Tetrahedron 71 (2015) 4192–4202

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of marine brominated alkaloid amathamide F: a palladium-catalyzed enamide synthesis

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ARTICLE INFO

Article history:
Received 29 March 2015
Received in revised form 22 April 2015
Accepted 24 April 2015
Available online 1 May 2015

Keywords:
Alkaloids
Amathamides
Natural products
Palladium catalysis
Structure revision

ABSTRACT

Synthesis of brominated marine natural product amathamide F is described. Various strategies to construct the enamide functionality required for its synthesis have been explored. Finally, we succeeded in constructing the enamide moiety under a palladium-catalyzed condition. Facile transformation of 2,3,4-tribromo-5-methoxybenzaldehyde to the reported structure of amathamide F involved initial one-carbon-elongation of the aldehyde group followed by its conversion to corresponding enol acetate derivative prior to crucial Pd(II)-catalyzed cross-coupling with (*S*)-1-methylpyrrolidine-2-carboxamide. However, due to nonconformity of its NMR spectral data to that of the reported natural isolate, we have confirmed its actual structure through a synthesis.

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1. Introduction

With the continuous emergence of novel synthetic methods and techniques, the synthesis of natural products, over the last several decades, has witnessed a sea change in its goals among, which the structural confirmation, particularly the unambiguous attribution of different substituents within the structural framework of the newly isolated bioactive species still remains greatly inspirational as pointed out recently by R. W. Hoffman.[1] Natural products of marine origin possess novel skeletal architecture as well as unique biological activities, therefore fascinating to both chemists and biologists. A plethora of such molecules of marine origin are structurally characterized by one or more enamide moieties.[2,3] Enamides exhibit an array of biological activities including antitumor, antibiotic, and enzyme inhibitory activities.[2,3] Amathamides are members of a small family of enamide metabolites (Fig. 1).[4] They were isolated from the Tasmanian bryozoan *Amathia wilsoni*.[4] Their structures, as expressed in Fig. 1, were deduced by classical spectroscopic analyses, which reveal that they are brominated proline derived alkaloids differing from each other in the degree of bromination or methylation at the aromatic skeleton, presence of stereochemistry about a benzylic double bond and methylation at amide nitrogen atom.[4] Although naturally occurring enamides are documented to display potent biological properties,[2,3] however, except for amathamides C and H, which show moderate antimalarial and antitrypanosomal activities,[4e] majority of amathamides are relatively less explored towards similar biological activities probably because of their inadequate supply from natural sources as well as limited or complete lack of synthetic routes for each members. However, unique structural features coupled with unknown biological activity and limited supply made them unique candidates for total synthesis.[5,6]

As a consequence of our continued interests in the chemistry of halogenated phenol derivatives,[7,8] recently, we revised the structure of one member of this natural product family, amathamide D via a sequential synthesis of both the reported and actual molecular structure.[5] However, despite efforts towards the synthesis of few members of amathamide family described by Osuna and coworkers in 2002[6] and more recently by us,[5] to the best of our knowledge, no total synthesis has been reported for amathamide F. Amathamide F was originally proposed by Blackman and coworkers,[4b,c] who first reported their isolation, to compose of a 2,3,4-tribromo-5-methoxyphenyl residue connected with a pyrrolidine moiety via an interlinking enamide functionality of *cis* geometry (**7**, Fig. 1), however, recently it was postulated by Carroll et al. to contain 2,4,6-tribromo-3-methoxy substituted phenyl ring (**8**, Fig. 1).[4e,9] Nevertheless it has not been confirmed by its synthesis. As a synthetic curiousity we took this fact in our consideration. Earlier, two members of amathamide family, amathamides A (**1**) and B (**6**) as well as few of their analogues were synthesized

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http://dx.doi.org/10.1016/j.tet.2015.04.091
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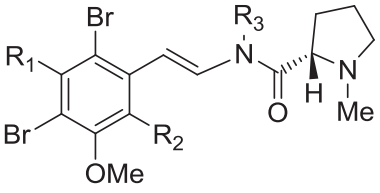
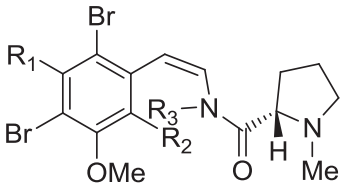


1: $R_1 = R_2 = R_3 = H$; amathamide A
2: $R_1 = H$, $R_2 = Br$, $R_3 = CH_3$; amathamide C
3: $R_1 = Br$, $R_2 = R_3 = H$; amathamide E
(Originally proposed by Blackman et al.[4b])
4: $R_2 = Br$, $R_1 = R_3 = H$; amathamide E
(Postulated by Carroll et al.[4e,9])
5: $R_1 = Br$, $R_2 = OCH_3$, $R_3 = CH_3$; amathamide G



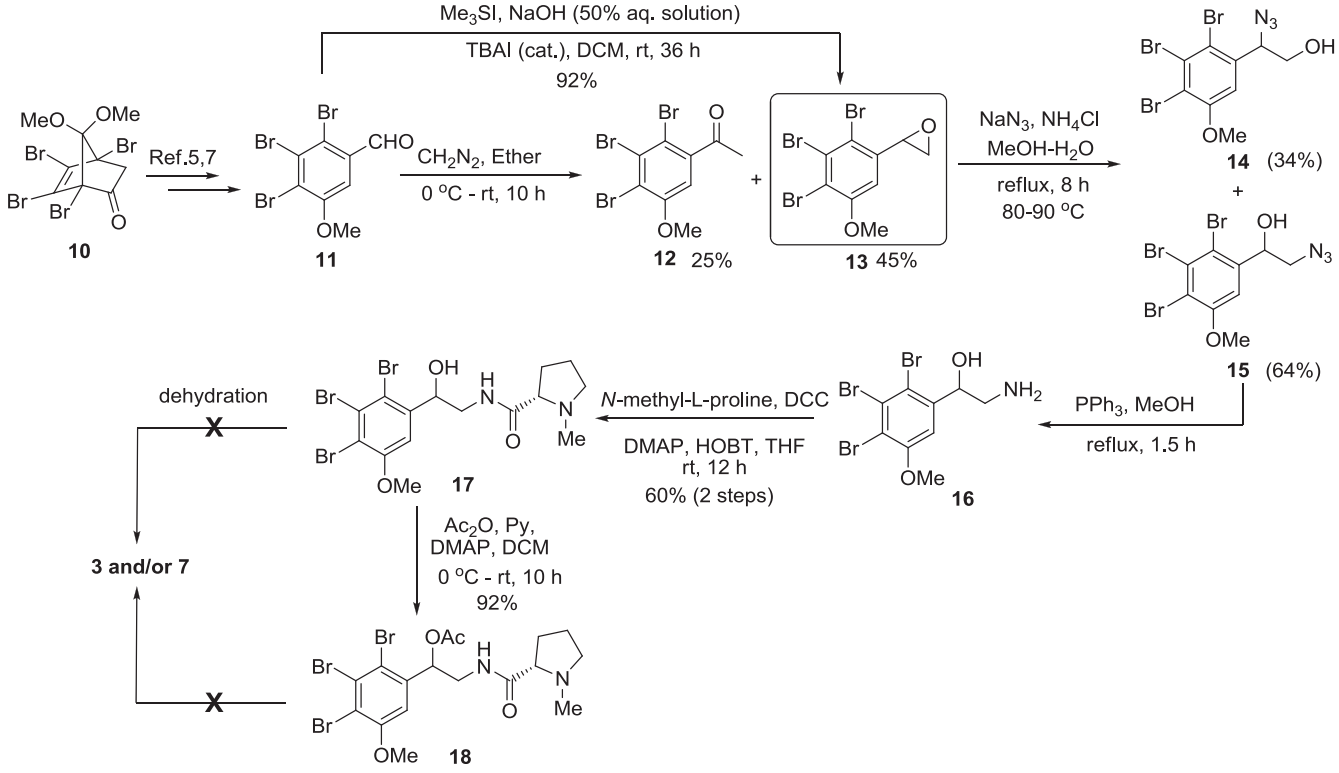
6: $R_1 = R_2 = R_3 = H$; amathamide B
7: $R_1 = Br$, $R_2 = R_3 = H$; amathamide F
(Originally proposed by Blackman et al.[4b,c])
8: $R_2 = Br$, $R_1 = R_3 = H$; amathamide F
(Postulated by Carroll et al.[4e,9])
9: $R_1 = H$, $R_2 = Br$, $R_3 = CH_3$; amathamide H

