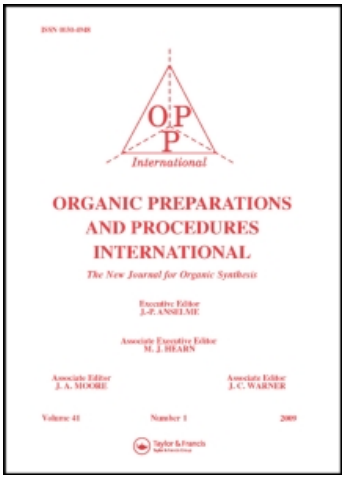

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

REGIOSELECTIVE SYNTHESIS OF 10-HYDROXY-11-METHOXYAPORPHINE FROM (RS)-10,11-DIHYDROXYAPORPHINE

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To cite this Article Kim, Jack C. and Park, Won-Woo(1994) 'REGIOSELECTIVE SYNTHESIS OF 10-HYDROXY-11-METHOXYAPORPHINE FROM (RS)-10,11-DIHYDROXYAPORPHINE', Organic Preparations and Procedures International, 26: 4, 479 — 482
To link to this Article: DOI: 10.1080/00304949409458042
URL: http://dx.doi.org/10.1080/00304949409458042

REGIOSELECTIVE SYNTHESIS OF 10-HYDROXY-11-METHOXYAPORPHINE FROM (RS)-10,11-DIHYDROXYAPORPHINE

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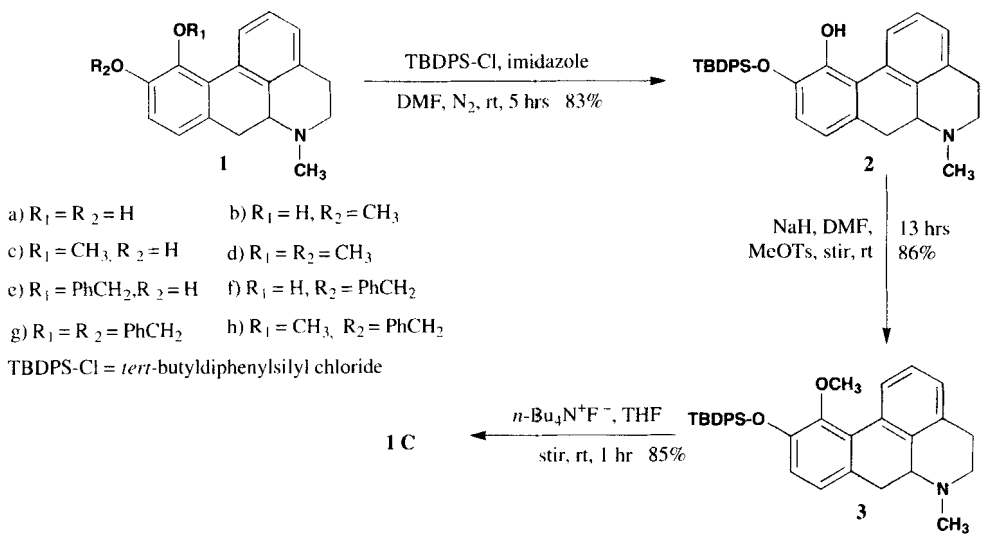
Considerable interest has been demonstrated in 10,11-dihydroxyaporphine (apomorphine, **1a**), because of its medicinal use of a powerful central acting emetic[1] and in the treatment of *Parkinsonism*,[2] and because of an active central and peripheral dopaminergic agonist[3]. In addition, the metabolic fate of apomorphine (**1a**) in mammalian systems showed that *in vivo* methylations[4] appear to be one of the important pathways in the biodisposition[5] of this compound. Metabolic reactions occurred at the 10- and 11-phenolic hydroxyl positions of apomorphine (**1a**) to give *para*-methylated product, 10-methoxy-11-hydroxyaporphine (*apocodeine*, **1b**) and *meta*-methylated product, 10-hydroxy-11-methoxyaporphine (*isoapocodeine*, **1c**).[5] In view of these biological activities, coupled with the metabolic biotransformations of apomorphine molecule, a regioselective synthesis from the readily available apomorphine (**1a**) was required in order to obtain sufficient quantities of **1c**. The isoapocodeine (**1c**) has been obtained not only by the total synthesis,[6] but also by the selective demethylation[7,8] of 10,11-dimethoxy-aporphine (**1d**). Direct methylation of apomorphine with methylating agents such as methyl iodide, diazomethane or methyl tosylate afforded solely 10,11-dimethoxyaporphine (**1d**) in quantitative yield; neither apocodeine (**1b**) nor isoapocodeine (**1c**) was formed in these synthetic alkylation procedures. Cannon and his group[9] had obtained isoapocodeine (**1c**) in only 5% yield; treatment of apomorphine with 1 equivalent of benzyl bromide afforded three spots on *TLC*, in addition to one spot for unreacted apomorphine and it was concluded that these three spots



