The methoxime reduction potency of this suspension was standardized as effectively 0.125 M by measuring the volume required to convert 0.1 mmole of 4–t–butylcyclohexanone methoxime to 4–t–butylcyclohexanone (a quantitative conversion at 23° for 15 min). This solid reagent and a number of other new effective reagents for the conversion of methoximes to ketones will be reported in more detail in a separate paper.

15. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, **92**, 397 (1970).

16. This research was assisted in part by grants from the National Institutes of Health and the National Science Foundation. We are grateful to Prof. Jeremy Knowles of this department for a generous gift of α–cyclodextrin.

(Received in USA 4 February 1986)