Fig. 1. Amathamide family of natural products.

wherein the key reaction involved was the installation of benzylic double bond in a stereoselective fashion (hence forming the requisite enamide functionality) at the final step taking recourse of the oxidative desulphurization strategy over a suitably functionalized advanced precursor.[6,10] However, yields of final enamides were poor to moderate, moreover, creation of double bond via sulfoxide elimination requires refluxing condition at higher temperature under basic condition.[6,10] Harsher reaction conditions as such may also attribute partial racemization of the stereocenter present. Therefore, in our pursuit for stereoselective synthesis of amathamide F, we were interested to develop a strategy that would enable us to generate the requisite benzylic double bond and hence the enamide functionality of the targets under milder reaction conditions. For that purpose, numerous strategies were employed and after several futile attempts, finally a palladium-catalyzed coupling between a suitably tailored β-substituted vinyl acetate derivative and *N*-methyl-L-prolinamide emerged successful in delivering the required enamide functionality of the targets. In this article, we present our overall synthetic efforts that led to the first total synthesis of amathamide F and also to the eventual conclusion based on unambiguous structural proof that it is in fact the regioisomer of proposed structure **7** (Fig. 1).

2. Results and discussion

The synthetic endeavor towards amathamides E (**3**) and F (**7**) commenced with the preparation of 2,3,4-tribromo-5-methoxybenzaldehyde **11** (Scheme 1) from easily accessible 1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-one **10** in 83% overall yield in four steps by our previously reported strategy (Scheme 1).[5,7] Exposure of aldehyde **11** to ethereal solution of diazomethane afforded the epoxide **13**, albeit in 45% yield along with undesired methyl ketone derivative **12** as a minor product in 25% yield (Scheme 1). Notwithstanding, epoxide **13** could be

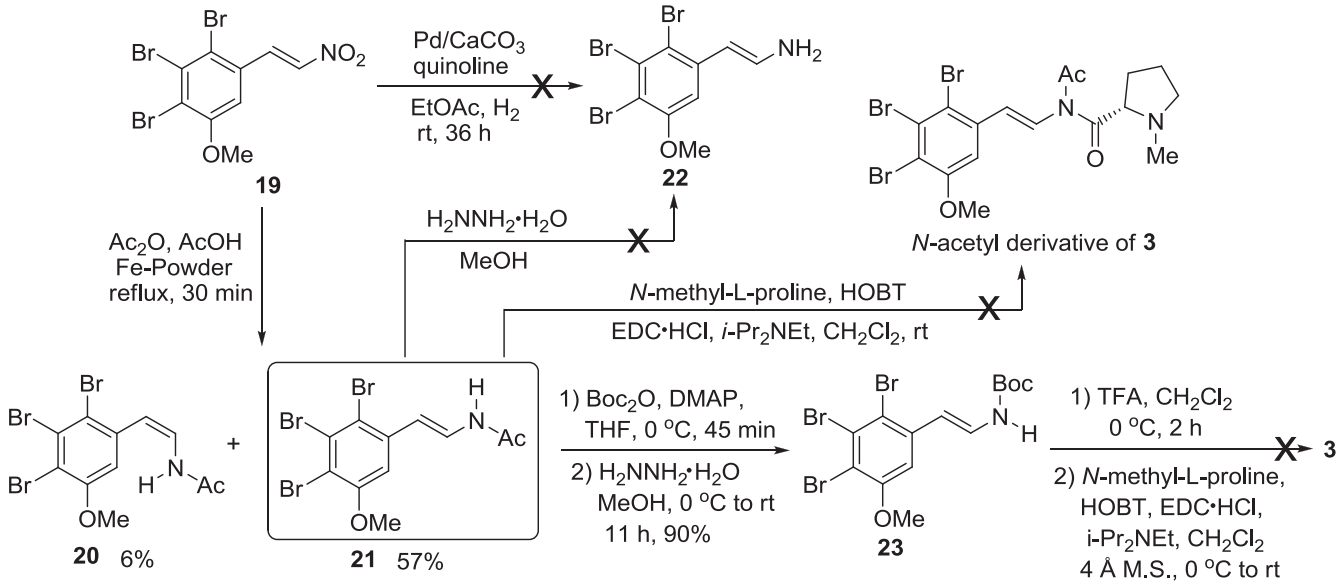


Scheme 1. Attempted synthesis of amathamides E, F (**3**, **7**) (structure as published in the literature) via plausible late-stage installation of benzylic double bond.

obtained exclusively in excellent yield through Corey-Chaykovsky reaction[11] employing trimethylsulphur iodide (TMSI) in combination with 20% aq NaOH and catalytic tetra-*n*-butylammonium iodide (TBAI) as a phase transfer catalyst in CH_2Cl_2 at room temperature. Epoxide ring opening of **13** was then accomplished in a quantitative reaction employing NaN_3 in MeOH[12] to furnish the regioisomeric mixture of hydroxy azides, **14** and **15** in 34% and 64% yield, respectively. They were chromatographically separable and after separation the required **15** was advanced further. Subsequent azide reduction of **15** was carried out using PPh_3 in refluxing MeOH[13] to obtain the hydroxy amine **16**, which, without further purification, was coupled with *N*-methyl-L-proline[14] employing DCC, HOBt in combination with catalytic DMAP in THF furnishing the advanced precursor **17** in overall yield of 60% for the two steps (Scheme 1). The moment was now at hand to test the feasibility of creating the double bond at the benzylic position and hence the access to desired amathamides E (**3**) and/or F (**7**) presumably via dehydration of **17** (Scheme 1).

However, to our dismay, inducing such a transformation on **17** proved to be more challenging than otherwise expected as could be realized from the analyses of ^{1}H NMR spectra of crude reaction mixtures (Scheme 1). Indeed, all our attempts utilizing a variety of standard dehydrating agents including conc H_2SO_4, PPTS, *p*-TsOH, and EDC, CuCl[15] or $SOCl_2$, Et_3N, DBU[16] as well as conventional methods based on mesylation or tosylation failed to afford the desired compound (Scheme 1). Implementation of specific dehydrating agents such as Burgess salt[17] or Martin sulfurane[18] also proved futile. Extensive experimentation in this context discovered surprising complexities associated with this apparently straightforward projected transformation, the exact reasons of which remain unclear. The hydroxyl group of **17** was then acetylated employing Ac_2O, pyridine in presence of catalytic DMAP to furnish **18** in 92% yield. Disappointingly, attempted deacetylation of **18** with generation of requisite benzylic double bond was fruitless and we could not obtain the required final product despite implementation of either base mediated protocol with varying reaction condition or pyrolytic reaction strategy (Scheme 1).[19]

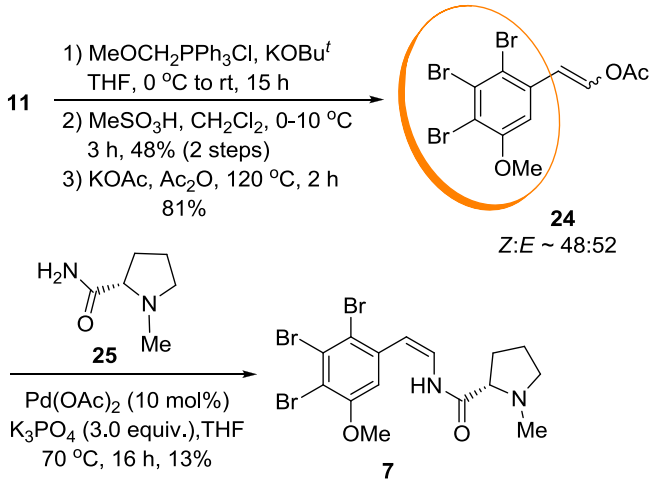
Our lack of success in the crucial installation of benzylic double bond present in the target molecules (**3**, **7**), forced us to revise our approach and to consider the introduction of double bond prior to attachment of prolinamide segment. Along this line, our endeavor started with α,β-unsaturated nitro compound **19**.[5] Since, our aim was to reduce the nitro group of compound **19** without concomitant reduction of the double bond, it was subjected to hydrogenation in presence of Lindlar catalyst (Scheme 2).[20] Unfortunately this reaction did not work. We then turned our attention to Fe-powder in Ac_2O/AcOH[21] as a potential cock-tail to achieve the goal of selective reduction over **19**. It was highly gratifying to note that indeed this condition worked well furnishing a chromatographically separable *cis* (**20**) and *trans* (**21**) *N*-acetylated enamines, albeit in modest yields. At this juncture, direct coupling between compound **21** and *N*-methyl-L-proline would furnish the *N*-acetyl derivative of amathamide E (**3**), however it could not be achieved (Scheme 2). Further attempt for the removal of acetyl group of **21** with hydrazine hydrate to get free enamine **22** was also unsuccessful.



