Pergamon

Tetrahedron Vol. 50, No. 38, pp. 11113-11122, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00695-4

Concise, Efficient New Synthesis of Pipercide, an Insecticidal Unsaturated Amide from *Piper nigrum*, and Related Compounds[1]

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Key Words: Piper; insecticides; aldol; fragmentation; bis[N,N-bis(trimethylsilyl)amino]tin(II).

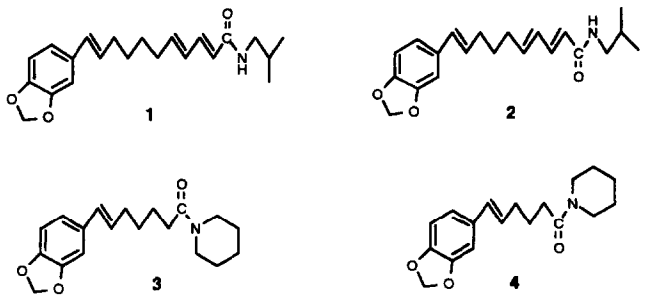
Abstract: *Pipercide and piperolein A, unsaturated amides from Piper nigrum, were prepared in overall yields of 21% and 35% respectively, by a new, short and efficient strategy, in which the key step was the aldol-Grob-type fragmentation sequence recently reported by Sakai et al.. (but using propylene- rather than ethylene glycol) . The nor-homologues of these natural products were similarly prepared. In the final steps, the amides could be prepared directly from the esters by Roskamp's method involving treatment with $Sn[N(TMS)_2]_2$ and the appropriate amines, or from the corresponding carboxylic acids by conventional methodology.*

Problems associated with the widespread use of broad-spectrum synthetic pesticides in agriculture and forestry, as well as heightened public concern about environmental issues, have stimulated the quest for more selective and less persistant pest control agents from natural sources. Thus, for example, *Bacillus thuringiensis* has found favour as an operational insecticide in protection of the spruce-fir forests of eastern North America against the depredations of the spruce budworm, *Choristoneura fumiferana*.[2] Research on the redoubtable botanical insecticide-antifeedant azadirachtin from the neem tree, indicates that it shows considerable potential as a control agent for *C. fumiferana*,[3] as it does for many important insect pests.[4] Other botanical sources of insecticidal natural products include, *inter alia*, members of the Compositae, Piperaceae, and Rutaceae families, whose bioactive principles are straight-chain unsaturated amides.[5,6]

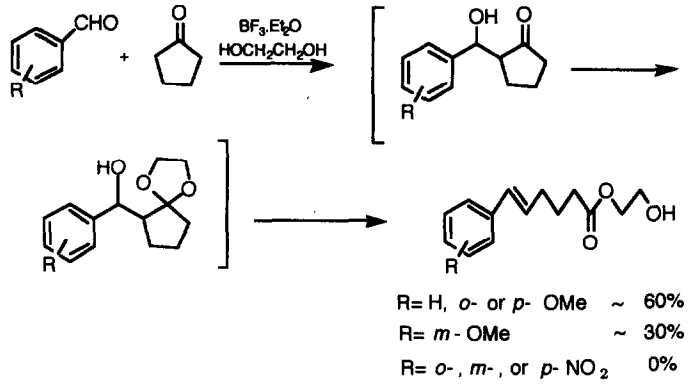
The insecticidal unsaturated isobutylamide pipercide, **1**,[7] and the piperidinylamide piperolein A, **3**,[8] are examples of products isolated from black pepper, *Piper nigrum*. Pipercide has been synthesized by several routes, generally involving some nine to twelve steps, and in rather modest overall yields.[6,7,9]

We describe here a new, concise, and efficient synthetic route to pipercide, **1**, norpipercide, **2**, piperolein A, **3**, and its nor-homologue, **4**, based on a modification of the aldol condensation-Grob-type fragmentation sequence recently reported by Sakai *et al.* [10] In an example described by these authors, reaction of cyclopentanone with benzaldehyde in the presence of BF_3-etherate and ethylene glycol yielded stereoselectively the ethylene glycol ester of 6-phenyl-5*E*-hexenoic acid in 61% yield, as depicted in Scheme 1.

This paper is dedicated to Professor Wesley Cocker, who in his 87th year is still active in research and retains the infectious enthusiasm for organic chemistry that has been an inspiration to generations of his students at Trinity College Dublin.



