Highly Efficient Synthesis of Optically Active Drimanic Sesquiterpenes, (+)-Fuegin, (+)-Epifutronolide (7β-Hydroxyisodrimenin) and (+)-7-Ketoisodrimenin.

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Abstract: A highly efficient synthesis of (+)-fuegin **4**, (+)-7-epifutronolide (7β-hydroxyisodrimenin) **5a** and (+)-7-ketoisodrimenin **6** from manool **1**, is reported. © 1999 Elsevier Science Ltd. All rights reserved.

We have recently elaborated a highly efficient strategy for the synthesis of the optically active drimane-type sesquiterpenes, (+)-confertifolin, (+)-isodrimenin, (+)-euryfuran, (-)-warburganal, (+)-albicanol, (+)-bicyclofarnesol,[1] (+)-valdiviolide and (+)-winterin.[2] The key step in this strategy was the Norrish type II cleavage of the ketone **2**, obtainable from the oxidation of commercially available manool **1**, to the diene **3**[3] (53% overall yield). Compound **3** served as a common precursor for the synthesis of these natural products.

Scheme 1

| 1 | 2 | 3 |

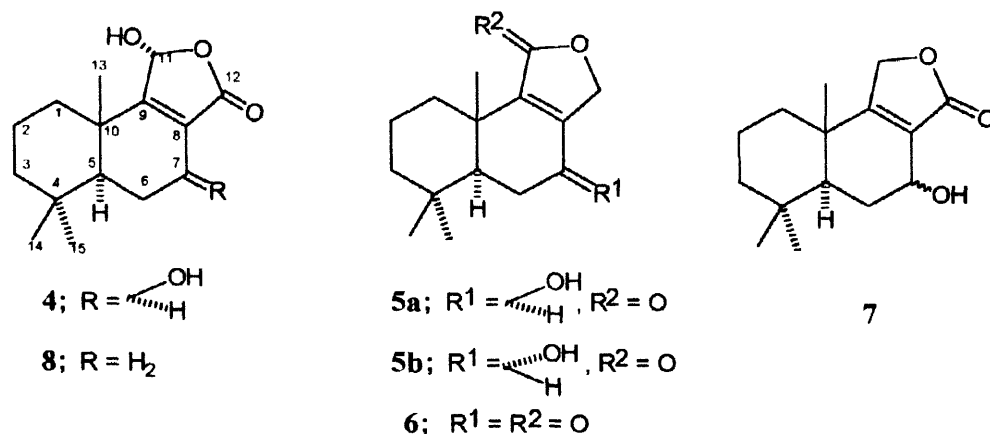* Corresponding author: Fax: (582)5041350; E-mail: tnakano@quimica.ivic.ve

This paper presents a further extension of our work to the synthesis of (+)-fuegin **4**, (+)-7-epifutronolide (7β-hydroxyisodrimenin) **5a** and (+)-7-ketoisodrimenin **6**.


4; R = ⟋OH / H

8; R = H₂

5a; R¹ = ⟋OH / H , R² = O

5b; R¹ = ⟋OH / H , R² = O

6; R¹ = R² = O

7

In 1963 Appel et al.[4] isolated (+)-fuegin **4** and (+)-futronolide from *Drimys winteri* Forst. In 1993 Kingston et al.[5] reported the isolation of (+)-7-ketoisodrimenin **6** from *Porella cordeana* (Hueb). (+)-Futronolide has been assigned the structure **7** by Appel et al., but Kitahara et al. [6] later synthesized (±)-futronolide and reported that its structure should be formulated as **5b** and the 7-epimer, as **5a**.