Scheme 2. Attempted synthesis of amathamides E, F (**3**, **7**) via coupling reaction with several enamines.

We then thought of replacing acetyl protecting group on enamine nitrogen atom in **21** with a Boc-group to examine its response towards the coupling reaction. For this purpose, **21** was converted to *N*-Boc-protected enamine **23** in excellent yield in two steps, first protection of amine in **21** with Boc-group followed by removal of acetyl group using hydrazine hydrate.[22] However, our attempts to deprotect the Boc-group of **23** with TFA/CH_2Cl_2 at 0 °C under anhydrous condition for the subsequent in situ coupling of resultant α,β-unsaturated amine with *N*-methyl-L-proline, as planned, met with failure (Scheme 2).

Having been thwarted in achieving the targets, we then sought to explore few alternative strategies to construct the enamide functionality for amathamides. We found many reports in the literature, which describe the synthesis of enamide by taking appropriate amides and enol triflates or vinyl halides.[23] Recently, Xu et al. also reported a palladium (II)-catalyzed N-vinylation of acyl amide derivative eventually forming an enamide under mild condition wherein vinyl acetate was used as the source of vinyl moiety in the final product.[24] From the generality of this methodology as well as the proposed reaction mechanism, it occurred to us that instead of using simple vinyl acetate if we would employ its suitably substituted derivative (e.g., β-substitution by brominated phenolic ether moiety of vinyl acetate **24**, Scheme 3), it may end up



Scheme 3. Successful synthesis of amathamide F (**7**) (structure as published in the literature) via palladium(II)-catalyzed coupling reaction.

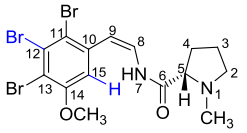
producing corresponding enamides under similar reaction conditions, thus completing the synthesis of amathamides E (**3**) and F (**7**). To check our assumption, required vinyl acetate derivative **24** was first prepared from aldehyde **11** via one-carbon homologation[5] followed by treatment with KOAc/Ac_2O[25] as an inseparable ~1:1 mixture of *Z* and *E* isomers. The as derived **24** was then subjected to palladium(II)-catalyzed N-vinylation over prolinamide **25**[26] i.e., (*S*)-1-methylpyrrolidine-2-carboxamide, under a modified coupling protocol developed recently by Guo et al.,[24] as shown (Scheme 3). It was observed that under a suitable reaction condition, which will be revealed in the subsequent sections as an optimum one (vide infra), surprisingly, only the *Z*-enamide **7** was obtained, albeit in 13% yield (Scheme 3). The *cis*-configuration of olefin in **7** was unequivocally established from the characteristic coupling constant at 9.5 Hz between the two vicinal olefinic protons (see the Experimental section). We do not yet know the precise reason for the exclusive formation of Z-isomer, albeit in low yield. Even the alteration of reaction conditions could not change the outcome, which remains to be fully clarified and recognized. Unfortunately, the NMR data of our synthetic **7** was incongruent with those reported for the natural isolate, to which the same chemical structure was assigned by Blackman et al.,[4b,c] indicating that the structure of amathamide F needed to be revisited.

At this stage, a thorough comparison of ^{1}H and ^{13}C NMR spectra of synthetic **7** and natural one was carried out (Table 1). The most prominent difference observed in ^{1}H NMR of synthetic **7** was for the aromatic proton, which appears substantially upfield of the corresponding nuclei in the natural compound (chemical shift variation, $\Delta\delta \sim 0.85$ ppm, Table 1) while in the ^{13}C NMR, peaks in the aromatic region displayed variations, $\Delta\delta$, ranging between ~0.7 and 7 ppm (Table 1).[4b,c] Although we determined its specific rotation value (see the Experimental section), but due to unavailability of optical rotation value for the natural compound,[4b,c] it could not be compared. For the purpose of finding out, which isomer of **7** corresponds to natural amathamide F, we investigated some of the closely related aromatic derivatives having bromine substituents at the 1,3,5-positions with respect to each other as well as we took the fact in our consideration as postulated by Carroll et al.[4e,9] The reported chemical shift value for the lone aromatic proton for the natural isolate at 7.84 ppm in the ^{1}H NMR spectrum[4b,c] strongly indicated that three bromines might be positioned symmetrically

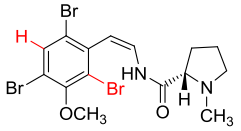
Table 1
^{1}H and ^{13}C NMR data for natural amathamide F (**7**) (as originally proposed),[4b,c] synthetic **7** (having originally proposed structure) and synthetic **8** (having revised and actual structure)[4e,9] in $CDCl_3$

Position	Amathamide F (**7**) (as originally proposed),[4b,c]		Synthetic **7** (having originally proposed structure)		Synthetic **8** (having revised and actual structure)	
	δ_{1H}[a] (mult, *J* in Hz, int.)	δ_{13C}[b]	δ_{1H}[c] (mult, *J* in Hz, int.)	δ_{13C}[d]	δ_{1H}[c] (mult, *J* in Hz, int.)	δ_{13C}[e]
1-NMe	2.39 (s, 3H)	42.0	2.34 (s, 3H)	42.2	2.29 (s, 3H)	42.1
2	2.21 (m, 1H)	56.7	2.38–2.27 (m, 1H)	56.7	2.32–2.27 (m, 1H)	56.7
	2.98 (m, 1H)		3.0 (dd, *J*=5.5 Hz, 10.4 Hz)		2.95 (dd, *J*=4.9 Hz, 10.4 Hz)	
3	1.72 (m, 1H)	24.6	1.73–1.63 (m, 1H)	24.5	1.77–1.64 (m, 2H)	24.6
	1.72 (m, 1H)		1.83–1.77 (m, 1H)			
4	1.85 (m, 1H)	31.1	1.91–1.84 (m, 1H),	31.0	1.90–1.84 (m, 1H),	31.2
	1.88 (m, 1H)		2.28–2.22 (m, 1H),		2.24–2.16 (m, 1H),	
5	3.09 (m, 1H)	68.6	3.05 (t, 1H, *J*=7.8 Hz)	68.9	2.99 (t, 1H, *J*=7.2 Hz)	68.7
6	—	172.4	—	172.5	—	172.6
7-NH	8.90 (d, 1H, *J*=12 Hz)		9.40 (d, 1H, *J*=11.6 Hz)		8.87 (d, 1H, *J*=11.3 Hz)	
8	7.03 (dd, 1H, *J*=9 Hz, 12 Hz)	123.8	7.04 (dd, 1H, *J*=9.6 Hz, 12.1 Hz)	123.1	7.02 (dd, 1H, *J*=9.3 Hz, 12.1 Hz)	123.9
9	5.58 (d, 1H, *J*=9 Hz)	108.9	5.81 (d, 1H, *J*=9.5 Hz)	110.5	5.57 (d, 1H, *J*=9.5 Hz)	108.8
10	—	136.8	—	130.4	—	137.2
11	—	117.2	—	110.3	—	117.3
12	—	119.3	—	114.7	—	119.3
13	—	121.0	—	118.1	—	121.0
14	—	154.2	—	156.2	—	154.3
14-OMe	3.89 (s, 3H)	60.6	3.89 (s, 3H)	56.7	3.88 (s, 3H)	60.6
15	**7.84 (s, 1H)**	**135.7**	**6.89 (s, 1H)**	**137.0**	**7.82 (s, 1H)**	**135.6**

[a] 300 MHz.
[b] 75 MHz.
[c] 500 MHz.
[d] 100 MHz.
[e] 125 MHz.