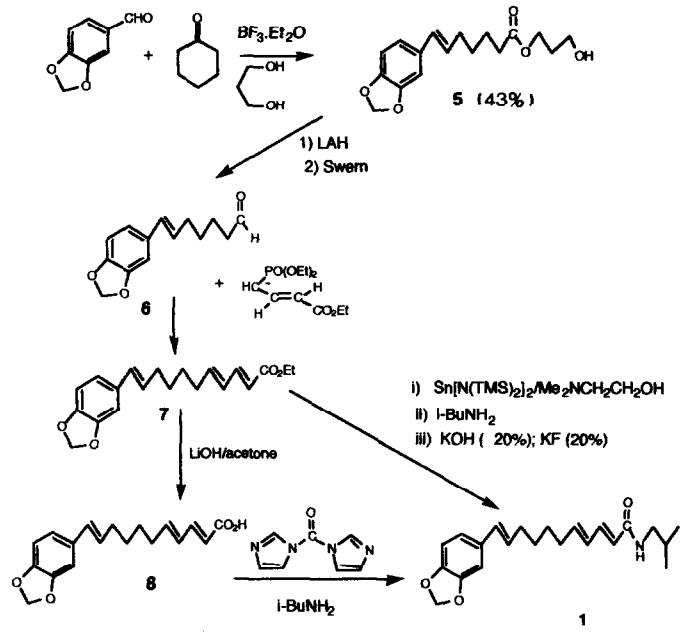
Electron-releasing substituents (OMe) in the *ortho* and *para* positions had little effect on the yield, but a *meta*-methoxyl substituent in the aromatic ring caused the yield to drop to 30%. When an electron-withdrawing group such as nitro was present in any position on the ring, only the acetal of the corresponding nitrobenzaldehyde was obtained.



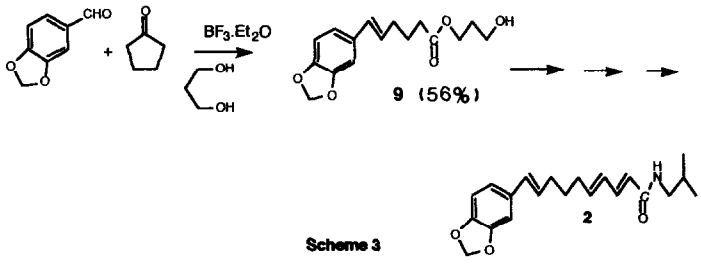
Scheme 1

Notwithstanding some reduction in yield expected to be associated with the *meta* ether component of the methylenedioxy group, we have found that the Sakai methodology, in modified form, provides an expedient synthetic entry to some of the *Piper* amides as well as their homologues (Schemes 2-5).

In the reaction of aryl aldehydes, e.g., piperonal, with cyclohexanone (or cyclopentanone) and ethylene glycol under boron trifluoride catalysis, we have observed that the yield was significantly influenced by the amount of time allowed for the initial aldol condensation before the addition of ethylene glycol, and this required optimization for each system. In general, the aldol reactions involving cyclohexanone required less time than those with cyclopentanone.

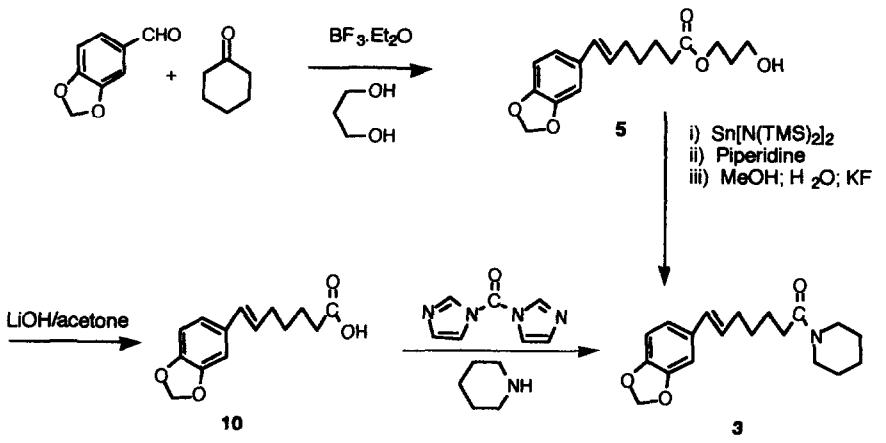


Scheme 2

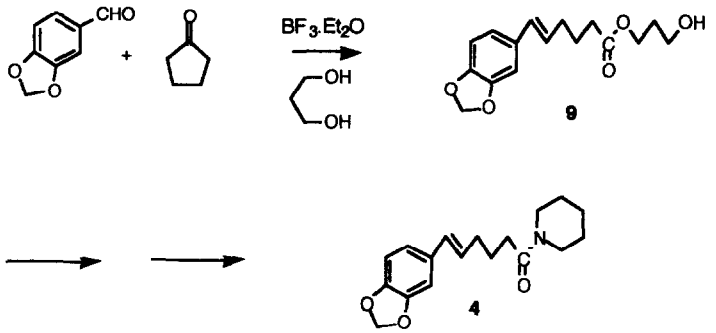


Scheme 3

Under appropriate conditions, yields of the ethylene glycol ester of stereochemically pure 7-(3,4-methylenedioxyphenyl)-6*E*-heptenoic acid of up to 22% could be obtained. Significantly improved yields in the Grob-type fragmentation could be realized, *via* the *1,3-dioxane* rather than the *1,3-dioxolane*, by substituting *1,3-propanediol* for *ethylene glycol*. This result may be rationalized on the grounds of stereoelectronic effects,[11] with electron pairs of the two acetal oxygens more readily adopting an antiperiplanar orientation with respect to the fragmenting bond in the spiro 1,3-dioxane than in the dioxolane system. Thus, the boron trifluoride-catalyzed reaction of piperonal and cyclohexanone, with subsequent addition of 1,3-propane diol, gave the ester **5** in 43% yield (Scheme 2). Lithium aluminum hydride (LAH) reduction of **5**, followed by Swern oxidation, proving to be superior to direct DIBAL reduction, afforded the aldehyde **6** in 76% yield.



