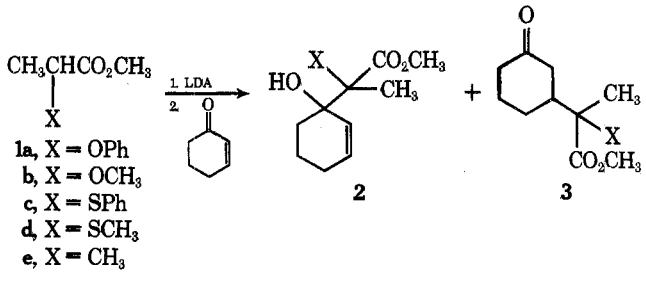
Table I. Product Distribution as a Function of Reaction Temperature for Addition of Ester Enolates to 2-Cyclohexen-1-one

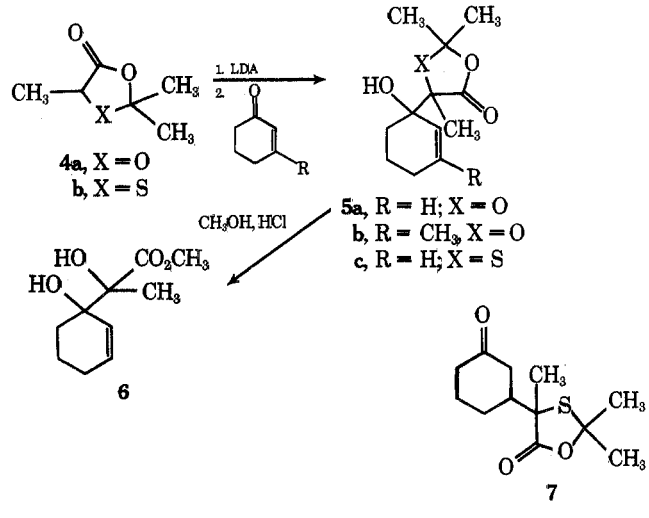
	−78 °C reaction		25 °C reaction	
Ester	% 1,2 addition	% 1,4 addition	% 1,2 addition	% 1,4 addition[a]
1a	88	8		84
1b	75	12	5	62[b]
1c		75		86
1d	63	7		85
1e	88	5	7	83

[a] Isolated yields; all other yields were determined by NMR and VPC analysis. Our limits of detectability were estimated to be ≤2%. [b] With shorter reaction time, yields were ~85–90%; however, much more 1,2-addition product was present.



We also have examined the reactivity of four other enolates derived from α-substituted methyl propionates and the results are presented in Table I. With ester enolates derived from **1b, 1d,** and **1e,** the 1,2-addition products **2b, 2d,** and **2e** were isolated and, as with **2a,** undergo conversion to **3b, 3d** and **3e,** respectively when treated with LDA at −78 °C and then warmed to 25 °C. Thus, kinetic addition is predominately (if not exclusively) taking place at the carbonyl carbon atom. Conjugate addition products arise by reversible formation of 1,2 adducts and subsequent 1,4 addition. With the ester enolate of methyl-2-thiophenoxypropionate (**1c**), however, equilibration occurs even at −78 °C (see Table I).

An interesting change in enolate reactivity was observed with the acetonide **4a.** Reaction with cyclohexenone at either −78 or 25 °C over prolonged reaction times gives only the product of 1,2 addition, **5a** (82% isolated yield, bp 93–95 °C



at 0.05 mm, chemical ionization mass spectrum *m/e* 227). Substitution of 3-methyl-2-cyclohexen-1-one for cyclohexenone gives only **5b,** isolated in 80% yield. When reaction of the ester enolate of **4a** with cyclohexenone is performed as usual, but is followed by addition of 1 equiv of 3-methylcyclohexenone with stirring for 1 h at 25 °C, only **5a** and unreacted 3-methylcyclohexenone are recovered. Clearly, with the enolate of **4a** and cyclohexenone, 1,2 addition is irreversible under these reaction conditions. With thiaacetonide **4b,** however, 1,2 addition is reversible and gives the product of conjugate addition **7** at 25 °C.