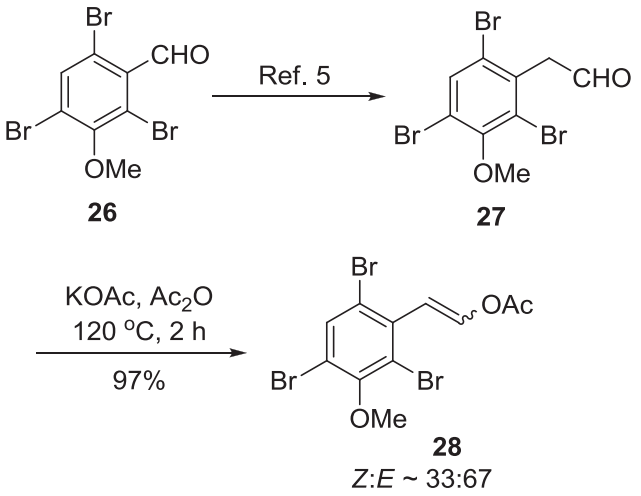
7
(reported **incorrect** structure
of amathamide F) (Ref. 4b,c)



8
(revised **actual** structure
of amathamide F) (Ref. 4e,9)

within the aromatic ring rather than being contiguous as assigned in **7**. To authenticate our assumption, we conceived of synthesizing an equivalent structure of **7** with symmetrically substituted bromines in the aromatic moiety.

Our endeavor towards structure revision of amathamide F began with 2 -(2,4,6-tribromo-3-methoxyphenyl)acetaldehyde **27**, which could be obtained from easily accessible 2,4,6-tribromo-3-methoxybenzaldehyde **26** via standard one-carbon homologation strategy (Scheme 4).[5] The vinyl acetate derivative **28**, required for final palladium (II)-catalyzed coupling, was achieved from aldehyde **27** by treatment with KOAc/Ac_2O[25] as an inseparable ~1:2 mixture of *Z* and *E* isomers (Scheme 4).

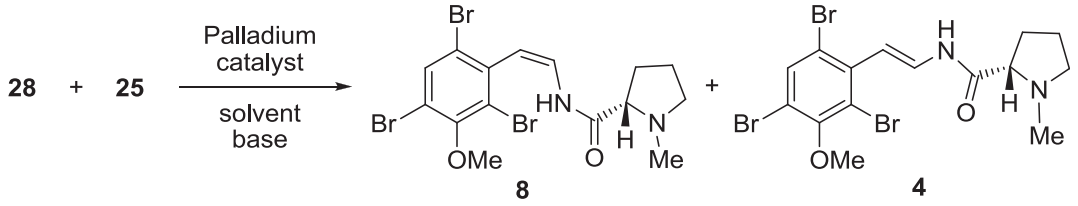


Scheme 4. Preparation of substituted vinyl acetate derivative.

Subsequently, as shown earlier (Scheme 3), the so obtained styryl acetate **28** was employed as a source of substituted vinyl moiety in the palladium(II)-catalyzed coupling reaction with (*S*)-1-methylpyrrolidine-2-carboxamide **25**. As illustrated in Table 2, a variety of conditions were explored. When $Pd(OAc)_2$ was employed in combination with K_3PO_4 in CH_3CN at 65 °C for a period of 12 h, to our pleasure, chromatographically separable *Z*-enamide **8** and *E*-enamide **4** were obtained in 4.4% and 16.9% yields, respectively (Table 2, entry 1). Employing slightly elevated temperature and increasing the reaction time, better yield of the enamides (**8**, **4**) could be achieved (Table 2, entry 2). In presence of pyridine as solvent as well as base, no reaction took place (Table 2, entry 3).

Moreover, solvents like DMF, DMSO and *t*-BuOH showed deleterious results (Table 2, entries 4, 5 and 8), while comparatively better yields of enamides were observed in THF (yield 40%, Table 2, entry 6) and dioxane (yield 36%, Table 2, entry 7). Thus, THF emerged as the solvent of choice for this reaction. Furthermore, we screened several bases to find out the optimum condition. Weaker bases like K_2CO_3, KOAc and Et_3N gave no reaction (Table 2, entries 9, 11 and 12), while stronger Cs_2CO_3 gave enamides in 36% yield (Table 2, entry 10). Among all the bases examined, K_3PO_4 was found to be the best for this reaction. Further optimization revealed that use of palladium-catalysts like $PdCl_2$, $Pd(PhCN)_2Cl_2$ and $(dba)_2Pd_2$ gave reduced yields compared to $Pd(OAc)_2$ (Table 2, entries 13, 15 and 16 vs 2), while $Pd(PPh_3)_2Cl_2$ delivered improved yield of enamides (Table 2, entry 14). Additional improvement in the yield of enamides could be achieved using increased amount of K_3PO_4 (3.0 equiv) (Table 2, entry 17), however, added increase in its ratio

Table 2
Screening of conditions for the synthesis of enamides **8** and **4** via Pd-catalyzed coupling reaction[a]

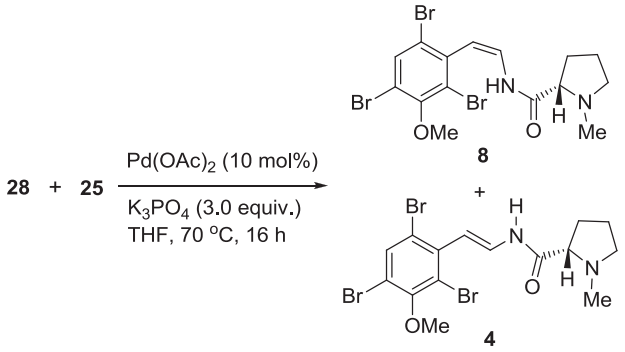


Entry	Ratio **28**:**25**	Solvent	Catalyst (10 mol %)	Base (equiv.)	Temp (°C)/time (h)	Conversion (%)[b]	Yield (%)[c]	Ratio **8**:**4**[d]
1	1.2:1[e]	CH_3CN	$Pd(OAc)_2$	K_3PO_4 (1.2)	65/12	75[f]	21 (28)[g]	21:79
2	1:1	CH_3CN	$Pd(OAc)_2$	K_3PO_4 (1.2)	60–80/23	83	38 (54)	27:73
3	1:1	Pyridine	$Pd(OAc)_2$	—	reflux/7	100	nd	—
4	1:1	DMF	$Pd(OAc)_2$	K_3PO_4 (1.2)	76/3	100	16	37:63
5	1:1	DMSO	$Pd(OAc)_2$	K_3PO_4 (1.2)	68/3	100	8	48:52
6	1:1	THF	$Pd(OAc)_2$	K_3PO_4 (1.2)	60–70/23	95	40 (42)	23:77
7	1:1	Dioxane	$Pd(OAc)_2$	K_3PO_4 (1.2)	reflux/7	100	36	19:81
8	1:1	*t*-BuOH	$Pd(OAc)_2$	K_3PO_4 (1.2)	85/22	97	17 (18)	5:95
9	1:1	THF	$Pd(OAc)_2$	K_2CO_3 (1.2)	70/12	nr	—	—
10	1:1	THF	$Pd(OAc)_2$	Cs_2CO_3 (1.2)	70/12	93	36 (39)	19:81
11	1:1	THF	$Pd(OAc)_2$	KOAc (1.2)	70/12	nr	—	—
12	2:1	THF	$Pd(OAc)_2$	Et_3N (1.2)	70/16	nr	—	—
13	2:1	THF	$PdCl_2$	K_3PO_4 (1.2)	70/63	100	29	5:95
14	2:1	THF	$Pd(PPh_3)_2Cl$	K_3PO_4 (1.2)	70/63	100	46	23:77
15	2:1	THF	$Pd(PhCN)_2Cl_2$	K_3PO_4 (1.2)	70/40	100	23	7:93
16	2:1	THF	$(dba)_2Pd_2$	K_3PO_4 (1.2)	70/40	100	22	4:96
17	**2:1**	**THF**	**$Pd(OAc)_2$**	**K_3PO_4 (3.0)**	**70/13**	**100**	**55**	**27:73**
18	2:1	THF	$Pd(OAc)_2$	K_3PO_4 (8.0)	70/13	100	50	19:81

[a] Reaction condition: **28** (0.1 or 0.2 mmol), **25** (0.1 mmol), solvent (1 mL), $Pd(OAc)_2$ (0.01 mmol,10 mol %) and base (as given) under argon atmosphere at the temperature as mentioned.
[b] Conversion based on recovered starting material **28**.
[c] Isolated combined yield of compounds **8** and **4** based on recovered starting material **28.**
[d] **8**/**4** ratio was calculated from the corresponding ^1H NMR analysis.
[e] 0.12 mmol of **28** was taken.
[f] Conversion based on recovered starting material **25**.
[g] Isolated yield of (**8**+**4**) based on recovered starting material **25**; nd: product not detected, nr: no reaction.