Scheme 4



Scheme 5

Generation of the ylid of triethyl 4-phosphonocrotonate for the subsequent Wadsworth-Emmons reaction with *n*-butyllithium, gave a substantially better yield (84%) of **7** than use of sodium ethoxide for this purpose.[6]

The synthesis was completed by hydrolysis to the acid and coupling with isobutylamine as depicted in Scheme 2, and afforded pipercide (2*E*, 4*E*, 10*E*) in an overall yield (from piperonal) of 21%. The alkaloid thus synthesized exhibited physical and spectroscopic characteristics in full accord with published data.[6,7] Alternatively, the ethyl ester **7** could be converted *directly*, but in only modest yield, to pipercide by treatment with bis[N,N-bis(trimethylsilyl)amino]tin(II) and isobutylamine, using Roskamp's recently reported method.[12] (Scheme 2).

The synthesis of the lower homologue, nor-pipercide, **2**, from piperonal and cyclopentanone was completed analogously (*via* the carboxylic acid) in 34% overall yield, as shown in Scheme 3.

Clearly, the ester **5**, from piperonal and cyclohexanone, is also a ready precursor of the *P. nigrum* amide, piperolein A, **3**,[8], and it was transformed into this natural product by one or two simple steps (*vide supra*) in a yield of 82% (Scheme 4). In a like manner, nor-piperolein A was synthesized from the piperonal-cyclopentanone product, in a yield of 83%. (Scheme 5). In the direct conversion of these glycol esters to the amides through the agency of the bis[N,N-bis(trimethylsilyl)amino]tin(II)-amine reagent, we found that the transformation, although giving excellent yields, proceeds somewhat more slowly for the propylene- than the corresponding ethylene glycol esters (82-95%). This observation seems to be consistent with the proposed mechanism[12b] involving intramolecular delivery of the amine, a process that might be expected to be somewhat less favorable in the former than the latter cases.

Other approaches to abbreviated efficient syntheses of *Piper* amides and analogues, and their effects on economically important insect pests will be described in a future communication.

EXPERIMENTAL

General

Melting points were determined on a hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Philips Pye Unicam PU9516 infrared spectrophotometer. Accurate mass measurements were made on a Kratos MS-50 instrument. NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer operating at a frequency of 200.068 MHz for ^1H, and on a Varian Unity 400 operating at a frequency of 100.564 MHz for ^{13}C.

7-(3',4'-methylenedioxyphenyl)-E-6-heptenoic acid propylene glycol ester (5). To a solution of piperonal (891 mg, 5.94 mmol) in anhydrous THF (20 mL) at 0°C under an argon atmosphere, was added $BF_3.Et_2O$ (5.3 mL, 42 mmol) dropwise, with stirring. After 10 min, a solution of cyclohexanone (0.61 mL, 5.94 mmol) in dry THF (5 mL) was added slowly. The reaction mixture was allowed to reach ambient temperature and was stirred for a further 8 h. To the resulting dark red solution propylene glycol (2.33 g, 30 mmol) was added dropwise, and the mixture was set aside with stirring, becoming purple in color overnight. The product was worked up by addition of the mixture to a saturated aqueous solution of $NaHCO_3$ and extraction with ether (2 x 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (2 x 50 mL), dried over $MgSO_4$, and the solvent was removed under vacuum. The crude orange-colored oily product was purified by chromatography on silica gel with hexane-ethyl acetate (4:1; 3:2) as eluent. The chromatographically pure ester **5** (782 mg; 43% yield) was a pale yellow oil: IR ($CHCl_3$) 3600, 3500, 2925, 1720, 1600, 1480, 1440, 1020, 960, 935, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.4-1.6 (2H, m), 1.65-1.75 (2H, m), 1.84 (2H, m), 2.17 (2H, m), 2.32 (2H, t, J=7.2 Hz), 3.66 (2H, t, J=6 Hz), 4.21 (2H, t, J=6.2 Hz), 5.90 (2H, s), 6.0 (1H, dt), 6.27 (1H, d, J=16 Hz), 6.71 (2H, s), 6.86 (1H, s); HRMS, calc. for $C_{17}H_{22}O_5$, 306.1467; found 306.1474 (M^+, 84 %), 248.1044 (8) ($C_{14}H_{16}O_4$) (M^+-C_3H_6O), 231.1017 (24) ($C_{14}H_{15}O_3$) (M^+-$C_3H_7O_2$), 188.0834 (20) ($C_{12}H_{12}O_2$) (M^+-$C_5H_{10}O_3$), 174.0682 (61) ($C_{11}H_{10}O_2$) (M^+-$C_6H_{12}O_3$), 161.0591 (51) ($C_{10}H_9O_2$) (M^+-$C_7H_{13}O_3$), 148.0520 (20) ($C_9H_8O_2$) (M^+-$C_8H_{14}O_3$), 135.0443 (55%) ($C_8H_7O_2$), 131.0498 (100) (C_9H_7O) .