For the synthesis of (+)-fuegin **4** we first thought of oxidizing (+)-valdiviolide **8**, synthesized earlier by us,[2] after protecting its 11-OH group. However, when this oxidation was attempted with various known reagents, either recovered starting material or a complex mixture of products resulted. Therefore, for the synthesis of the title three sesquiterpenes we have proceeded in the following way. The olefinic 1,4-diol **9a**, prepared by the photo-oxygenation of the diene **3**, followed by the reduction of the resulting *endo*-peroxide with lithium aluminum hydride, as previously described,[7] was converted with acetic anhydride-pyridine to the acetate **9b** (100%). This acetate was then oxidized with chromium trioxide-acetic acid to the 7-keto-derivative **10a**[8] (69%). Hydrolysis of this compound was then attempted with 10% methanolic sodium hydroxide in order to obtain the 7-keto olefinic 1,4-diol **10b**. However, the product was found not to be compound **10b**, but a 3:1 mixture of the hemiacetals **11a,b** (50% yield). Separation of these two epimers was not attempted and their structures were assigned on the basis of their ^{1}H and ^{13}C NMR spectra. The presence of the hemiacetal moieties was confirmed by the signals at δ_H 6.19 (1H, m) and δ_C 103.1 and at δ_H 6.12 (1H, m) and δ_C 101.7, the intensities of which signals were 3:1, respectively. These signals must result from the -CH(OH)-O- grouping at C-11. The two protons at C-12 resonated at δ 4.82 (2H, m) and 4.58 (2H, m). That the OH group was situated at C-11 (not at C-12) was verified by oxidation of this mixture of hemiacetals with pyridinium chlorochromate[9] to (+)-7-ketoisodrimenin **6** (88%). The regioselective aerial oxidation of **10b** to **11a,b** may reasonably be explained as follows. Removal of a hydrogen atom from the carbinol carbon at C-9 to form the conjugated radical would be faster than hydrogen abstraction from the carbinol carbon at C-8 to form the cross conjugated radical. The resulting

aldehyde group at C-9 would then form a mixture of epimeric hemiacetals with the adjacent OH group at C-8.

Scheme 2
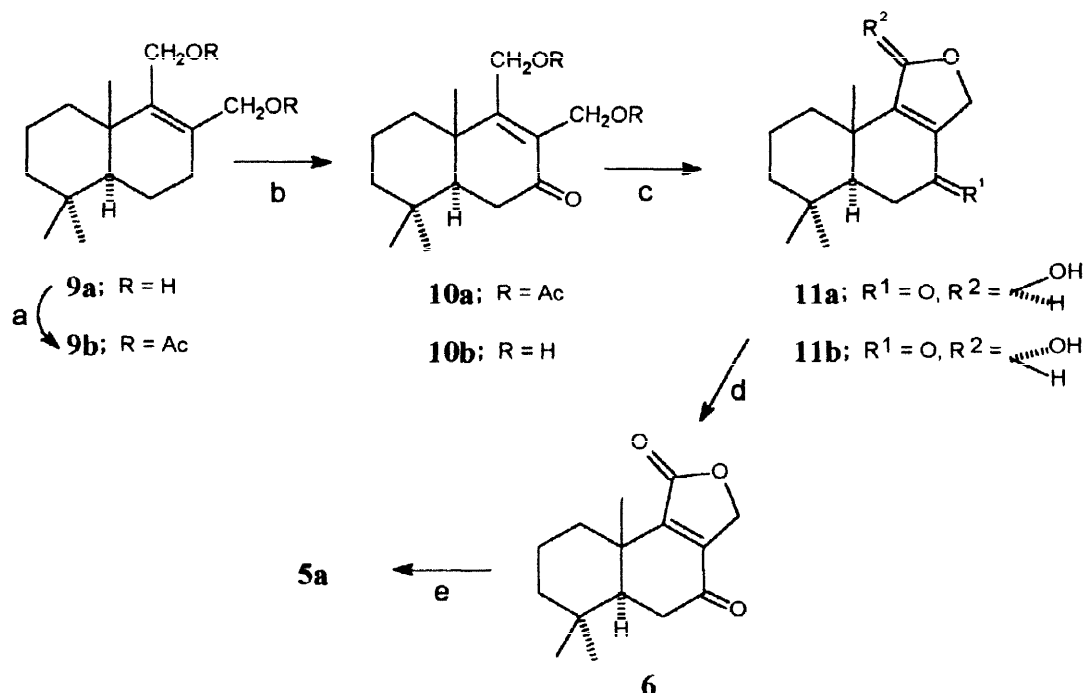
(a) Ac₂O, pyridine; (b) CrO₃, AcOH; (c) 10% methanolic NaOH; (d) pyridinium chlorochromate, CH₂Cl₂; (e) NaBH₄, EtOH.