(8.0 equiv) was found to be associated with slightly decreased yield (Table 2, entry 18).

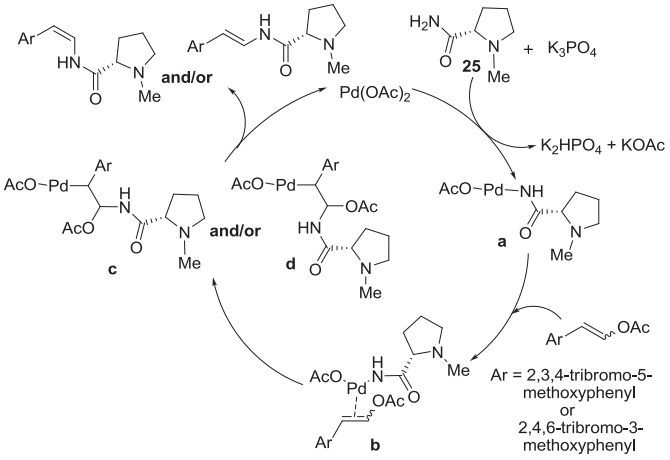
Thus, after substantial experimentation, we found that coupling of vinyl acetate **28** and amide **25** was best performed, as depicted in entry 17 (Table 2) with catalytic $Pd(OAc)_2$ and K_3PO_4 as the base in THF. Under this optimized condition *Z*-enamide **8** and *E*-enamide **4** were obtained in 15% and 40% yields, respectively (Scheme 5). In-



Scheme 5. Successful synthesis of amathamide F (**8**) for structure revision.

spection of the diagnostic coupling constants at 9.5 Hz and 15.0 for the vicinal olefinic protons in **8** and **4**, respectively, proved unambiguously the *cis*- and *trans*-olefin geometry of the products (see the Experimental section).

Based on the outcome of the reaction and Xu et al. hypothesis[24] we propose a mechanism for the synthesis of enamides (Scheme 6).



Scheme 6. Proposed reaction mechanism.

In the first step, prolinamide **25** makes a Pd–N bond in presence of K_3PO_4 and gives intermediate **a**, which coordinates with styryl acetate to give **b**. After insertion of styryl acetate into the Pd–N bond intermediates **c** and/or **d** forms, which on β-OAc elimination yield corresponding enamides.

Gratifyingly, the ^1H and ^{13}C NMR data of synthetic **8** are wholly consistent with its assigned structure, and they are in good agreement with those reported for the natural amathamide F (Table 1). Fig. 2 represents a ^1H NMR comparison of published and revised structures of amathamide F, which reveals one major discrepancy, as discussed earlier (Table 1), arising from the resonance of aromatic proton. Because we were unable to obtain an authentic sample of natural isolate, a direct comparison with the synthetic sample was not possible. Nevertheless, the almost identical spectroscopic data (Table 1) strongly suggest that the structure of amathamide F proposed by Blackman and co-workers as **7** (Fig. 1)[4b,c] is incorrect and should be represented by **8**[4e,9] (Scheme 5).

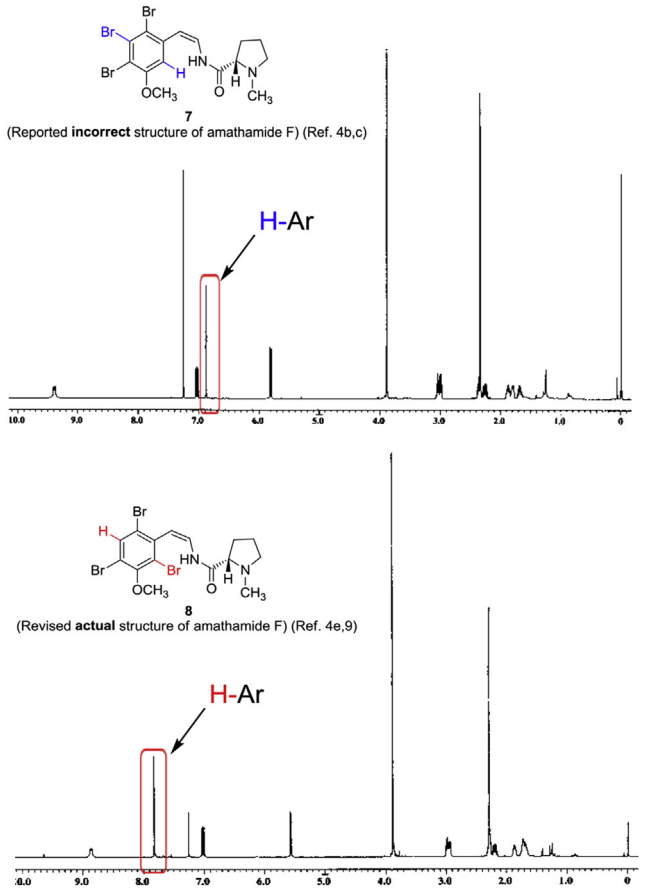


Fig. 2. Comparison of ^1H NMR spectra (in $CDCl_3$) of reported structure of (synthetic) amathamide F (**7**) and revised actual structure of (synthetic) amathamide F (**8**).

At this stage, a careful analysis of ^1H and ^{13}C NMR spectra of isolated amathamides having *E*-enamide moiety, i.e. amathamides A (**1**), C (**2**), E (**3**) and G (**5**) (Fig. 1)[4b] vis-a-vis those of the so obtained *E*-enamide **4** was carried out. To our delight, remarkable similarities were noticed between the chemical shift values of *E*-enamide **4** and reported NMR values of amathamide E (see Supplementary data)[4b] suggesting that *E*-enamide **4** would be the correct structure of amathamide E (**3**). Further, the structure of *E*-enamide **4** was unambiguously proved by single crystal X-ray analysis (Fig. 3).[27]

Note that to achieve the target amathamides E and F in improved yields, two alternative strategies were also undertaken (Scheme 7). Inspired by a recent report for stereoselective

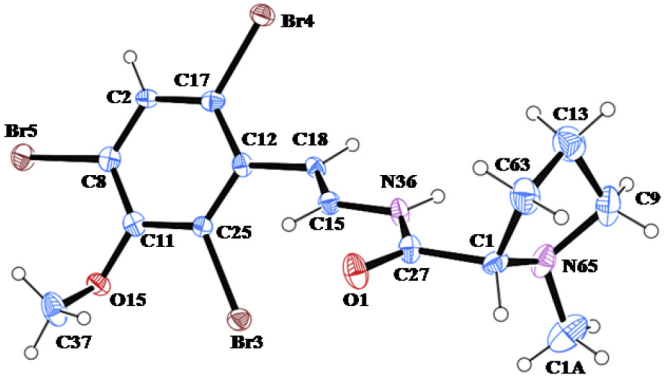
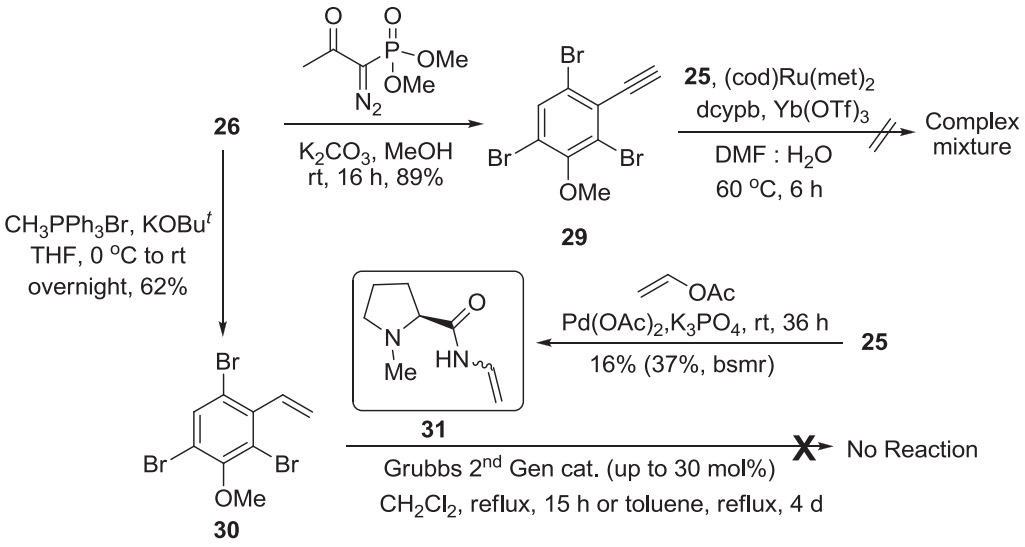