7-(3',4'-methylenedioxyphenyl)-6-E -heptenal **(6).** To a stirred slurry of LAH (134 mg; 3.54 mmol) in dry THF (20 mL) at 0°C, was added a solution of ester 5 (542 mg, 1.77 mmol) in THF (2 mL) dropwise. The mixture was allowed to reach ambient temperature with stirring during 1.5 h, at which time tlc analysis showed it to be complete. Work-up involved cautious addition of water (0.1 eq) followed by 15% aqueous NaOH (0.1 eq) and an additional 0.3 eq of water. The mixture was set aside with stirring for 20 min, after which anhydrous Na_2SO_4 was added, the solution was filtered through Celite and the solvent was removed under vacuum. The alcohol product was a low-melting colorless solid (406 mg, 98% yield), sufficiently pure to be used directly in the subsequent oxidation: IR ($CHCl_3$) 3600, 2925, 1600, 1480, 1440, 1100, 1040, 960, 940, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.5-1.7 (6H,m), 2.17 (2H,m), 3.63 (2H, t, J=6.4 Hz), 5.91 (2H, s), 6.0 (1H, dt), 6.27 (1H, d, J=15.6 Hz), 6.72 (2H, s), 6.87 (1H, s); HRMS, calc. for $C_{14}H_{18}O_3$, 234.1256; found 234.1261 (M^+·86%), 174.0685 (10) ($C_{11}H_{10}O_2$) (M^+-C_3H_8O), 161.0601 (51) ($C_{10}H_9O_2$) (M^+-C_4H_9O), 148.0518 (22) ($C_9H_8O_2$) (M^+-$C_5H_{10}O$), 135.0440 (55) ($C_8H_7O_2$), 131.0497 (100) (C_9H_7O)

The alcohol (250 mg, 1.1 mmol) was oxidized using Swern conditions,[13] yielding aldehyde **6** (191 mg, 78%) as a colorless oil; IR ($CHCl_3$) 2925, 1720, 1600, 1490, 1440, 1100, 1040, and 960 cm^{-1}; ^1H NMR (200 MHz) d 1.7-1.8 (2H, m), 1.8-1.9 (2H, m), 2.19 (2H, m) 2.44 (2H, dt, J=1.6Hz and 7.1 Hz), 5.91 (2H, s), 6.00 (1H, dt, J=15.8 Hz and 6.8 Hz), 6.28 (1H, d, J=15.8 Hz), 6.72 (2H,s), 6.87 (1H, s), 9.75 (1H, t, J=1.8 Hz); HRMS, calc. for $C_{14}H_{16}O_3$, 232.1099; found 232.1104 (M^+·86%), 204.1153 (21) ($C_{13}H_{16}O_2$) (M^+-CO), 161.0607 (45) ($C_{10}H_9O_2$) (M^+-C_4H_7O), 148.0530 (21) ($C_9H_8O_2$) , 135.0454 (33) ($C_8H_7O_2$), 131.0499 (100) (C_9H_7O).

Ethyl 11-(3',4'-methylenedioxyphenyl)-2E,4E,10E undecatrienoate **(7).** To a solution of triethyl 4-phosphonocrotonate (246 mg, 0.98 mmol) in anhydrous THF (15 mL) at -78°C under an argon atmosphere was added with stirring, dropwise by syringe, *n*-butyllithium (0.39 mL of 2.5 M solution in hexanes, 0.98 mmol). After 15 min, a solution of aldehyde **6** (191 mg, 0.82 mmol) in dry THF (3 mL) was added. After stirring for a further 10 min at -78°C, the mixture was allowed to attain ambient temperature during 45 min. Aqueous 1% NH_4Cl (10 mL) was then added cautiously, and the mixture was extracted with ether (1 x 50 mL; 2 x 20 mL). The combined extracts were washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness on a rotary vacuum evaporator. The crude product was chromatographed on silica gel, with hexane-EtOAc (6:1) as eluent, affording the ester **7** [194 mg, 84% (based on consumed starting material)] as a colorless oil. The ester showed IR ($CHCl_3$) 2925, 1700, 1640, 1610, 1490, 1440, 1370, 1300, 1065, 1040, 1000, 960, 940, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.27 (3H, t, J=7 Hz), 1.45 (4H, m), 2.2-2.3 (4H, m), 4.17 (2H, q, J=7.2 Hz), 5.76 (1H, d, J=15.4 Hz), 5.91 (2H, s), 6.0-6.2 (3H, m), 6.27 (1H, d, J=15.6 Hz), 6.73 (2H, s), 6.87 (1H,s), 7.26 (1H,dd): HRMS, calc. for $C_{20}H_{24}O_4$, 328.1675; found 328.1675 (M^+, 40%), 255.1379 (17) ($C_{17}H_{19}O_2$) (M^+-$C_3H_5O_2$), 215.1081 (15) ($C_{14}H_{15}O_2$) (M^+-$C_6H_9O_2$), 161.0602 (29) ($C_{10}H_9O_2$), 148.0514 (34) ($C_9H_8O_2$), 135.0454 (100) ($C_8H_7O_2$).

