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First stereoselective total synthesis and anticancer activity of new amide alkaloids of roots of pepper

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ABSTRACT

The first stereoselective total synthesis of new natural amide alkaloids **1**–**3** have been achieved from commercially available starting materials. Wittig olefination, Sharpless asymmetric dihydroxylation, epoxidation, a *trans* regioselective opening of 2,3-epoxy alcohol, Horner–Wadsworth–Emmons (HWE) olefination and amide coupling are the key steps. The amide alkaloids **1**–**3** are evaluated for their anticancer activity against colon (HT-29), breast (MCF-7) and lung (A-549) human cancer cell lines for the first time.

Natural Products are biologically interesting molecules[1] and play an important role in modern drug discovery. Piperidine and pyrrolidine amide alkaloids[2] are known to occur in *Piper nigrum* (Piperaceae, black pepper) and possess a variety of pharmacological activities such as CNS stimulant,[3] analgesic[4] and antipyretic.[4] In addition to these, other activities such as antifungal,[5] anti-diarrhoeal,[6] anti-inflammatory,[7] insecticidal,[8] anti-tuberculosis and anti-plasmodial,[9] as well as inhibition of 5-lipoxygenase,[10] cyclooxegenase-1[10] and CYP3A4[11] are also reported. Recently Nikaido and co-workers,[12] isolated new amide alkaloids from roots of *Piper nigrum* such as (±)-*threo*-1-(1-oxo-4,5-dihydroxy-2*E*-decaenyl)piperidine, (±)-*threo*-*N*-isobutyl-4,5-dihydroxy-2*E*-octaenamide, (±)-*erythro*-1-(1-oxo-4,5-dihydroxy-2*E*-decaenyl)piperidine and established their structure. Asymmetric molecules and their syntheses play significant roles in obtaining enantiomerically pure or enriched compounds of natural products, pharmaceuticals and agrochemicals. In accordance of our continuing synthetic efforts[13] towards the molecules with intriguing characteristics and usefulness, we embarked on the synthesis of amide alkaloids (alkenamides) **1–3** (Fig. 1). The structural similarities between these compounds **1–3** led us to design a common strategy.

The synthetic approach for natural amide alkaloids **1** and **2** initiated from commercially available butanal and hexanal as illustrated in Scheme 1. Aldehyde was subjected to Wittig olefination[14] to furnish the *E*-α,β-unsaturated esters **5/6**. The unsaturated ester **5/6** on Sharpless dihydroxylation using AD-mix-β[15] provided the key intermediate, chiral dihydroxy ester **7/8** with an excellent enantio-selectivity. The compounds **7/8** were converted to the corresponding acetonide esters **9/10** using 2,2-dimethoxy propane in presence of *p*-TSA in high yields. Acetonide ester **9/10** were then converted[16] into corresponding aldehyde **11/12** using DIBAL-H at −78 °C and followed by two carbon homologation with methyl-2-(diethoxyphosphoryl)acetate under Horner–Wadsworth–Emmons (HWE) conditions[17] to furnish the *E*-α,β-unsaturated ester **13/14**. The obtained ester **13/14** was hydrolysed[18] with LiOH to give corresponding carboxylic acid **15/17**. The acid **15** was coupled with piperidine using 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl)[19] to furnish corresponding amide **16** which on subsequent acetonide deprotection afforded (4*R*,5*R*)-2*E*-4,5-dihydroxy-1-(piperidin-1-yl)dec-2-en-1-one (**1**) in 95% yield

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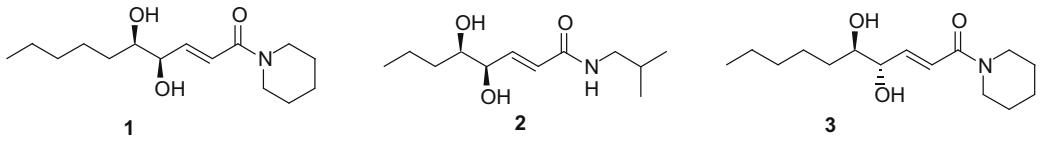


Figure 1.