Fig. 3. X-ray crystal structure (ORTEP) of *E*-enamide **4**.



Scheme 7. Two unsuccessful approaches towards amathamides E and F.

syntheses of enamides under ruthenium catalyzed condition starting from primary amides and terminal alkynes,[28] alkyne **29**, prepared from aldehyde **26**[6] using Ohira-Bestmann reagent,[29] was subjected to couple with amide **25** under (cod)Ru(met)$_2$/dcypb/Yb(OTf)$_3$/DMF:H$_2$O condition,[28] but disappointingly, it yielded a complex mixture (Scheme 7). Further attempt to make enamide functionality by applying Grubbs cross-metathesis strategy between styrene **30**, obtained from aldehyde **26** via Wittig olefination,[30] and *N*-vinyl prolinamide derivative **31**, prepared from amide **25** under palladium-catalyzed condition,[24] also appeared fruitless even employing high loading (up to 30 mol %) of Grubbs' second-generation catalyst in refluxing toluene for a long (Scheme 7).[31]

3. Conclusions

In summary, we have confirmed the reported and actual structures of amathamide F through a synthesis. The synthesis, which requires only four steps from easily accessible starting material, features a late-stage palladium(II)-catalyzed N-vinylation of a primary amide functionality with a suitably tailored styryl acetate derivative to install the requisite benzylic double bond, a seemingly straightforward task eventually emerged highly challenging. In spite of low yield in the enamide forming last step, the good to excellent yields in the preceding steps enabled us to afford the natural alkaloid amathamide F. Moreover, we have also synthesized amathamide E as structure postulated. Possible extension of this methodology to synthesizing other members of amathamide can also be envisioned. Towards this journey, synthesis of several late-stage intermediates en route to target amathamides has been accomplished. Regrettably, the recalcitrance towards either successful manipulation of those advanced precursors or engineering a required union between suitable fragments to the target compounds prevented the culmination of several proposed expeditious routes; rather it led to surprising findings, which served to grow our understanding regarding the reactivities of the apparently simple amathamide core system. Furthermore, the explicit and conclusive evidence supporting the initial misassignment of substituents in the structural framework of marine-originated alkaloid as illustrated herein for amathamide F, substantiates the significance of total synthesis in unambiguous structural elucidation of natural products.

4. Experimental section

4.1. General methods

All reactions were performed in oven dried apparatus under inert atmosphere. All commercial grade solvents were distilled by using standard protocol and then used in the reactions. Melting points were obtained in open capillary tubes and are uncorrected. Optical rotations were measured using a 2 mL cell with a 1 dm path length and are reported as $[\alpha]_D^{22}$ (c=g/100 mL, solvent). IR spectra were recorded as KBr pellets (solids) or thin films (liquids).^{1}H NMR and proton-decoupled ^{13}C NMR spectra were recorded on JEOL or BRUKER spectrometer at 400 or 500 and 100 or 125 MHz, respectively. Samples for NMR were made in $CDCl_3$. The chemical shifts (δ ppm) and coupling constants J (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Data are reported as follows: (s=singlet, d=doublet, t=triplet, q=quartet, brs=broad singlet, m=multiplet). High-resolution mass spectra were recorded on a WATERS or Agilent Q-TOF micro mass spectrometer using electron spray ionization (ESI) mode or APCI (atmospheric pressure chemical ionization) mode and WATERS GCT micro mass spectrometer using electron ionization (EI) mode. Elemental analyses were done using CE-440 Elemental Analyzer of Exeter Analytical Inc at the Department of Chemistry, Indian Institute of Technology Kanpur, India.

4.2. Synthesis of 2-(2,3,4-tribromo-5-methoxyphenyl)oxirane 13

To a solution of **11** (80 mg, 0.21 mmol) in diethyl ether (10 mL) at 0 °C was added a freshly distilled solution of diazomethane in diethyl ether (5 mL) [prepared from 250 mg *N*-nitroso-*N*-methyl urea and 1 mL 60% aqueous KOH solution (0.6 gm KOH)] and allowed to come to room temperature. After completion of starting material (10 h) as indicated by TLC monitoring, the solvent was evaporated in rotavapor. The crude residue thus obtained was chromatographed over silica gel using (3–5% EtOAc/hexane) as eluent to furnish epoxide **13** (38 mg, 45%) as a white solid; mp 108–110 °C; [Found: C, 27.99; H, 1.81. $C_9H_7Br_3O_2$ requires C, 27.94; H, 1.82%]; R_f (10% EtOAc/hexane) 0.6; ν_{max} (KBr) 1560, 1520, 1440, 1400, 1340, 1220, 1180, 1060, 1000, 920, 840 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 4.09 (dd,

J=2.7, 3.9 Hz, 1H), 3.88 (s, 3H), 3.20 (dd, J=2.6, 5.5 Hz, 1H), 2.59 (dd, J=2.6, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 139.3, 129.3, 115.7, 115.4, 107.8, 56.9, 53.7, 50.7.

Further elution of the column with 10% EtOAc/hexane furnished 1-(2,3,4-tribromo-5-methoxy-phenyl)-ethanone **12** (21 mg, 25%) as a white solid; mp 120–122 °C; [Found: C, 28.36; H, 1.81. $C_9H_7Br_3O_2$ requires C, 27.94; H, 1.82%]; R_f (10% EtOAc/hexane) 0.4; ν_{max} (KBr) 1680, 1560, 1440, 1400, 1340, 1200, 1120, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 3.92 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 156.5, 143.7, 130.6, 118.2, 111.9, 109.1, 57.0, 30.3.

Employing Corey-Chaykovsky reaction, however, the epoxide **13** was achieved as an exclusive product. This was done according to following procedure: To a well stirred solution of aldehyde **11** (1.0 gm, 2.68 mmol) in CH_2Cl_2 (20 mL) was added tetra-*n*-butylammonium iodide (TBAI) (99 mg, 0.27 mmol, 10 mol %) and 50% aqueous NaOH (10 mL). Trimethyl sulphonium iodide (TMSI) (656 mg, 3.22 mmol, 1.2 equiv) was then added to the biphasic mixture and allowed to stir vigorously at room temperature over a period of 36 h whereupon the originally undissolved sulphonium salt slowly disappeared. The reaction mixture was then poured on to ice. The organic phase was separated and aqueous layer was extracted further with CH_2Cl_2 (2×10 mL). The organic phases were pooled, washed with water and brine and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuo and the residue was chromatographed over silica gel (5–8% EtOAc/hexane) as eluent to furnish the epoxide **13** (954 mg, 92%) as a white solid; mp 108–110 °C. The spectral data are similar to that detailed earlier.