11-(3',4'-methylenedioxyphenyl)-2E,4E,10E-undecatrienoic acid iso-butylamide : Pipercide **(1).** *(a) via hydrolysis and 1,1'-carbonyldiimidazole coupling.* The ester **7** (116mg, 0.35 mmol) was heated under reflux for 1.5 h in acetone (3 mL) and aqueous LiOH (3 mL, 1.0 *M*). The mixture was evaporated to near dryness under reduced pressure, and the solid residue was extracted (4 x 30 mL) with saturated

$NaHCO_3$. The aqueous solution was washed with ether (3 x 30 mL), then made acidic by addition of concentrated HCl. The acid product was extracted with ether (5 x 40 mL) and the combined extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The resulting colorless crystalline product, 11-(3',4'-methylenedioxyphenyl)-2*E*,4*E*,10*E*-undecatrienoic acid, **8**, (91 mg, 86%), was pure enough to be used directly in the subsequent amidation step. A sample, recrystallized from hexane-CH_2Cl_2, melted at 137-138°C; IR ($CHCl_3$) 2600-3400, 2925, 1680, 1640, 1600, 1490, 1440, 1100,1000, 980, 960, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.4-1.6 (4H, m), 2.15-2.20 (4H, m), 5.76 (1H, d, J=15.2 Hz), 5.91 (2H, s), 6.0-6.2 (4H, m), 6.72 (2H, s), 6.87 (1H, s), 7.26 (1H, m), HRMS, calc. for $C_{18}H_{20}O_4$, 300.1362; found 300.1355 (M^+, 100%), 215.1063 (14) ($C_{14}H_{15}O_2$) (M^+-$C_4H_5O_2$), 187.0749 (38) ($C_{12}H_{11}O_2$), 173.0598 (46) ($C_{11}H_9O_2$), 161.0601 (23) ($C_{10}H_9O_2$), 148.0529 (43) ($C_9H_8O_2$), 135.0449 (86) ($C_8H_7O_2$).

The carboxylic acid (67 mg, 0.22 mmol) dissolved in CH_2Cl_2 (5 mL) was stirred with 1,1'-carbonyldiimidazole (43 mg, 0.26 mmol) at 0°C for 30 min, after which isobutylamine (39 mg, 0.53 mmol) in CH_2Cl_2 (1 mL) was added. The solution was stirred overnight, and water (10 mL) was then added. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined extracts, after drying over $MgSO_4$, were evaporated *in vacuo*. The crude product was chromatographed on a preparative-layer silica gel plate, with hexane-EtOAc (3:2) as eluent, to yield (71 mg, 89%) pure pipercide, **1**, as a colorless crystalline solid; MP 112-118°C, (lit.[6] 120°C *after prior softening*); IR ($CHCl_3$) 3540, 2950, 2925, 1660, 1630, 1610, 1500, 1490, 1440, 1100, 1040 1000, and 905 cm^{-1}; ^1H NMR (200 MHz) δ 0.90 (6H, d, J=6.8 Hz), 1.44 (4H, m), 1.78 (1H, sept), 2.14-2.17 (4H, m), 3.14 (2H, dd, J=6Hz and 6.4 Hz), 5.47 (1H, br^{w}t), 5.73 (1H, d, J=14.8 Hz), 5.91 (2H,s), 6.0-6.15 (3H, m), 6.26 (1H, d, J=16 Hz), 6.72 (2H, s), 6.87 (1H, s), 7.17 (1H, dd, J=14.8 Hz and 10.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 28.3, 28.6, 28.9, 32.7, 32.8, 46.9, 100.9, 105.4, 108.2, 120.2, 122.0, 128.4, 128.9, 129.5, 132.3, 141.2, 142.7, 146.6, 147.9, 166.3; HRMS, calc. for $C_{22}H_{29}NO_3$, 355.2147; found 355.2141 (M^+, 28 %), 255.1382 (9) ($C_{17}H_{19}O_2$) (M^+-$C_5H_{10}NO$), 240.1162 (13) ($C_{16}H_{16}O_2$) (M^+-$C_6H_{13}NO$), 220.1698 (36) ($C_{14}H_{22}NO$), 180.1393 (10) ($C_{11}H_{18}NO$), 161.0608 (10) ($C_{10}H_9O_2$), 152.1086 (33) ($C_9H_{14}NO$), 148.0524 (18) ($C_9H_8O_2$), 135.0452 (100) ($C_8H_7O_2$).

(b) Directly via bis[N,N-bis(trimethylsilyl)amino]tin(II)-N,N-dimethyl-ethanolamine reagent. The ethyl ester, **7** (39 mg, 0.11 mmol) in dry THF (1.5 mL) was treated with the N,N-dimethylethanolamine-modified Roskamp reagent[12b] derived from $Sn[N(TMS)_2]_2$ (71 mg, 1.7 mmol) and N,N-dimethylethanolamine (14 mg, 1.7 mmol) in hexane (2.0 mL). Isobutylamine (11.6 mg, 1.7 mmol) in dry THF (0.5 mL) was then added and the mixture was stirred at ambient temperature for 14 h and worked up as described[12b]. The crude product (36 mg) contained 89% unreacted starting material and 11% pipercide, **1**, by NMR analysis.