represented the two isomeric monobenzyl ethers, 10-hydroxy-11-benzyloxyaporphine (**1e**) and 10-benzyloxy-11-hydroxyaporphine (**1f**) and the dibenzyl ether 10,11-dibenzyloxyaporphine (**1g**). Treatment of sodium salt of **1f** from NaH with methyl tosylate induced the formation of 10-benzyloxy-11-methoxyaporphine (**1h**), which upon reductive debenzylation, afforded 10-hydroxy-11-methoxyaporphine (isoapocodeine, **1c**).

Since X-ray analysis[10] had indicated that the phenolic 11-hydroxyl group of the biphenyl portion in the apomorphine system is apparently strained due to its steric repulsion with the 1-*peri* hydrogen, we have developed a simple and practical method for the conversion of apomorphine (**1a**) into isoapocodeine (**1c**) in excellent yield. Due to the sterically hindered nature of 11-hydroxy group of apomorphine, the use of the bulky *tert*-butyldiphenylsilyl chloride led to exclusive regioselective O-silylation of the 10-hydroxy group (to give **2**), thus leaving the 11-hydroxy group intact. Compound **2** (as its sodium salt) was then methylated with methyl tosylate to give (RS)-10-*tert*-butyldiphenylsilyloxy-11-methoxyaporphine (**3**). Desilylation of the compound **3** with *tetra-n*-butylammonium fluoride afforded the desired 10-hydroxy-11-methoxyaporphine-(isoapocodeine, **1c**) in excellent yield.

In conclusion, this simple synthetic procedure is the most practical one for converting apomorphine to isoapocodeine and, to the best of our knowledge, it is the first demonstration in the apomorphine series since various other methods failed to effect the direct methylation of apomorphine.

EXPERIMENTAL SECTION

Column chromatography was carried out on E. Merck silica gel 60 (230-400 mesh). Reagents were purified according to known procedures. Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Reactions were monitored by the analytical TLC using 2x5cm aluminum sheets precoated with silica gel 60 F_{254}(Merck) and detection by UV light and charring with H_2SO_4. ^1H NMR spectra were recorded on a Brucker AM-250 spectrometer with TMS as internal standard.

(RS)-10-*tert*-Butyldiphenylsilyloxy-11-hydroxyaporphine (2).- To a stirred solution of apomorphine (**1a**, 2.79g, 10.4 mmol) and imidazole (2.04g, 30 mmol) in dry DMF (40 mL) was slowly added *tert*-butyldiphenylsilyl chloride (3 mL, 11.5 mmol) in dry DMF (10 mL) under a N_2 atmosphere: the reaction mixture was stirred at rt for 5 hrs. The mixture was evaporated *in vacuo* to yield a light yellow oily residue, which was chromatographed on silica gel (CH_3OH:$CHCl_3$:NH_4OH = 1:19:0.2) to yield **2** as a colorless oil (4.36g, 83%).

^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, t-Bu), 2.84 (s, 3H, -N-CH_3), 3.25 (m, 7H, aliph-H), 5.90 (broad s, 1H, phenol, exchangeable with D_2O), 7.40-7.72 (m, 10H, Si-Ph_2; 4H, aromat-2H, 3H, 8H, 9H), 8.23 (d, 1H, aromat-1H).

Anal. Calcd. for $C_{33}H_{35}NO_2Si$: C, 78.37; H, 6.98; N, 2.77. Found : C, 78.31; H, 6.97; N, 2.69

(RS)-10-*tert*-Butyldiphenylsilyloxy-11-methoxyaporphine (3).- To a stirred solution of 57% oil suspension of NaH (0.243g, 10.11 mmol)in dry DMF (80 mL) was added 10-*tert*-butyldiphenylsilyloxy-11-hydroxyaporphine (**2**, 4.00g, 7.88 mmol), then methyl *p*-toluenesulfonate (1.69g, 9.06 mmol)

in anhydrous Et_2O (40 mL) was slowly added. The reaction mixture was stirred at rt for 13 hrs and was permitted to stand at rt for additional 10 hrs. After addition of water (120 mL) to the reaction mixture, it was concentrated, and taken up in EtOAc (150 mL) which was washed with three portions of brine (100 mLx3) and then dried ($MgSO_4$). Filtration and evaporation of the filtrate under reduced pressure gave an oily residue which was chromatographed on silica gel (hexane:EtOAc = 7:3) to yield **3** as a semi-solid (3.53g, 86%).