Thus, we have shown that, by simple structural modifications (e.g., **1a** and **1b** compared to **4a**) and careful control of reaction temperature, it is possible to direct ester enolates to either direct or conjugate addition with cyclohexenone. Furthermore, we note that the product of acetonide 1,2 addition, **5,** may be converted to the allylic pinacol **6** in nearly quantitative yield on treatment with methanolic hydrogen chloride, thus providing an exceptionally simple synthesis of this useful functionality.

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA 16624-02).

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(2) G. Stork and L. Maldonado, *J. Am. Chem. Soc.,* **96,** 5272 (1974), and references cited therein.
(3) J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.,* 3271 (1973).
(4) This type of equilibration may occur in the addition of other stabilized carbanions to enones; for example, see ref 2.
(5) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.,* **93,** 2318 (1971).
(6) For examples of conjugate addition of simple ester enolates to Michael acceptors in which 1,2-addition is precluded, see J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Lett.,* 4711 (1973). A dithiane ester enolate derived from ethyl glyoxalate undergoes 1,4 addition with 5,5-dimethyl-3-chloro-2-cyclohexen-1-one, presumably at −78 °C, in 94% yield: J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *ibid.,* 2599 (1973). In light of this example, note our results with the ester enolate derived from **1c.**

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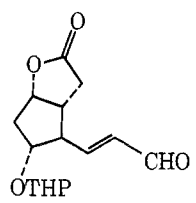
Prostaglandin Metabolites. Synthesis of E and F Urinary Metabolites

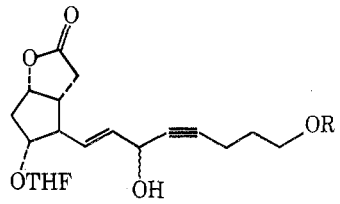
Summary: The synthesis of major urinary metabolites of E prostaglandins, 11α-hydroxy-9,15-dioxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid (**7a**), and F prostaglandins, 9α,11α-dihydroxy-15-oxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid δ-lactone (**8a**) is described.

Sir: The structure of the major human urinary metabolites of PGE_2[1] and $PGF_{2\alpha}$[2] has been determined by mass spectral analysis. The synthesis of those various metabolites have been reported.[3] We wish to report a highly efficient synthesis of one of the major human urinary metabolites of the PGE series, 11α-hydroxy-9,15-dioxo-2,3,5,20-pentanor-19-carboxyprostanoic acid (**7a**), and PGF series, 9α,11α-dihydoxy-15-oxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid δ-lactone (**8a**).[4]

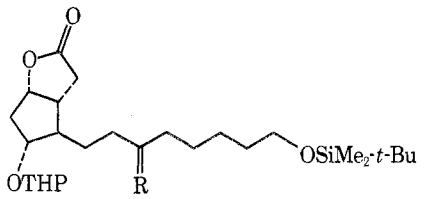
The synthesis was designed to meet three important considerations: (1) the incorporation of deuterium or tritium could be easily accomplished, to enable synthesis of labeled metabolites; (2) the steps involved should be simple and efficient; (3) the intermediates should be flexible enough to allow for possible variations. The present synthesis meets those criteria and allows the synthesis of both E and F metabolites from a common precursor, **6a.**



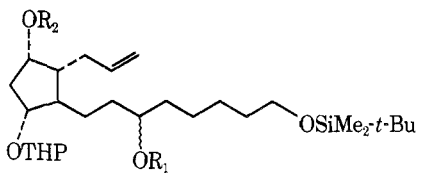
1



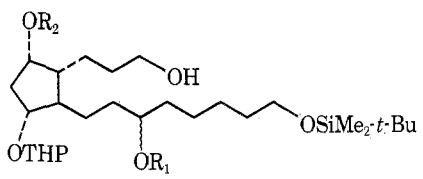
2a, R = $SiMe_2$-*t*-Bu
b, R = $SiMe_3$
c, R = H



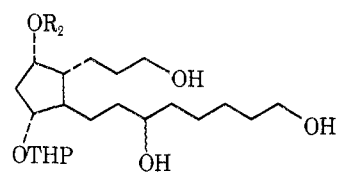
3a, R = OH, H
b, R = $OSiMe_2$-*t*-Bu, H
c, R = O