Reduction of compound **6** with sodium borohydride gave (+)-7-epifutronolide (7β-hydroxyisodrimenin) **5a** (86%). The β (equatorial) stereochemistry of the 7-OH group was deduced from the ¹H NMR spectrum. The 7-proton absorbed at δ 4.50 (1H, m, half-height width 17 Hz), which indicated that it was axially oriented.

For the synthesis of (+)-fuegin **4** we have utilized the hemiacetals **11a,b**. On dehydration with thionyl chloride-pyridine compounds **11a,b** afforded 7-ketoeuryfuran **12a** (78%). The presence of a furan ring was demonstrated by the proton signals at δ 7.12 (1H, d, *J* 1.4 Hz, 11-H) and 7.86 (1H, d, *J* 1.4 Hz, 12-H). Reduction of compound **12a** with sodium borohydride yielded 7-hydroxyeuryfuran **12b** (94%). In the ¹H NMR spectrum of this compound, two furanoid protons resonated at δ 7.03 (1H, d, *J* 1.4 Hz) and 7.36 (1H, dd, *J* 1.4, 1.4 Hz). The proton at C-7 absorbed at δ 4.73 (1H, ddd, *J* 9.8, 7.1, 1.4 Hz, half-height width 15 Hz), indicating that it was axially oriented.

Photo-oxygenation of compound **12b** in *t*-butyl alcohol-2,6-lutidine (2:1) containing eosin[10] afforded a butenolide (40%). Its structure was deduced from 2D NMR ^{1}H and ^{13}C-single bond and multiple bond correlation studies. The carbonyl carbon signal appeared at δ 171.4. The tetra-substituted double bond carbons resonated at δ 128.5 and δ 170.5. The signal at higher field (δ 128.5) must be due to the carbon adjacent to the CO group. The other olefinic carbon at lower field (δ 170.5) showed correlation through three bonds to the C-13 methyl protons (δ 1.29) and also through two bonds to the carbon bearing the OH group which resonated at δ 97.84. The 7-proton appeared at δ 4.54 (1H, ddd, *J* 9.8, 7.1, 1.4 Hz, half-height width 15 Hz), indicating that it was axially oriented and hence the 7-OH group should possess the β configuration.[11] The foregoing results evidenced that this butenolide should be formulated as **4**. Its identity with (+)-fuegin has been established by comparison with physical as well as spectroscopic data.

Scheme 3

11a,b $\xrightarrow{\text{a}}$

12a; R = O
12b; R = $\sim$OH / H

4
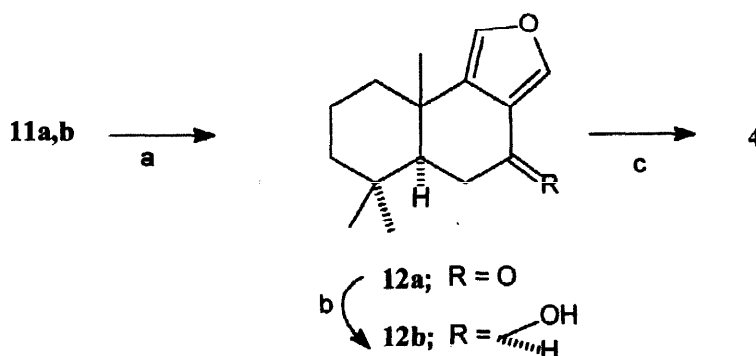
(a) SOCl₂, pyridine; (b) NaBH₄, EtOH; (c) ^{1}O₂, eosin, t-BuOH-2,6-lutidine (2:1).

The α stereochemistry[11] of the 11-OH group in fuegin was deduced from the reaction mechanism of the photo-oxygenation. The oxygenation must have taken place from the less sterically hindered α-face of the furan ring. Subsequent breakdown of the resulting α-*endo*-peroxide **13** would produce the biradical species **14**. The reaction would then terminate by disproportion in two ways, as illustrated in Scheme 4. One would lead to fuegin **4**, while the other would result in the formation of its 11-keto isomer **15**.

In the photo-oxygenation[2] of euryfuran (R=H₂ in formula **12a**), both 11- and 12-keto isomers had been obtained. However, in that of compound **12b** possessing a hydroxyl group at C-7, the 11-keto isomer **15** was not detected. This suggested that the 7-hydroxyl group in **12b** would facilitate the formation of thermodynamically more stable 12-keto isomer **4** by hydrogen bonding.