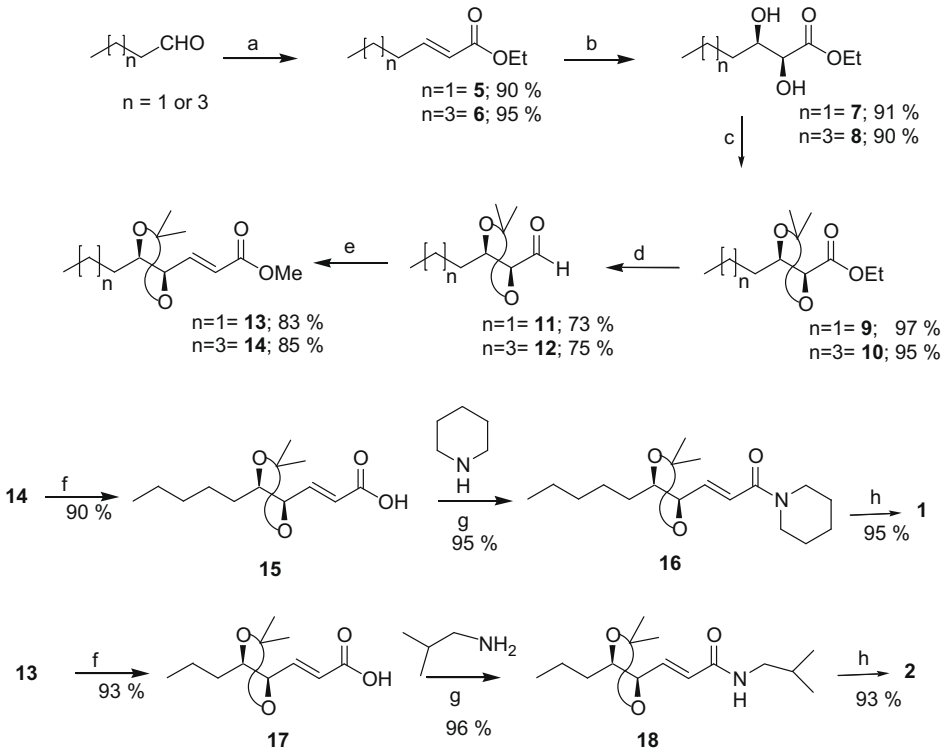
as a colorless viscous oil[25] (Scheme 1). The same procedure of hydrolysis and amide coupling with isobutyl amine adopted on **17** to get (4*R*,5R)-2*E*-4,5-dihydroxy-*N*-isobutyloct-2-enamide (**2**) in 93% yield as a colorless viscous oil.[25]

Next we have chosen the synthesis of amide alkaloid **3** and is outlined in the Scheme 2. We envisioned the two stereocentres could be constructed by the Sharpless asymmetric epoxidation on allylic alcohol and then *trans* regioselective ring opening of the epoxide alcohol. The synthesis of the natural amide alkaloid **3** started from previously synthesized α,β-unsaturated ester **6** which was converted to allylic alcohol **19** and subjected to Sharpless epoxidation[20] (Scheme 2) to afford the epoxy alcohol **20**. The titanium assisted *trans* regioselective opening[21] of the 2,3-epoxy alcohol was accomplished with benzoic acid to get **21**, which was further converted into triol **22**. Selective protection[22] of the primary hydroxyl group of **22** with *tert*-butyldimethylsilylchloride gave silylether **23** and then the secondary hydroxyl groups were protected with 2,2-dimethoxy propane in presence of *p*-TSA to afford **24**.

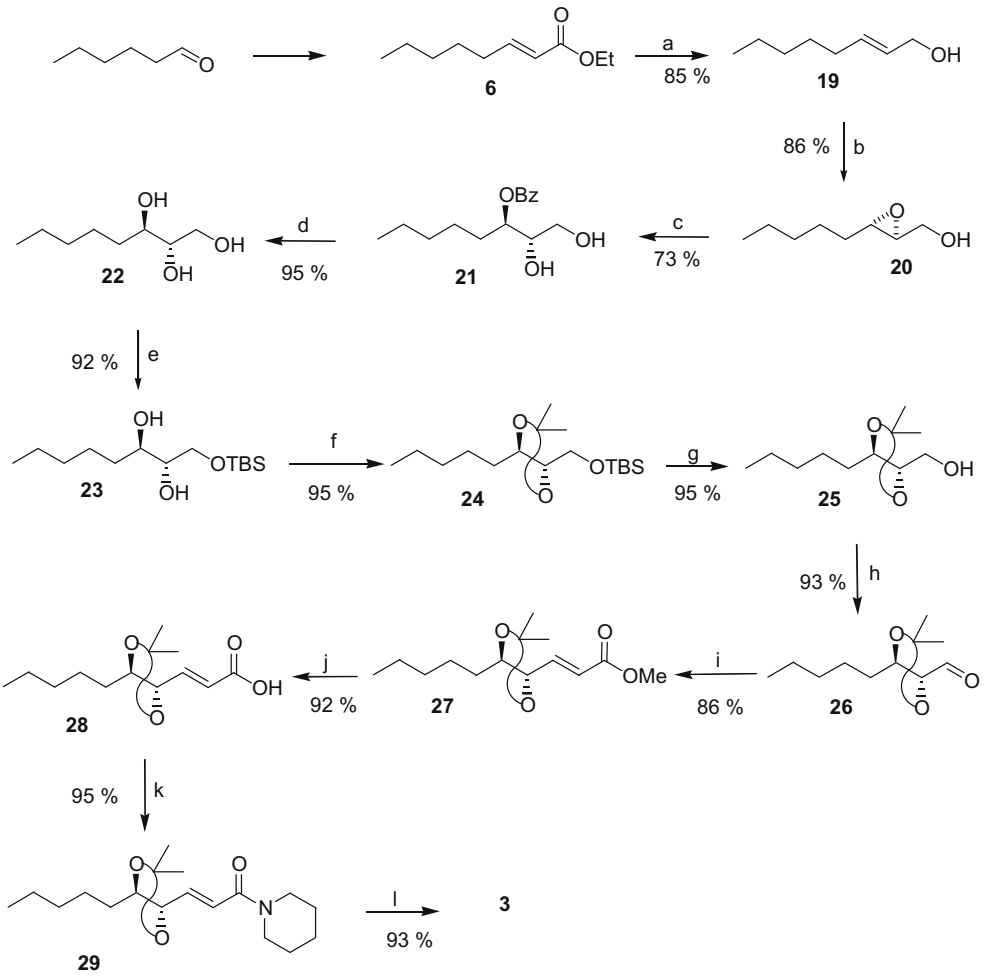
The compound **24** was deprotected using TBAF[22] to give alcohol **25** followed by Swern oxidation[23] to give the corresponding aldehyde **26**. HWE olefination was adopted to convert **26** to the *E*-α,β-unsaturated ester **27**. The obtained ester **27** was hydrolyzed with LiOH to afford carboxylic acid **28**. The acid **28** was coupled with piperidine using HOBt and EDC·HCl to give amide **29**, which on subsequent acetonide deprotection using *p*-TSA afforded the new natural amide alkaloid (4*S*,5*R*)-2*E*-4,5-dihydroxy-1-(piperidin-1-yl)dec-2-en-1-one (**3**) in 93% yield as a white solid.[25]