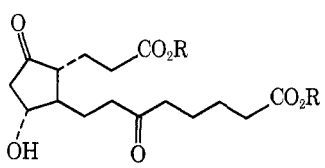
4a, R_1 = R_2 = H
b, R_1 = $SiMe_2$-*t*-Bu; R_2 = H
c, R_1 = $SiMe_2$-*t*-Bu; R_2 = THP



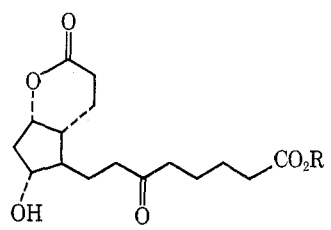
5a, R_1 = R_2 = H
b, R_1 = $SiMe_2$-*t*-Bu; R_2 = THP



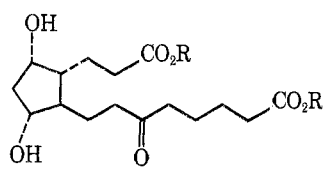
6a, R = H
b, R = THP



7a, R = H
b, R = CH_3



8a, R = H
b, R = CH_3



9a, R = H
b, R = CH_3

The synthesis started from a versatile lactone–aldehyde intermediate, **1**.[5] When the lactone–aldehyde reacted with 1~1.2 equiv of 1-dimethyl-*tert*-butylsilyloxy-4-pentynyllithium[6] at −70~−60 °C in THF (20–30 min), the adduct, **2a**, was isolated in 65~75% yield: ir (cm^{-1}) 3420, 2220, 1775, 975; NMR (CCl_4, δ) 5.72~5.52 (m, 2 H, –CH=CH–), 5.14~4.52 [m, 3 H, –OCHO–, –CHOCO–, –C=CCHC≡C–], 0.86 (s, 9 H, –OSi-*t*-Bu); high resolution mass spectrum (as TMS derivative) $M^+ - C_4H_9$ 493.2433 (calcd for $M^+ - C_4H_9$, $C_{22}H_{41}Si_2O_6$, 493.2442).[7] Catalytic (5% rhodium on alumina, in ethyl acetate) hydrogenation of **2a** yielded 63% **3a** and 25% **3c** (ir 1780, 1710 cm^{-1}). On the other hand, when the hydrogenation was followed by sodium borohydride reduction (−10~0 °C in methanol), **3a** was obtained in better than 90% yield: ir (cm^{-1}) 3460, 1775; NMR (CCl_4, δ) 5.10~4.80 (m, 1 H, –CHOCO–), 4.76~4.54 (m, 1 H, –OCHO–), 4.18~3.28 (m, 6 H, –CHO–, $-CH_2O-$), 0.88 (s, 9 H, –Si-*t*-Bu).