Scheme 4

13   →   14

4   15
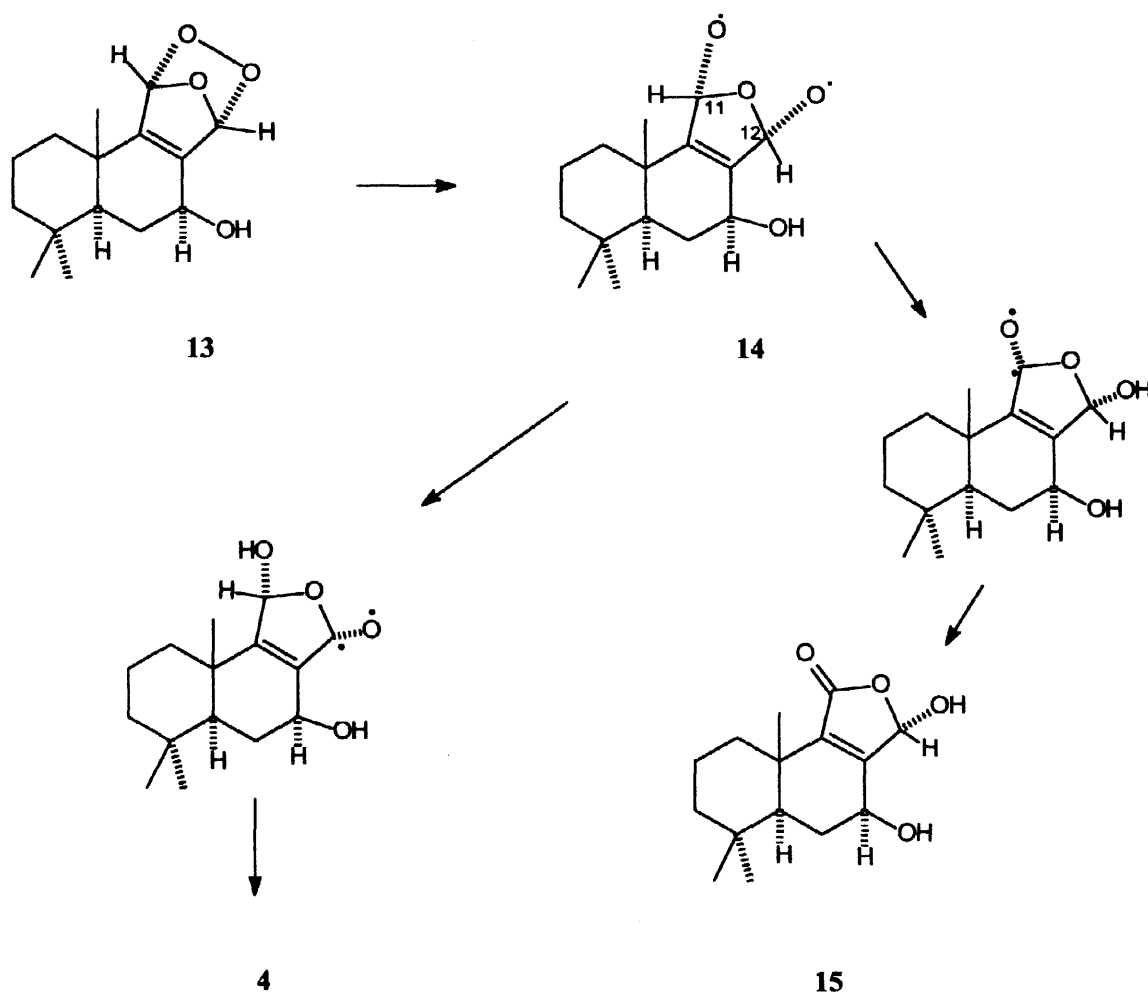
EXPERIMENTAL

Melting points were measured with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded with a Bruker AM-300 spectrometer for solutions in $CDCl_3$. Mass spectra were determined with a Kratos MS25RFA at 70 eV using a direct inlet system. Rotations were measured at 23°C with a Zeiss '0.01' polarimeter. Merck silica gel (70-230 mesh ASTM) was used for column chromatography. TLC plates were prepared on Merck silica gel 60 G_{254} and the spots were observed either by exposure to iodine vapour or by UV light. All organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure below 60°C.