6-(3',4'-methylenedioxyphenyl)-E-5-hexenoic acid propylene glycol ester, (9.) The procedure for preparation of **9**, from piperonal and cyclopentanone was analogous to that described above for **5**, except for the time required to effect the aldol condensation. The best yield (56%) was realized when the aldol reaction was allowed to proceed for 14 h before the propylene glycol was added. The ester **9** was a pale yellow oil, IR ($CHCl_3$) 3640, 3600, 3550 (br), 2950, 2900, 1725, 1605, 1480, 1440, 1020, 985, and 935

cm^{-1}; ^1H NMR (200 MHz) δ 1.76-1.89 (4H, m), 2.22 (2H,m), 2.37 (2H, t, J=7.4 Hz), 3.68 (2H, t, J=6.2 Hz), 4.23 (2H, t, J=6 Hz), 5.93 (2H,s), 5.99 (1H, dt, J=15.8 Hz and 6.8 Hz), 6.31 (1H, d, J=15.8 Hz), 6.74 (2H, s), 6.89 (1H, s); HRMS, calc. for $C_{16}H_{20}O_5$, 292.1310; found 292.1319 (M^+, 69%), 217.0858 (19) ($C_{13}H_{13}O_3$) (M^+-$C_3H_7O_2$), 188.0832 (14) ($C_{12}H_{12}O_2$) (M^+-$C_4H_8O_3$), 174.0689 (100) ($C_{11}H_{10}O_2$) (M^+-$C_5H_{10}O_3$), 161.0599 (14) ($C_{10}H_9O_2$).

6-(3',4'-methylenedioxyphenyl)-5E-hexenol. Reduction of **9** with LAH to the corresponding alcohol, 6-(3',4'-methylenedioxyphenyl)-*E*-5-hexenol, was effected as above in 96% yield: IR ($CHCl_3$) 3600, 2950, 1600, 1480, 1440,1100, 1040, 900, 960, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.5-1.7 (4H, br m), 2.19 (2H, m), 3.65 (2H, t, J=6.2 Hz), 5.91 (2H,s), 6.00 (1H, dt), 6.28 (1H, d, J=15.6 Hz), 6.72 (2H, s), 6.87 (1H, s); HRMS, calc. for $C_{13}H_{16}O_3$, 220.1099; found 220.1101 (M^+,100%), 161.0610 (27) ($C_{10}H_9O_2$) (M^+-C_3H_7O), 135.0459 (65) ($C_8H_7O_2$), 131.0504 (87) (C_9H_7O).

6-(3',4'-methylenedioxyphenyl)-5E-hexenal. Swern oxidation[13] of the product afforded the aldehyde, 6-(3',4'-methylenedioxyphenyl)-5*E*-hexenal, in a yield of 83% ; IR ($CHCl_3$) 2950, 2940, 1720, 1600, 1480, 1440, 1040, 960, 940, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.78 (2H,m), 2.21 (2H, m), 2.47 (2H, dt, J=1.4 Hz and 7.2 Hz), 5.92 (2H s), 6.0 (1H, dt), 6.27 (1H, d, J=15.6 Hz), 6.72 (2H, s), 6.87 (1H, s), 9.77 (1H, t, J=1.6 Hz); HRMS, calc. for $C_{13}H_{14}O_3$, 218.0943; found 218.0951 (M^+, 100), 190.0985 (27) ($C_{12}H_{14}O_2$) (M^+-CO), 174.0683 (66) ($C_{11}H_{10}O_2$) (M^+-C_2H_4O), 161.0605 (27) ($C_{10}H_9O_2$) (M^+-C_3H_5O), 131.0498 (88) (C_9H_7O).

Ethyl 10-(3',4'-methylenedioxyphenyl)-2E,4E,9E-decatrienoate. Wadsworth-Emmons reaction proceeded smoothly to produce the ester, ethyl 10-(3',4'-methylenedioxyphenyl)-2*E*,4*E*,9*E*-decatrienoate, in 91% yield: IR ($CHCl_3$) 2925, 1700, 1640, 1620, 1490, 1440, 1370,1300, 1155, 1140, 1100, 1040, 1000, 960, 940, and 865 cm^{-1}; ^1H NMR (200 MHz) δ 1.27 (3H,t, J=7.2 Hz), 1.57 (2H, m), 2.20 (4H, br m), 4.18 (2H, q, J=7 Hz), 5.77 (1H, d, J=15.2 Hz), 5.95 (2H, s), 6.0-6.2 (3H, m), 6.27 (1H,d, J=15.8 Hz), 6.72 (2H, s), 6.87 (1H, s), 7.24 (1H, dd); HRMS, calc. for $C_{19}H_{22}O_4$, 314.1518; found 314.1520 (M^+, 61), 285.1119 (37) ($C_{17}H_{17}O_4$) (M^+-C_2H_5), 241.1226 (25) ($C_{16}H_{17}O_2$) (M^+-$C_3H_5O_2$), 201.0920 (20) ($C_{13}H_{13}O_2$), 135.0458 (84) ($C_8H_7O_2$), 131.0493 (100) (C_9H_7O).