The extension of the upper side chain by one extra carbon was easily accomplished via the following sequence. Diisobutylaluminum hydride reaction of lactone **3a** (−70~−60 °C in toluene, 1 h) followed by Wittig reaction (ylide generated from methyltriphenylphosphonium bromide and *n*-butyllithium in THF, 4 h at room temperature) afforded the diol, **4a**, in 75% yield: ir (cm^{-1}) 3440, 3080, 1640; NMR (CCl_4, δ) 6.30~4.80 (m, 3 H, $-CH=CH_2$); high resolution mass spectrum (as TMS derivative) $M^+ - C_5H_9O$ 543.3726 (calcd for $C_{28}H_{59}Si_3O_4$, 543.3721). Hydroboration–9-BBN oxidation[8] gave the triol, **5a**, in 90% yield after purification by high pressure liquid chromatography: NMR ($CDCl_3$, δ) 4.76~4.54 (m, 1 H, –OCHO–), 4.24~3.24 (m, 9 H, –CHO–, $-CH_2O-$), 0.88 (s, 9 H, –Si-*t*-Bu); high resolution mass spectrum (as TMS derivative) $M^+ - C_5H_9O$ 633.4208 (calcd for $C_{31}H_{69}Si_4O_5$, 633.4222). Treatment of the triol, **5a**, with tetra-*n*-butylammonium fluoride in THF[9] yielded the tetraol,[10] **6a**: NMR ($CDCl_3$, δ) 4.80~4.50 (m, 1 H, –OCHO–), 4.30~3.30 (m, 9 H, –CHO–, $-CH_2O-$); high resolution mass spectrum (as TMS derivative) M^+ 676.4410 (calcd for $C_{33}H_{72}Si_4O_6$, 676.4406). The most difficult steps in the sequence were the conversion of the tetraol, **6a**, to the final products (**7a** and **8a**). Difficulties in purification and isolation of the diacid (**7a**) and lactone–acid (**8a**) added to the problem. Jones oxidation (−10~0 °C, 10 min) followed by hydrolysis [HOAc–THF–H_2O (3:1:1) at 40 °C for 4 h] and purification via high pressure liquid chromatography afforded 30~35% **7a** and 20~25% **8a** in pure form. The structure of **7a** was confirmed by analysis of the dimethyl ester, **7b**: ir (cm^{-1}) 3500, 1750, 1740, 1710; NMR ($CDCl_3$, δ) 4.32~3.80 (m, 1 H, –CHO–), 3.68 (s, 6 H, $-CO_2CH_3$); high resolution mass spectrum (as TMS derivative) M^+ 428.2224 (calcd for $C_{21}H_{36}SiO_7$, 428.2230). The GC–mass spectrum of **7b** (as methyl oxime–TMS derivative) showed a pattern identical with that obtained from the authentic PGE_2 urinary metabolites, M^+ 486.[1,11] The structure of **8a** was also confirmed by analysis of its methyl ester, **8b**: ir (cm^{-1}) 3460, 1740, 1715; NMR ($CDCl_3$, δ) 4.90~4.50 (m, 1 H, –CHOCO), 4.10~3.60 (m, 1 H, –CHO–), 3.68 (s, 3 H, $-CO_2CH_3$); high resolution mass spectrum (as TMS derivative), M^+ 398.2101 (calcd for $C_{20}H_{34}SiO_6$, 398.2125). The GC–mass spectrum of **8b** (as methyl oxime–TMS derivative) also showed a pattern identical with that obtained from the authentic $PGF_{2\alpha}$ urinary metabolites, M^+ 427.[2,12]

The structure of lactone–ester, **8b**, was further confirmed by an independent synthesis. Protection of the free hydroxyl group **3a** by dimethyl-*tert*-butylsilyl group[9] gave **3b**. Without purification of **3b**, diisobutylaluminum hydride reduction was followed by Wittig reaction to give **4b** (84%). Protection of the new free hydroxyl group as its tetrahydropyranyl ether (**4c**, 95%) followed by hydroboration–9-BBN oxidation[8] afforded **5b** (93%). Removal of the dimethyl-*tert*-butylsilyl groups (tetra-*n*-butylammonium fluoride),[9] Jones oxidation, hydrolysis, and methylation with diazomethane gave **8b** in 31% overall yield. Spectral analyses and TLC mobility were identical with those of **8b** obtained from **8a** described previously.

Procedure for 6a → 7a + 8a. A solution containing 776 mg (2.0 mmol) of **6a** in 20 ml of acetone was cooled to −10~5 °C and 4.5 ml (12 mmol) of Jones reagent (2.67 M) diluted with 60 ml of acetone was added dropwise over a period of 5 min. After stirring an additional 5 min at −5~0 °C, the reaction was stopped by addition of 5 ml of 2-propanol (or aqueous sodium bisulfite). Acetone was removed under reduced pressure and the residue was extracted with ethyl acetate (3 × 300 ml). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded the oxidation product. Without purifying, this product was stirred in 10 ml of HOAc–H_2O–THF (3:1:1) at 40~45 °C for 5 h. The reagent was removed under reduced pressure with occasional addition of toluene to facilitate the removal of acetic acid and water. The residue was purified by HPLC [68 g of 30~50-μ silica gel; the column was washed with 300 ml of 5% HOAc in EtOAc, followed by 300 ml of EtOAc–hexane (3:1) before the injection of sample; 30 ml/fraction was collected; EtOAc–hexane (3:1) elution, fractions 1–40; EtOAc elution, fractions 41–100]. The fractions homogeneous on TLC analysis [A-IX[13]–HOAc (10:1)] were collected. The following were isolated: pure **7a** (fractions 19–47, 234 mg, 35%, amorphous solid), NMR ($CDCl_3$ + 10% CD_3OD, δ) 4.32~3.80, (m, 1 H, –CHO–); **8a** (fractions 52–100, 135 mg, 21%), NMR ($CDCl_3$, δ) 4.72 (br s, 2 H, $-CO_2H$, –OH), 4.90~4.50 (m, 1 H, –CHOCO–), 4.10~3.60 (m, 1 H, –CHO–). The diacid, **7a**, is stable at room temperature for only a few

days. A very slow formation of less polar product (A-type metabolite) is observed. In the freezer, the dehydration occurs considerably slower. The δ-lactone–hydroxy acid, **8a**, by standing at room temperature, forms additional polar spot on TLC. It appears that the equilibrium mixture of δ-lactone–hydroxy acid and dihydroxy diacid is formed.[4]