Acetylation of the olefinic 1,4-diol 9a. Compound 9a (0.180 g) was treated with acetic anhydride-pyridine (1:2, 5 ml) at room temperature for 3 h. Usual work-up afforded compound 9b[8] (0.251 g, 100%) as

an oil; δ_H (300 MHz) 0.82 (3H, s, Me), 0.87 (3H, s, Me), 0.97 (3H, s, 13-Me), 2.0 (3H, s, Ac), 2.02 (3H, s, Ac) and 4.4-4.6 (4H, m, 11- and 12-H).

Oxidation of compound 9b. To a solution of compound 9b (0.210 g) in acetic acid (5 ml) was added chromium trioxide (0.195 g) and the mixture was left under stirring at room temperature overnight. Water was added, the product was extracted with ether and then chromatographed over silica gel. Elution with hexane-ether (9:1) afforded compound 10a[8] (0.150 g, 69%) as an oil; δ_H (300 MHz) 0.81 (3H, s, Me), 0.84 (3H, s, Me), 1.08 (3H, s, 12-Me), 4.73 (2H, AB system, J 12 Hz, CH_2OAc) and 4.74 (2H, broad s, CH_2OAc).

Alkaline hydrolysis of compound 10a. Compound 10a (0.24 g) was stirred with 10% methanolic potassium hydroxide (5 ml) at room temperature for 12 h. Water was added and the product was extracted with ether. The crude product obtained was chromatographed over silica gel. Elution with 40% ether in hexane afforded a mixture of hemiacetals 11a and 11b (0.12 g, 50%) as crystals, m.p. 161-163°C; m/z 232 (M^+-18); δ_H (300 MHz) 0.87 (3H, s, Me), 0.88 (3H, s, Me), 0.94 (6H, s, two Me). 1.31 (6H, s, two 13-Me), 4.58, 4.82 (2H each, m, 12-H) and 6.12, 6.19 (1H each, m, 11-H); δ_C (75.45 MHz) 34.5 (C-1), 18.0, 18.1 (C-2), 41.1, 41.0 (C-3), 32.6, 32.8 (C-4), 52.6 (C-5), 35.9 (C-6), 197.5 (C-7), 133.9 (C-8), 165.6 (C-9), 36.8, 36.9 (C-10), 103.1 (C-11), 71.3 (C-12), 18.4 (C-13), 21.1, 21.1 (C-14) and 33.9, 33.1 (C-15).

Oxidation of the mixture of compounds 11a and 11b. A mixture of compounds 11a and 11b (27 mg) was dissolved in dichloromethane (4 ml) and oxidized with pyridinium chlorochromate (34.6 mg) at room temperature for 1 h. The reaction mixture was filtered on silica gel and the filtrate was evaporated. The resulting crude product was chromatographed over silica gel. Elution with hexane-ether afforded compound 6, m.p. 109-111°C (23 mg, 88%); $[\alpha]_D$ +40° (c 1.5); literature data[5]: amorphous powder, $[\alpha]_D$ +40° (c 0.6, $CHCl_3$); ν_{max} 1768 (lactone CO) and 1690 (C=O); m/z 248 (M^+); δ_H (300 MHz) 0.90, 094 (3H each, s, Me), 1.26 (3H, s, 13-Me), 1.85 (1H, dd, J 13.9, 3.3 Hz, 5-H), 2.47 (1H, dd, 17.6, 13.9 Hz, 6-axial H), 2.62 (1H, dd, J 17.6, 3.3 Hz, 6-equatorial H) and 4.80 (2H, s, 12-H); δ_C (75.45 MHz) 33.2 (C-1), 17.9 (C-2), 41.1 (C-3), 33.1 (C-4), 52.0 (C-5), 36.1 (C-6), 196.3 (C-7), 149.0 (C-8), 152.5 (C-9), 36.7 (C-10), 170.8 (C-11), 67.2 (C-12), 18.0 (C-13), 20.9 (C-14) and 32.8 (C-15).

