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SYNTHESIS OF RETROFRACTAMIDE A

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Key Word Index—*Piper retrofractum*; Piperaceae; alkaloid; retrofractamide A; synthesis.

Abstract—The synthesis of the isobutylamide retrofractamide A is described.

Retrofractamide A, a new unsaturated isobutylamide, was isolated and characterised by us from *Piper retrofractum* [1]. The present communication reports its synthesis by a sequence whose two key steps involve stereoselective Wittig reactions. γ-Butyrolactone was converted by refluxing with a large excess of ethanolic sulphuric acid to ethyl 4-hydroxybutanoate. This was oxidised to ethyl 3-formylpropanoate by pyridinium chlorochromate (PCC). Wittig reaction of this aldehyde with the ylid derived from piperonyl triphenylphosphonium bromide and sodium hydride in DMSO occurred stereoselectively to generate ethyl-5[3′,4′-methylenedioxyphenyl]-4-pentenoate (**1**) with an *E*:*Z* ratio of 9:1 as revealed by ^{1}H NMR. Lithium aluminium hydride reduction of (**1**) in benzene furnished alcohol (**2**), which was then oxidised to aldehyde (**3**) by PCC. A Wittig–Horner–Emmons reaction with methyl 4-diethylphosphono-*E*-crotonate and NaH in DMF occurred with high stereoselectivity to give the 2*E*,4*E*-dienoate ester (**4**). Hydrolysis to acid (**5**) followed by conversion to the acyl chloride (**6**) and subsequent treatment with excess *iso*-butylamine in dry ether furnished the crude amide (**7**) consisting of a *ca* 17:3 ratio of the 2*E*, 4*E*, 8*E* and 2*E*, 4*E*, 8*Z* isomers. Chromatography and repeated crystallization furnished the pure *N*-isobutyl-(3′,4′-methylenedioxyphenyl) 2*E*,4*E*,8*E*-nonatrienamide which was identical in all respects with retrofractamide A (mp, mmp, superimposable IR and ^{1}H NMR spectra). The structure and stereochemistry of retrofractamide A are thus confirmed.

EXPERIMENTAL

Mps are uncorr. ^{1}H NMR spectra were recorded at 80 or 100 MHz.

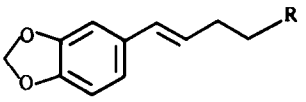
Ethyl 4-oxobutanoate. γ-Butyrolactone (11.5 g, 103 mmol) was refluxed with dry EtOH (60 ml) and Amberlyst-15 (5 g) for 24 hr. The resin was filtered off and the filtrate fractionated under red. pres. to give 3.2 g of a 5:1 mixture of ethyl-4-hydroxybutanoate and γ-butyrolactone. IR (neat) ν_{max} cm^{-1}: 3400–3500 (*br*, –OH); 1725, 1250–1280, 1200 (–CO_2Et); 1770 (γ-butyrolactone). The reaction was also done with conc H_2SO_4 as the catalyst when 7.67 g of the crude product was obtained from 20.85 g of the lactone.

The crude ethyl 4-hydroxybutanoate (10.5 g, ~ 70 mmol) in dry CH_2Cl_2 (25 ml) was added with stirring to a suspension of pyridinium chlorochromate (PCC) (32.3 g) in dry CH_2Cl_2 (150 ml). Stirring was continued for 2 hr after which dry Et_2O was added. The supernatant was decanted from the black gum and the insol. residue washed thoroughly with Et_2O (5 × 50 ml). The combined organic soln was filtered through a bed of Florisil and the solvent removed by dist. The residue was distd under red. pres. to obtain ethyl 4-oxobutanoate [3] (4.5 g) at 84°/12 mm. IR (neat) ν_{max} cm^{-1}: (no –OH band), 1720 (> C=O), 1275, 1200, 1050 (ester).

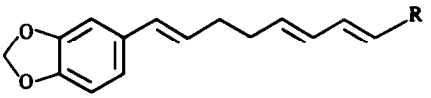
Ethyl-5-(3′,4′-methylenedioxyphenyl)-4-pentenoate (**1**). NaH (0.8 g, 33 mmol, 1.6 g of 50% oil dispersion) was added to dry DMSO (30 ml) and stirred for 1 hr under N_2. Triphenyl piperonyl phosphonium bromide [1] (15 g, 31 mmol) was then added with stirring, the flask being cooled by ice. An orange colour immediately developed and stirring was continued for another 10 min. Ethyl 4-oxobutanoate (3.5 g, 30 mmol) in DMSO (10 ml) was added dropwise over 45 min with stirring at room temp. The reaction mixt was stirred overnight, then dil. with H_2O and extd with Et_2O. Chromatography of the extd material over silica gel afforded (**1**) (2.9 g, 41%) as an oily liquid in the petrol–C_6H_6 (1:1) eluate. IR ν_{max}^{Nujol} cm^{-1}: 1735 (C=O), 1612 (C=C), 870, 812 (1,2,4-trisubstituted benzene), 1040, 932 (methylenedioxy). 80 MHz ^{1}H NMR ($CDCl_3$): δ6.5–6.8 (3H, *m*, Ar-H), 6.18 (*d*, *J* = 13.8 Hz, (C-5H), 5.7 (*dt*, *J* = 13.8, 6.4 Hz, C-4 H), 5.93 (2H, *s*, –O–CH_2–O–), 4.12 (2H, *q*, *J* = 6.9 Hz, –O<u>CH_2</u> Me), 2.4–2.7 (4H, *m*, –CH_2–CH_2–), 1.25 (3H, *t*, *J* = 6.9 Hz, –OCH_2–<u>Me</u>). A *d* at δ6.12 (*d*, *J* = 10 Hz, C-5H) and a *m* at *ca* δ5.4 (C-4 H) corresponded to the *Z*-isomer. Integration showed that the *E*:*Z* ratio was *ca* 9:1.