The synthesized new amide alkaloid compounds (4*R*,5*R*)-2*E*-4,5-dihydroxy-1-(piperidin-1-yl)dec-2-en-1-one (**1**), (4*R*,5*R*)-2*E*-4,5-dihydroxy-*N*-isobutyloct-2-enamide (**2**) and (4*S*,5*R*)-2*E*-4,5-dihydroxy-1-(piperidin-1-yl)dec-2-en-1-one (**3**) have been evaluated for their in vitro anti cancer activity for the first time against three cancer cell lines (Table 1) using MTT method.[24] Compound **1** exhibits activity against both colon (HT-29) and lung cancer (A-549) (IC_{50} values of 125 μg/mL and 135 μg/mL, respectively), cell line, compound **2** exhibits activity against colon cancer (HT-29 with IC_{50} value of 181 μg/mL) cell line and compound **3** exhibits activity against lung cancer (A-549 with IC_{50} value of 182 μg/mL) cell line.

In conclusion, the present letter describes an efficient first total stereoselective synthesis of natural amide alkaloids **1**–**3** (roots of pepper) in very good yields. Thus synthesized compounds are new and evaluated for their in vitro anticancer activity in three cell lines.



Scheme 1. Reagents and conditions: (a) Ph_3P=CHCOOEt, benzene, rt; (b) AD-mix-β, *t*-BuOH/H_2O (1:1), 0 °C; (c) 2,2-DMP, *p*-TSA (cat.), CH_2Cl_2; (d) DIBAL-H, dry CH_2Cl_2, −78 °C; (e) $(H_5C_2O)_2P(O)CH_2COOMe$, NaH, dry benzene, 0 °C–rt; (f) LiOH, THF/H_2O (3:2), 45 °C; (g) HOBt, EDC, CH_2Cl_2, 0 °C–rt; (h) MeOH, *p*-TSA, rt.



Scheme 2. Reagents and conditions: (a) DIBAL-H, dry CH_2Cl_2, 0 °C to rt; (b) $Ti(O^iPr)_4$, (+)-DET, cumene hydroperoxide, 4 Å MS, dry CH_2Cl_2, −22 °C; (c) PhCOOH, $Ti(O^iPr)_4$, CH_2Cl_2, rt; (d) K_2CO_3, MeOH, 0 °C; (e) TBSCl, imidazole, dry DMF, 0 °C; (f) 2,2-DMP, *p*-TSA (cat.), CH_2Cl_2; (g) TBAF, THF, 0 °C; (h) $(COCl)_2$, dry DMSO, Et_3N, dry CH_2Cl_2, −78 °C; (i) $(H_5C_2O)_2P(O)CH_2COOMe$, NaH, dry benzene, 0 °C–rt; (j) LiOH, THF/H_2O (3:2), 45 °C; (k) HOBt, EDC, CH_2Cl_2, 0 °C to rt; (l) MeOH, *p*-TSA.

Table 1
In vitro anti cancer activity of **1**, **2** and **3** on cancer cell lines

Cancer panel/cell line	IC_{50} (μg/mL)		
	1	**2**	**3**
Colon HT-29	125	181	NA
Breast MCF-7	NA	NA	NA
Lung A-549	135	NA	182

NA = not active.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.08.056.

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