Reduction of compound 6 with sodium borohydride. Compound 6 (0.1 g) in ethanol (5 ml) was treated with sodium borohydride (13.3 mg) at room temperature for 30 min. After addition of water the product was extracted with ether and then chromatographed over silica gel. Elution with 25% ether in hexane afforded compound 5a, m.p. 166-168°C (86 mg, 86%); $[\alpha]_D$ + 27° (c 3.1); m/z 250 (M^+); δ_H (300 MHz) 0.91, 0.95 (3H each, Me), 1.12 (3H, s, 13-Me), 4.50 (1H, m, half-height width 17 Hz) and 4.64, 4.85 (1H each, d, J 17 Hz, 12-H); δ_C (75.45 MHz) 34.0 (C-1), 18.1 (C-2), 41.3 (C-3), 32.8 (C-4), 51.2 (C-5), 29.2 (C-6), 69.2 (C-7), 160.2 (C-8), 136.6 (C-9), 35.4 (C-10), 172.5 (C-11), 67.8 (C-12), 19.8 (C-13), 21.4 (C-14) and 33.3 (C-15).

Dehydration of the mixture of compounds 11a and 11b. To a solution of the mixture of compounds 11a and 11b (0.1 g) in pyridine (5 ml) was added with stirring four drops of thionyl chloride. After 15 min, water was added and the product was extracted with ether. Chromatography over silica gel with 2% ether in hexane afforded compound 12a (72 mg, 78%) as an oil; δ_H (300 MHz) 0.88, 0.91, 1.21 (3H each, s, Me), 2.39-2.57 (2H, m, 6-H), 7.12 (1H d, J 1.4 Hz, 11-H) and 7.86 (1H, d, J 1.4 Hz, 12-H); δ_C (75.45 MHz) 51.1 (C-5), 196.7 (C-7), 123.0, 135.8, 138.5 and 144.1 (furanoid carbons) (Found: M^+, 232.1458. $C_{15}H_{20}O_2$ requires 232.1463).

Reduction of compound 12a with sodium borohydride. Compound 12a (96 mg) in ethanol (5 ml) was treated with sodium borohydride (23.4 mg) at room temperature for 1 h. The product was worked up as usual. Compound 12b (91 mg, 94%) was obtained as a semi-solid; δ_H (300 MHz) 0.87, 0.90, 1.21 (3H, s, Me), 4.73 (1H, ddd, J 9.8, 7.1, 1.4 Hz, half-height width 15 Hz, 7-H), 7.03 (1H, d, J 1.4 Hz) and 7.36 (1H, dd, J 1.4, 1.4 Hz); δ_C (75.45 MHz) 50.6 (C-5), 66.4 (C-7), 125.0, 135.2, 136.9, 138.9 (furanoid carbons) (Found: M^+, 234.1622. $C_{15}H_{22}O_2$ requires 234.1619).

Photo-oxygenation of compound 12b. A solution of compound 12b (105 mg) in t-butyl alcohol-2,6-lutidine (9 ml, 2:1) containing eosin (3 mg) was irradiated with an external 150 W tungsten lamp for 166 h during which time oxygen was bubbled through the reaction mixture. The temperature in the reaction flask was maintained at 15°C. Solvent was removed from the reaction mixture under reduced pressure and the residue was submitted to column chromatography over silica gel. Elution with 60% ether in hexane afforded compound 4, m.p. 174-176°C (42 mg, 40%); $[\alpha]_D$ + 50° (c 1.8); literature data[4]: m. p. 170-172°, $[\alpha]_D$ +76° (c 1.1, CHCl₃); δ_H (300 MHz) 0.90 (6H, s, 2-Me), 1.29 (3H, s, 13-Me), 4.54 (1H, m, half-height width 15 Hz, 7-H) and 6.05 (1H, d, J 1.4 Hz, 11-H); δ_C (75.45 MHz) 34.8 (C-1), 18.0 (C-2), 41.2 (C-3), 33.1 (C-4), 51.1 (C-5), 27.6 (C-6), 64.9 (C-7), 128.5 (C-8), 170.5 (C-9), 37.9 (C-10), 97.8 (C-11), 171.4 (C-12), 19.8 (C-13), 21.5 (C-14) and 33.2 (C-15).

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11.   The stereochemistries of the 7- and 11-OH groups in (+)-fuegin **4** have remained to be established (see ref. 4)