Amidation was effected, stepwise as above, by hydrolysis to the acid (92%) and CDI-promoted coupling with isobutylamide (92%), to give norpipercide, **2**, in 34% overall yield:

10-(3',4'-methylenedioxyphenyl)-2E,4E,9E-decatrienoic acid. MP 89-90°C, IR ($CHCl_3$) 2600-3400, 2925, 1690, 1640, 1600, 1490, 1440, 1040, 1000, 960, 940,and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.5-1.7, (2H, br m), 2.1-2.3 (4H, br m), 5.77 (1H, d, J=15.2 Hz), 5.92 (2H, s), 6.0-6.3 (4H), 6.73 (2H, s), 6.87 (1H,s), 7.26 (1H, m); HRMS, calc. for $C_{17}H_{18}O_4$, 286.1205; found 286.1207 (M^+, 92%), 188.0832 (20) ($C_{12}H_{12}O_2$) (M^+-$C_5H_6O_2$), 173.0597 (27) ($C_{11}H_9O_2$), 161.0600 (27) ($C_{10}H_9O_2$), 148.0529 (18) ($C_9H_8O_2$), 135.0445 (100) ($C_8H_7O_2$), 131.0496 (76) (C_9H_7O).

10-(3',4'-methylenedioxyphenyl)-2E,4E,9E-decatrienoic acid iso-butylamide : Nor-pipercide (2). MP 105-111°C; IR ($CHCl_3$) 3450, 2950, 2925, 1660, 1630, 1610, 1500, 1495, 1440, 1040, 1000, 960, 940, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 0.90, (6H, d, J=6.8 Hz), 1.56 (2H, m), 1.78 (1H, sept), 2.20 (4H, m), 3.15 (2H, dd, J=6.0 and 6.4 Hz), 5.49 (1H, br t), 5.74 (1H, d, J=15.2 Hz), 5.91 (2H,s), 6.0-6.15 (3H, m),

6.27 (1H, d, J=15.6 Hz), 6.72 (2H, s), 6.87 (1H, s), 7.18 (1H, dd, J=10.0 Hz and 15.0 Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ 20.1, 28.5, 28.6, 32.3, 32.3, 46.9, 76.7, 100.9, 105.4, 108.2, 120.2, 121.9, 128.5, 128.6, 129.9, 132.2, 141.1, 142.4, 146.6, 147.9, 166.3; HRMS, calc. for $C_{21}H_{27}NO_3$, 341.1991; found 341.1983 (M^+, 100%), 241.1227 (29) ($C_{16}H_{17}O_2$) (M^+-$C_5H_{10}NO$), 226.0986 (21) ($C_{15}H_{14}O_2$) (M^+-$C_6H_{13}NO$), 206.1545 (24) ($C_{13}H_{20}NO$), 174.0674 (18) ($C_{11}H_{10}O_2$), 167.1311 (67) ($C_{10}H_{17}NO$), 152.1081 (23) ($C_9H_{14}NO$), 148.0520 (11) ($C_9H_8O_2$), 135.0458 (40) ($C_8H_7O_2$). Alternatively, direct conversion of the ethyl ester, using the modified Roskamp reagent prepared from bis[N,N-bis(trimethylsilyl)amino]tin(II)-N,N-dimethylethanolamine, produced **2** in a yield of 40% (by NMR).

7-(3',4'-methylenedioxyphenyl)-E-6-heptenoic acid piperidylamide: Piperolein A (3). The ester **5** (326 mg, 1.1 mmol) in acetone (5 mL) and aqueous LiOH (5 mL, 1 *M*) was heated under reflux for 30 min. The mixture was evaporated to dryness *in vacuo*, and the residue was extracted into saturated $NaHCO_3$ (4 x 50 mL). The aqueous solution was washed with ether (3 x 30 mL) and then made acidic by addition of concentrated HCl. The mixture was extracted with ether (5 x 30 mL), and the extracts, after drying over $MgSO_4$ and removal of solvent under reduced pressure, afforded 7-(3',4'-methylenedioxyphenyl)-*E*-6-heptenoic acid,**10**, as a colorless crystalline solid (252 mg, 91%); MP 96-97°C, (lit[8] 95°C); IR ($CHCl_3$) 2600-3400, 2925, 1700, 1600, 1480, 1440, 1040, 960, 940, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.4-1.6 (2H, m), 1.6-1.8 (2H, m), 2.18 (2H, m), 2.36 (2H, t, J=7.2 Hz), 5.91 (2H, s), 6.0 (1H, dt), 6.27 (1H, d, J=15.8 Hz), 6.72 (2H, s), 6.87 (1H, s); HRMS, calc. for $C_{14}H_{16}O_4$, 248.1049; found 248.1043 (M^+,99%), 188.0846 (10) ($C_{12}H_{12}O_2$) (M^+-$C_2H_4O_2$), 161.0598 (53) ($C_{10}H_9O_2$), 131.0496 (100) (C_9H_7O).