5-(3′,4′-methylenedioxyphenyl-4-pentenal (**3**). **1** (2.8 g, 12 mmol) in C_6H_6 (20 ml) was added to a well-stirred suspension of $LiAlH_4$ (1 g) in C_6H_6 (100 ml) and the mixt heated to 60° for 8 hr. The reaction mixt. was decomposed with satd aq. sodium potassium tartarate and extd with Et_2O (4 × 50 ml). The combined organic extract containing (**2**) was dried and the solvent removed. To a well-stirred soln of PCC (5.5 g) in dry CH_2Cl_2 (30 ml) was added crude (**2**) in dry CH_2Cl_2 (20 ml) at room temp. Stirring was continued for 1.5 hr at room temp; the reaction mixt turned into a black gummy mass. Dry ether (100 ml) was added and the supernatant decanted. The black gum was washed several times with anhydrous Et_2O (5 × 20 ml) and the combined Et_2O extracts filtered through a pad of Florisil. Most of the solvent was removed by dist. and the residue chromatographed over silica gel. 5-(3′,4′-methylenedioxyphenyl)-4-pentenal (**3**) (1.22 g, 50%) was obtained as a gummy mass in the C_6H_6–EtOAc (9:1) eluates. IR ν_{max}^{Nujol}: 1720 (C=O), 1600 (C=C), 925 (*E*-double bond).

Unsaturated ester (**4**). Methyl-4-diethylphosphono-*E*-crotonate (635 mg, 5 mmol) in dry DMF (5 ml) was added dropwise to a slurry of NaH (120 mg, 5 ml) in dry DMF (20 ml) at 5°. The mixt was stirred at this temp. for 30 min and then the aldehyde (**3**) (900 mg, 4.5 mmol) in DMF (5 ml) was added



1 R = —CO_2Et
2 R = —CH_2OH
3 R = —CHO



4 R = —CO_2Me
5 R = —CO_2H
6 R = —COCl
7 R = —CONH

dropwise. After stirring for 2 hr at 5°, the mixt was allowed to warm up to room temp. and it was then stirred for an additional 16 hr. The reaction mixt. was dil. with H_2O and then extd with Et_2O. The thick oily residue of the ester (**6**) (400 mg, 33%), obtained on removal of the solvent was directly used in the next step. IR (neat) ν_{max} cm^{-1}: 1715 (C=O), 990 (C=C), 1040, 940 (–OCH_2–O–).

Retrofractamide A. The ester (**4**) (400 mg, 1.48 mmol) was refluxed for 3 hr with 10% ethanolic KOH (25 ml). The solvent was removed, the residue dil with H_2O (20 ml) and then acidified with 4N HCl. The pptd acid (**5**) was filtered off, washed with H_2O and dried *in vacuo*. The crude acid was suspended in dry C_6H_6 (10 ml) and treated with excess oxalyl chloride (400 mg) at room temp. under N_2. The soln was stirred for 30 min, then refluxed for another 30 min. The solvent and excess reagent were removed under red. pres. and the thick oily residue of the acyl chloride (**6**) taken up in dry Et_2O (50 ml). Isobutylamine (350 mg) in dry Et_2O (5 ml) was added and the reaction mixt. stood for 2 hr. It was then washed with cold 1 N H_2SO_4 (5°), dried and the solvent evapd. The crude product consisted of a *ca* 17:3 mixture of the 2*E*,4*E*,8*E* and 2*E*,4*E*,8*Z* isomers, respectively, as apparent from ^{1}H NMR analysis of the sample after D_2O exchange (a weak *m* was detected at δ5.5–5.6 corresponding to the 8*Z* isomer integrating for *ca* 15% of C-2 H *d* at δ5.76 [1]. On silica gel chromatography the material from the C_6H_6–EtOAc (5:1) eluates was repeatedly recrystallized from MeOH to give pure *N*-isobutyl-9(3',4'-methylenedioxyphenyl)-2*E*,4*E*,8*E*-nonatrienamide (**7**) (95 mg), mp 125°, (lit. [1] 129°) which was identical in all respects with naturally occurring retrofractamide A, (mp, mmp, superimposable IR and ^{1}H NMR spectra [1], 100 MHz ^{1}H NMR ($CDCl_3$): δ7.12 (*dd*, *J* = 15, 10 Hz, C-3H), 6.88 (*br s*, C-6'H), 6.67 (*br s*, C-2'H and C-5'H), 6.42–6.02 (*br m*, C-4H, C-5H, C-8H and C-9H). 6.93 (*s*, –O–CH_2–O–), 5.76 (*d*, *J* = 15 Hz, C-2H), 5.35–5.6 (*br s*, –NH– exchangeable with D_2O), 3.16 (*t*, *J* = 7 Hz, –NH–$\underline{CH_2}$–), 2.16–2.38 (*m*, allylic –CH_2), 1.48–1.92 (*br m* –$\underline{CH}Me_2$), 0.92 (*d*, *J* = 7 Hz, –$CH\underline{Me_2}$).

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