^{1}H NMR (DMSO-d_6) : δ 0.99 (s, 9H, t-Bu), 2.91 (s, 3H, N-CH_3), 3.02-3.74 (m, 7H,aliph-H), 3.90 (s, 3H, O-CH_3), 7.35-7.67 (m, 10H, Si-Ph_2; 4H, aromat-2H, 3H, 8H, 9H), 8.25 (q, 1H, aromat-1H).

Anal. Calcd. for $C_{34}H_{37}NO_2Si$: C, 78.57; H, 7.18; N, 2.70. Found : C, 78.41; H, 7.03; N, 2.59

(R,S)-10-Hydroxy-11-methoxyaporphine (1c).- A mixture of (R,S)-10-*tert*-butyldiphenylsilyloxy-11- methoxyaporphine (3, 5.45g, 10.45 mmol) and 1.0M *tetra-n*-butylammonium fluoride (11.32 mL, 11.32 mmol) in THF (75mL) was stirred at rt for 1 hr under a N_2 atmosphere, and the resulting reaction mixture was concentrated to dryness under reduced pressure. The foamy residue was chromatographed on silica gel and eluted with 99% EtOH. The eluate solution was taken up to pH 1 with ethanolic HCl, and was concentrated under reduced pressure to afford **1c** as an off-white solids (2.49g, 85%); mp 244 -248° (dec.).

^{1}H NMR ($CDCl_3$): δ 2.94 (s, 3H, N-CH_3), 3.75 (s, 3H, O-CH_3), 3.17-3.68 (m, 7H, aliph-H), 5.87 (broad s, 1H, phenol, exchangeable with D_2O), 7.33-7.69 (m, 4H, aromat 2H, 3H, 8H, 9H), 8.30 (q, 1H, aromat-1H).

Anal. Calcd. for $C_{18}H_{20}ClNO_2$: C, 76.84; H, 6.81; Cl, 11.66; N, 4.44
Found: C, 76.69; H, 6.80; Cl, 11.09; N, 4.49

Acknowledgement.- Financial support of this work by the Basic Science Research Institute Program, Ministry of Education (BSRI-93-308) was greatly appreciated.

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A SHORT SYNTHESIS OF TRIDEC-12-EN-2-ONE, THE MINOR CONSTITUENT OF THE BARK OF *LITSEA ELLIPTICA* (LAURACEAE)

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Several plant extracts exhibit diverse biological activities on insects *viz.* insecticidal, juvenile and antijuvenile, moulting hormonal, attractant, repellant etc. Recently, Arbain *et al.*[1] investigated a steam volatile oil obtained from the extraction of the fresh bark of *Litsea elliptica Bl.* tree which is known for its termite resistance and repellant properties. Undec-10-en-2-one (**2**) and tridec-12-en-2-one (**1**) the major and minor components of that volatile oil, were identified[1] by their spectroscopic properties.[1] Compound **1**, one of the defense secretion components of the termite soldiers *Rhinorefines Spp.*,[2] has been synthesized by a lengthy route starting from 11-dodecenal. Herein, we report a facile synthesis of **1** which establishes the structure unequivocally and provide sufficient quantities for biological evaluation.

The bifunctionalty of 10-undecenoic acid (**3**) an easily accessible and inexpensive material, has been explored by us in the synthesis of some natural products[3-5] and prostanoid synthons.[6] Our approach involves yet another example of the usefulness of **3**. LAH reduction of its methyl ester followed by bromination with PPh_3Br_2[5,7] resulted in bromide **4**. The latter on reaction with sodium acetylide[7,8] gave enyne **5**; it is to be noted that **5** is also useful as a versatile synthon for the preparation of several insect pheromones.[9] The acetylene function in enyne **5** on hydration in aq. methanol containing catalytic amount of Hg^{2+} ions and H_2SO_4[10,11] yielded the title compound **1**. Its physical and spectral data are in agreement with those reported,[1] thus confirming the structure of the natural product.