4.3. Synthesis of 2-azido-1-(2,3,4-tribromo-5-methoxyphenyl)ethanol 15

To a stirred suspension of epoxide **13** (450 mg, 1.16 mmol) in MeOH–H_2O (4:1, 9 mL) was added ammonium chloride (137 mg, 2.56 mmol, 2.2 equiv) and sodium azide (378 mg, 5.8 mmol) and the mixture was refluxed at 85–90 °C over a period of 4 h. The reaction mixture was concentrated under vacuo to remove the solvents and the resulting aqueous residue was extracted with CH_2Cl_2 (3×10 mL). The organic phases were pooled, washed with brine and finally dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuo furnished the crude residue, which was chromatographed over silica gel to give a separable diastereomeric mixture (~1:2) of alcohols **14** and **15**. Employing (10% EtOAc/hexane), 2-azido-1-(2,3,4-tribromo-5-methoxyphenyl)ethanol **15** (320 mg, 64%) was separated first as colorless viscous liquid, which solidified on cooling; mp 78–80 °C; R_f (10% EtOAc/hexane) 0.6; ν_{max} (KBr) 3500–2500 (OH), 2000, 1560, 1400, 1340, 1320, 1260, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 5.19–5.17 (m, 1H), 3.86 (s, 3H), 3.55–3.49 (m, 1H), 3.24–3.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 141.4, 129.7, 115.9, 115.0, 109.3, 73.8, 57.0, 55.9; HRMS (EI): M^+, found 426.8165. $C_9H_8Br_3N_3O_2$ requires 426.8167.

Further elution of the column with increased polarity (15% EtOAc/hexane) gave the other diastereomer 2-azido-2-(2,3,4-tribromo-5-methoxyphenyl)ethanol **14** (170 mg, 34%) as a white solid; mp 130–132 °C; R_f (10% EtOAc/hexane) 0.5; ν_{max} (KBr) 3500–2500 (OH), 2000, 1560, 1400, 1340, 1320, 1260, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 5.16–5.14 (m, 1H), 3.86 (s, 3H), 3.84–3.82 (m, 1H), 3.55–3.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 137.7, 130.1, 116.6, 116.5, 109.9, 68.3, 65.4, 57.0.

4.4. Synthesis of (2*R*)-*N*-[2-hydroxy-2-(2,3,4-tribromo-5-methoxyphenyl)ethyl)]-1-methylpyrrolidine-2-carboxamide 17

To a stirred solution of **15** (282 mg, 0.655 mmol) in MeOH was added PPh_3 (258 mg, 0.983 mmol) and the resulting mixture was heated to reflux. After completion of starting material (1.5 h) as observed from TLC monitoring, the reaction mixture was evaporated under vacuo to remove the solvents and the crude mass thus obtained was then used in the subsequent coupling with *N*-methyl-L-proline without further purification of the resulting amino alcohol **16**.

To a stirred suspension of *N*-methyl-L-proline (93 mg, 0.72 mmol) in dry THF (3 mL) was added a solution DCC (150 mg, 0.73 mmol) in THF (1 mL) drop wise followed by HOBt (89 mg, 0.73 mmol) and catalytic amount of DMAP (10 mg, 0.007 mmol, 10 mol %) at 0 °C. After stirring for 10 min, a solution of crude amino alcohol **16** in dry THF (5 mL) was added drop wise to the reaction mixture under argon at 0–5 °C. The resultant suspension was then allowed to come to room temperature and stirred for 12 h. The precipitate thus formed was removed by filtration through a Whatman filter paper. The filtrate was evaporated under vacuo, the crude residue thus obtained was dissolved in EtOAc (20 mL) and washed with 5% $NaHCO_3$ solution. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuo furnished the crude residue, which was purified by column chromatography over silica gel using (0.5–1% MeOH/$CHCl_3$) as eluent to furnish the amide **17** (204 mg, 60% for two steps from **15**) as viscous liquid. R_f (5% MeOH/$CHCl_3$) 0.6; ν_{max} (neat) 3200 (OH, NH), 2900, 1640 (CONH), 1500, 1400, 1340, 1240, 1180, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) [a pair of diastereomer arising from the racemic nature of benzylic carbon, H* denotes the protons of second diastereomer] δ 7.73 (brs, 1H+1H*), 7.21 (s, 1H), 7.20 (s, 1H*), 5.08–5.06 (m, 1H+1H*), 3.84 (s, 3H+3H*), 3.60–3.57 (m, 1H+1H*), 3.51–3.48 (m, 1H+1H*), 3.33–3.29 (m, 1H+1H*), 3.01–2.98 (m, 2H+2H*), 2.33 (s, 3H) overlapping with 2.33–2.27 (m, 1H+1H*), 2.20 (s, 3H), 1.96–1.93 (m, 1H+1H*), 1.73–1.69 (m, 2H+2H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 156.4, 143.12, 143.08, 129.4, 115.0, 114.8, 110.0, 75.33, 75.26, 68.5, 68.3, 56.9, 56.65, 56.60, 49.5, 46.0, 45.9, 41.7, 41.5, 31.1, 31.0, 30.8, 29.7, 24.3, 24.2, 17.7; HRMS (EI): M^+, found 511.8943. $C_{15}H_{19}Br_3N_2O_3$ requires 511.8946.

4.5. Synthesis of 2-[(*R*)-1-methylpyrrolidine-2-carboxamido]-1-(2,3,4-tribromo-5-methoxyphenyl)ethyl acetate 18

To a well-stirred solution of **17** (24 mg, 0.046 mmol) in CH_2Cl_2 at 0 °C was added Py (5 mg, 0.06 mmol) followed by Ac_2O (6 mg, 0.06 mmol) and DMAP (1 mg, 0.008 mmol). The reaction mixture was allowed to come to room temperature and stirred over a period of 2 h. The reaction mixture was then poured into water (2 mL) and extracted with CH_2Cl_2 (3×4 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuo and the residue was purified by silica gel column chromatography using (1–2% MeOH/$CHCl_3$) as eluent to furnish the acetate **18** (24 mg, 92%). R_f (5% MeOH/$CHCl_3$) 0.7; ν_{max} (neat) 3200 (NH), 2800, 1720 ($COCH_3$), 1640 (CONH), 1500, 1400, 1360, 1200, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) [exists as a mixture of diastereomers arising from the racemic nature of benzylic carbon but peaks are not resolved in ^{1}H NMR] δ 7.55–7.51 (m, 1H), 6.95 (s, 1H), 6.24–6.19 (m, 1H), 3.88 (s, 3H), 3.73–3.55 (m, 2H), 3.36–3.32 (m, 1H), 3.06–3.04 (m, 1H), 2.83–2.80 (m, 1H), 2.35–2.28 (m, 1H) overlapping with 2.28 (s, 3H), 2.09 (s, 3H), 2.01–1.94 (m, 1H), 1.73–1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 169.7, 156.6, 139.0, 130.1, 130.0, 116.6, 116.5, 116.4, 109.3, 109.2, 74.9, 74.6, 68.9, 57.0, 56.8, 49.5, 42.0, 41.8, 31.1, 30.8, 29.8, 29.7, 24.4, 21.0, 17.7; HRMS (EI): M^+, found 553.9052. $C_{17}H_{21}Br_3N_2O_4$ requires 553.9051.

4.6. Synthesis of *N*-acetyl enamines 20 and 21

A mixture of Fe-powder (1.3 g, 23.1 mmol), Ac_2O (3.0 mL) and AcOH (0.3 mL) was refluxed for 30 min, then α,β-unsaturated nitro compound **19** (480 mg, 1.15 mmol) was added in two portions over

a period of 30 min and refluxed continuously for more 30 min. Reaction solution was cooled up to room temperature, added MeOH (6 mL) and filtered. Filtrate was concentrated under reduced pressure and redissolved in MeOH (2.5 mL). The solution was basified with methanolic KOH (10% w/w) up to pH 12–14 and filtered through Celite pad. Filtrate was concentrated under reduced pressure and the residue was purified over silica gel column chromatography (5–50% EtOAc/hexane) to give *N*-acetyl *Z*-enamine **20** (31.3 mg, 6%) as a light yellowish solid and *N*-acetyl *E*-enamine **21** (280.2 mg, 57%) as a light brown solid.