Acknowledgment. The author wishes to thank Mr. J. R. Boal for running the GC–mass spectra and also Dr. R. C. Kelly and Dr. H. A. Karnes for making the starting material available. Helpful discussions with Dr. J. E. Pike of these laboratories are also acknowledged.

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(2) (a) E. Granström and B. Samuelsson, *J. Biol. Chem.*, **246**, 5254 (1971); (b) J. C. Cornette, K. T. Kirton, W. P. Schneider, F. F. Sun, R. A. Johnson, and E. G. Nidy, *Prostaglandins*, **9**, 323 (1975).
(3) (a) J. R. Boot, M. J. Foulis, N. J. A. Gutteridge, and C. W. Smith, *Prostaglandins*, **8**, 439 (1974); (b) D. Taub, Z. S. Zelawski, and N. L. Wendler, *Tetrahedron Lett.*, 3667 (1975); (c) E. G. Nidy and R. A. Johnson, *J. Org. Chem.*, **40**, 1415 (1975).
(4) Treatment of **8a** with base followed by reaction with diazomethane gave **9b**. However, it always resulted in equilibrium mixture of lactone (**8b**) and hydroxy ester (**9b**). (Observation by Dr. W. P. Schneider of these laboratories.)
(5) The synthesis of this versatile intermediate (with natural prostaglandin configuration) will be published shortly by Dr. R. C. Kelly of these laboratories.
(6) 1-Dimethyl-*tert*-butylsilyloxy-4-pentynyllithium was obtained in situ by reacting the corresponding alkyne with methyllithium at −20∼−10 °C for 10 min. The alkyne, 1-dimethyl-*tert*-butylsilyloxy-4-pentyne [bp 65 °C (9 mm)] was easily obtained by silylation[9] of 4-pentyn-1-ol (Farchan Co.).
(7) A similar result was obtained when 1-trimethylsilyloxy-1-pentyne was used (**1** → **2b**). Hydrolysis of trimethylsilyl group gave lactone–diol (**2c**) in 85% overall yield.
(8) C. G. Scouten and H. C. Brown, *J. Org. Chem.*, **38**, 4092 (1973).
(9) E. J. Corey and A. Venkateswarlu, *J. Org. Chem.*, **94**, 6190 (1972).
(10) Because of the similar solubility of both the tetraol, **6a**, and the reagent toward solvent and water, it became very difficult to remove the excess reagent. One solution to this problem was to prepare the TMS derivative directly from the reaction mixture. Extraction with hexane followed by aqueous washing removed the reagent. TMS groups were easily removed by stirring in 5% potassium carbonate in methanol–water (4:1).
(11) We thank Dr. E. G. Daniels of these laboratories for providing the GC–mass spectrum of the authentic sample for the comparison. He has identified this metabolite from the urine of single dose injection of PGE_2 into rats and rhesus monkeys: private communication from Dr. E. G. Daniels.
(12) We thank Dr. F. F. Sun and Dr. W. P. Schneider of these laboratories for providing us with the GC–mass spectrum of the authentic sample for the comparisons. See also F. F. Sun, *Biochim. Biophys. Acta*, **348**, 249 (1974); F. F. Sun and J. E. Stafford, *ibid.*, **369**, 95 (1974).
(13) M. Hamburg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).

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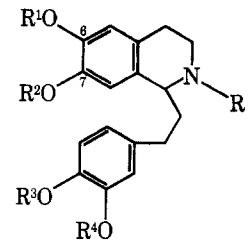
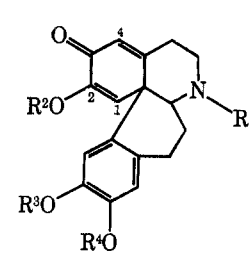
Novel Nonphenol Oxidative Coupling of Phenethylisoquinolines[1]

Summary: Oxidative coupling of nonphenolic phenethylisoquinolines **1a–c** with VOF_3–TFA gave homoaporphines **4a,g,h** in high yields via homoproerythrinadienone intermediates (e.g., 8).