A solution of the unsaturated carboxylic acid obtained above (15.2 mg, 0.06 mmol) in dry CH_2Cl_2 (3 mL) was stirred with 1,1'-carbonyldiimidazole (12 mg, 0.07 mmol) at 0°C for 30 min. A solution of piperidine (12.5 mg, 0.15 mmol) in the same solvent (1 mL) was added, and the mixture was stirred for 1 h. Water (10 mL) was then added, the mixture shaken and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL), the combined extracts were dried and the solvent removed. The residue was chromatographed on a preparative silica gel plate with hexane-EtOAc (3:2) as eluent to give piperolein A, **3** (17 mg, 90%) as a colorless oil; IR ($CHCl_3$) 2995, 2950, 2850, 1620, 1480, 1440, 1040, 960, and 940 cm^{-1}; ^1H NMR (200 MHz) δ 1.4-1.7 (10 H, br m), 2.25 (2H, m), 2.32 (2H, t, J=6.2 Hz), 3.37 (2H,br m), 3.52 (2H, br m), 5.91 (2H,s), 6.0 (1H, dt), 6.28 (1H, d, J=15.8 Hz), 6.71 (2H, s), 6.86 (1H, s); HRMS, calc. for $C_{19}H_{25}NO_3$, 315.1834; found 315.1828 (M^+,99%), 230.0938 (22) ($C_{14}H_{14}O_3$) (M^+-$C_5H_{11}N$), 202.0991 (13) ($C_{13}H_{14}O_2$) (M^+-$C_6H_{11}NO$), 180.1398 (21) ($C_{11}H_{18}NO$), 140.1081 (22) ($C_8H_{14}NO$), 135.0449 (18) ($C_8H_7O_2$), 131.0496 (18) (C_9H_7O), 127.1000 (100) ($C_7H_{13}NO$), 112.0763 (14) ($C_6H_{10}NO$).

Using the Roskamp reaction with $Sn[N(TMS)_2]_2$ and piperidine, 7-(3',4'-methylenedioxyphenyl)-*E*-6-heptenoic acid *ethylene glycol ester* (cf. **5**) was converted directly to **3** in a yield of 95%.

6-(3',4'-methylenedioxyphenyl)-5E-hexenoic acid piperidylamide: nor-piperolein A (4). Hydrolysis of the ester **9**, as described above, afforded an 85 % yield of the corresponding carboxylic acid, as a colorless crystalline solid, MP 81-82°C; IR ($CHCl_3$) 2600-3400, 2950, 2925, 1710, 1600, 1480, 1440, 1040, 960, 940, and 860 cm^{-1}; ^1H NMR (200 MHz) δ 1.78 (2H, m), 2.22 (2H, m), 2.38 (2H, t, J=7.6 Hz), 5.91 (2H, s), 6.0 (1H, dt), 6.30 (1H, d, J=15.8 Hz), 6.72 (2H, s), 6.87 (1H, s); HRMS, calc. for $C_{13}H_{14}O_4$, 234.0892;

found 234.0899 (M^+,100%), 174.0679 (31) ($C_{11}H_{10}O_2$) (M^+-$C_2H_4O_2$), 161.0598 (34) ($C_{10}H_9O_2$), 131.0499 (85) (C_9H_7O).

Formation of the amide, **4**, a colorless oil, was accomplished as above by coupling of the acid with piperidine (98%); IR ($CHCl_3$) 2950, 2935, 1620, 1490, 1440, 1040, 985, and 935 cm^{-1}; ^1H NMR (200 MHz) δ 1.50-1.65 (6H, m), 1.79 (2H, m), 2.22 (2H, m), 2.32 (2H, t, J=7.4 Hz), 3.35 (2H, t, br), 3.52 (2H, t, br), 5.91 (2H, s), 6.00 (1H, dt, J= 15.6 Hz and 6.8 Hz), 6.29 (1H, d, J=15.8 Hz), 6.72 (2H, s), 6.86 (1H, s); HRMS, calc. for $C_{18}H_{23}NO_3$, 301.1678; found 301.1673 (M^+,54%), 127.0989 (100) ($C_7H_{13}NO$), 112.0763 (15) ($C_6H_{10}NO$), 84.0810 (19) ($C_5H_{10}N$).

The yield obtained directly from the *propylene* glycol ester of 6-(3',4'-methylenedioxy-phenyl - *E*-5-hexenoic acid, **9**, by the Roskamp method was 82% (unconverted starting material recycled a second time). Using the *ethylene* glycol ester, the amide was obtained directly in 96% yield.

ACKNOWLEDGMENTS

Financial support from the Canadian Forest Service Green Plan NPIC Network and from NSERC is gratefully acknowledged. We are indebted to Dr Peter Penner and Mr Dan Drummond for recording the carbon NMR and mass spectra, respectively. We thank Mr Colin Abernethy for preparation of the Roskamp tin reagent. A stimulating discussion with Professor P. Deslongchamps concerning stereoelectronic aspects of the fragmentations is acknowledged.

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(*Received in USA* 9 *June* 1994; *accepted* 2 *August* 1994)