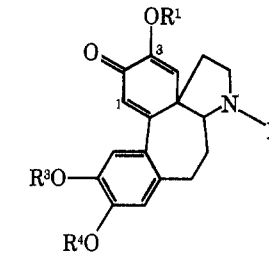
Sir: Nonphenol oxidative coupling reactions which yield spirodienone intermediates and products are currently subjects of great interest.[2-8] The first practical syntheses of this type involved electrooxidative coupling of benzylisoquinolines to morphinandienones.[2-4] Recent reports have also described the chemical intramolecular coupling of nonphenolic benzylisoquinolines with vanadium oxytrifluoride in trifluoroacetic acid (TFA) and demonstrated that the oxidations proceed via morphinandienone intermediates.[6-8] We report herein novel nonphenol oxidative coupling reactions



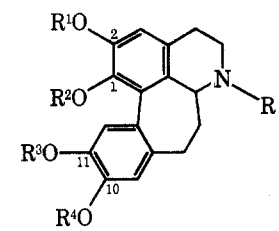
1a, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
b, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
c, $R^2 = CH_2Ph$; $R^1 = R^3 = R^4 = CH_3$; $R = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R = COCF_3$
e, $R^2 = R^3 = H$; $R^1 = R^4 = R = CH_3$
f, $R^1 = R^2 = R^3 = R^4 = R = CH_3$



2a,c,d



3a,b



4a,e,f

4g, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
h, $R^2 = H$; $R^1 = R^3 = R^4 = CH_3$; $R = COCF_3$

of phenethylisoquinolines **1a–c** using VOF_3–TFA which yield homoaporphines **4a,g,h** via homoproerythrinadienone intermediates (e.g., 8).

Treatment of a solution of (±)-*N*-trifluoroacetylhomonorlaudanosine (**1a**)[9,10] in CH_2Cl_2 and TFA[11] at −10 °C with VOF_3 in TFA for 10 min followed by aqueous workup gave homoproerythrinadienone **2a** (5%, mp 161–162 °C), homoneospirinedienone **3a** (64%, mp 171.5–172 °C), homoaporphine **4a** (2%, mp 167–169 °C), and aldehyde **5** (22%, mp 143–144 °C). To confirm the structure of **2a**, diphenolic precursor **1d** was first oxidized with VOF_3–TFA to homoproerythrinadienone **2d**[12] (78%); subsequent O-methylation of **2d** with diazomethane gave **2a**. In contrast to the acid-catalyzed rearrangement of proerythrinadienones to neospirinedienones,[13] homoproerythrinadienone[14] **2a** and homoneospirinedienone **3a** rearranged to homoaporphines **4g** (87%, mp 221–222 °C) and **4h** (84%, mp 200–201 °C), respectively, upon treatment with BF_3–Et_2O in CH_2Cl_2 at room temperature for 24 h. Treatment of **4g** and **4h** with diazomethane yielded **4a**. The structure of 1,2,10,11-tetrasubstituted homoaporphine **4a** was confirmed by an unambiguous synthesis. Thus oxidation of **1e** with VOF_3–TFA gave diastereoisomeric homoproaporphines[15] **6a** (38%, mp 193–194 °C dec; melting point, ir, uv, and NMR in good agreement with those of (±)-kreysiginone[16a]) and **6b** [30%, mp 198–200 °C dec (lit.[16a] mp 202 °C dec)]. Treatment of **6a** with BF_3–Et_2O in CH_2Cl_2 afforded diphenolic homoaporphine **4e** [87%, mp 185.5–187 °C (lit.[17] 185–187 °C)], which on methylation with diazomethane gave tetramethoxyhomoaporphine **4f**[18] (70% as the hydrochloride; mp 222–224 °C dec; melting point, mixture melting point, TLC, uv, NMR, and mass spectrum identical with those of a sample prepared by alkaline hydrolysis of **4a** followed by N-methylation with HCHO–$NaBH_4$).