*4.6.1. Data for N-acetyl Z-enamine **20**.* Mp 218–220 °C; R_f (50% EtOAc/hexane) 0.6; ν_{max} (neat) 3273, 2921, 2852, 1676, 1641, 1461, 1367, 1269, 1067, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, 1H, J=10.2 Hz), 7.05 (t, 1H, J=10.2 Hz), 6.85 (s, 1H), 5.74 (d, 1H, J=9.0 Hz), 3.89 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 156.3, 136.8, 130.5, 123.6, 118.0, 115.3, 111.1, 110.1, 57.0, 23.4; HRMS (ESI): MH^+, found 425.8336. $C_{11}H_{11}Br_3NO_2$ requires 425.8340.

*4.6.2. Data for N-acetyl E-enamine **21**.* Mp 237–239 °C (decomposed); R_f (50% EtOAc/hexane) 0.5; ν_{max} (neat) 3255, 3041, 2928, 2846, 1632, 1362, 1176, 1071, 941, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$:DMSO-d_6 5:1) δ 9.90 (d, 1H, J=10.0 Hz), 7.36 (dd, 1H, J=10.4, 14.4 Hz), 6.89 (s, 1H), 6.38 (d, 1H, J=14.4 Hz), 3.80 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$:DMSO-d_6 5:1) δ 168.2, 155.5, 137.9, 128.8, 126.7, 116.1, 112.9, 111.2, 106.4, 56.4, 22.5; HRMS (APCI): MH^+, found 425.8343. $C_{11}H_{11}Br_3NO_2$ requires 425.8340.

4.7. Synthesis of *N*-Boc enamine 23

To a cooled (0 °C) solution of compound **21** (230 mg, 0.54 mmol) in anhydrous THF (3 mL) were added Boc_2O (234 mg, 1.07 mmol) and DMAP (13 mg, 0.11 mmol). Resultant reaction solution was stirred at 0 °C for 45 min, then added MeOH (3 mL) and hydrazine hydrate ($H_2NNH_2 \cdot H_2O$, 107 mg, 1.07 mmol). The reaction solution was allowed to warm to room temperature and stirred for 11 h at room temperature. After completion of starting material, reaction solution was poured in CH_2Cl_2 and washed with 1N HCl, saturated aqueous $CuSO_4$ solution, saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified over silica gel column chromatography (2–10% EtOAc/hexane) to give *N*-Boc enamine **23** (235.2 mg, 90%) as a white solid; mp 180–182 °C (decomposed); R_f (10% EtOAc/hexane) 0.6; ν_{max} (neat) 3305, 2979, 1703, 1646, 1365, 1241, 1150, 1058, 951, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, 1H, J=12.5 Hz), 6.91 (s, 1H), 6.67 (d, 1H, J=5.5 Hz), 6.27 (d, 1H, J=14.4 Hz), 3.92 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 152.6, 138.1, 129.6, 127.7, 116.8, 113.7, 109.9, 106.8, 81.7, 56.9, 28.3; HRMS (ESI): MH−Boc$^+$, found 383.8229. $C_9H_9Br_3NO$ requires 383.8234.

4.8. Synthesis of 2,3,4-tribromo-5-methoxystyryl acetate 24

To a cooled (0 °C) solution of methoxymethyltriphenylphosphonium chloride ($MeOCH_2PPh_3Cl$, 3.77 g, 11.0 mmol) in anhydrous THF (10 mL) was added potassium *tert*-butoxide ($KOBu^t$, 1.20 g, 10.7 mmol). The mixture was stirred at 0 °C for 20 min and then for 1.5 h at room temperature, then a solution of aldehyde **11**[5] (2.0 g, 5.4 mmol) in anhydrous THF (27 mL) was added via cannula at 0 °C. The reaction solution was allowed to warm to room temperature and stirred for 15 h. The reaction solution was filtered through a short silica pad and the filtrate was then washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1–5% EtOAc/hexane) as eluent to furnish the Wittig-product, which was used as such in the next reaction.

To a cooled (0–10 °C) solution of the Wittig-product (obtained above) in anhydrous CH_2Cl_2 (70 mL) was added methanesulphonic acid ($MeSO_3H$, 1.3 g, 13.5 mmol) drop wise. After 3 h, the reaction was poured in saturated aqueous $NaHCO_3$ solution (20 mL), then organic phase was separated and washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2–10% EtOAc/hexane) to give homologated aldehyde (986 mg, 48% in two steps) as a white solid.

To a solution of homologated aldehyde (obtained above) (400 mg, 1.03 mmol) in Ac_2O (6 mL) was added KOAc (12.7 mg, 0.13 mmol). The resultant solution was stirred at 120 °C for 2 h, then reaction solution was cooled up to room temperature and all volatiles were removed under reduced pressure. The residue was taken in CH_2Cl_2 (30 mL) and washed with 10% aqueous Na_2CO_3 solution (4 mL), water (3 mL), brine (6 mL), dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (2–8% EtOAc/hexane) to give **24** (360 mg, 81%) 48:52 *cis*:*trans* mixture as a white solid; mp 133–135 °C; R_f(15% EtOAc/hexane) 0.6; ν_{max} (neat) 3087, 2933, 2852, 1761, 1570, 1415, 1366, 1197, 1109, 925, 851, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 and 7.40 (each d, due to geometrical isomer 1H, J=12.8 Hz and 7.3 Hz), 7.36 and 6.90 (each s, due to geometrical isomer, 1H), 6.75 and 6.07 (each d, due to geometrical isomer, 1H, J=12.5 Hz and 7.3 Hz), 3.91 and 3.90 (each s, due to geometrical isomer, 3H), 2.23 and 2.21 (each s, due to geometrical isomer 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 166.9, 156.2, 155.7, 138.5, 135.9, 134.9, 129.9, 129.6, 117.8, 117.8, 116.1, 115.4, 115.1, 112.2, 111.7, 108.1, 57.0, 56.7, 20.9, 20.8; HRMS (ESI): MNH_4^+, found 443.8445. $C_{11}H_{13}Br_3NO_3$ requires 443.8446.

4.9. Synthesis of enamide 7

To a solution of compound **24** (271 mg, 0.63 mmol) in anhydrous THF (2 mL) were added prolinamide **25**[26] (40.5 mg, 0.32 mmol), $Pd(OAc)_2$ (7.1 mg, 0.03 mmol) and K_3PO_4 (202 mg, 0.95 mmol). Resultant reaction solution was stirred at 70 °C for 16 h. After that reaction solution was cooled up to room temperature and filtered through a small silica gel pad and eluted with CH_2Cl_2. Filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (20–60% EtOAc/hexane) to give product **7** (20.6 mg, 13%) was obtained as a yellowish liquid. R_f (60% EtOAc/hexane) 0.4; $[\alpha]_D^{20}$ −6.3 (*c* 0.12, $CHCl_3$); ν_{max} (neat) 3326, 2922, 2852, 1695, 1644, 1464, 1389, 1262, 1064, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, 1H, J=11.6 Hz), 7.04 (dd, 1H, J=9.6 Hz, 12.1 Hz), 6.89 (s, 1H), 5.81 (d, 1H, J=9.5 Hz), 3.89 (s, 3H), 3.05 (t, 1H, J=7.8 Hz), 3.00 (dd, 1H, J=5.5 Hz, 10.4 Hz), 2.38–2.35 (m, 1H), 2.34 (s, 3H), 2.28–2.22 (m, 1H), 1.91–1.84 (m, 1H), 1.83–1.77 (m, 1H), 1.73–1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 156.2, 137.1, 130.5, 123.1, 118.2, 110.4, 68.9, 56.82, 56.77, 42.3, 31.1, 24.6; HRMS (ESI): MH^+, found 494.8914. $C_{15}H_{18}Br_3N_2O_2$ requires 494.8918.

4.10. Synthesis of 2,4,6-tribromo-3-methoxystyryl acetate 28

To a solution of 2-(2,4,6-tribromo-3-methoxyphenyl)acetaldehyde **27** (233 mg, 0.60 mmol) in Ac_2O (2 mL) was added KOAc (7.4 mg, 0.07 mmol). The resultant solution was stirred at 120 °C for 2 h, then reaction solution was cooled up to room temperature and all volatiles were removed under reduced pressure. The residue was taken in CH_2Cl_2 (20 mL) and washed with 10% aqueous Na_2CO_3 solution (3 mL), water (3 mL), brine (3 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (1–4% EtOAc/hexane) to give **28** (252 mg, 97%) 33:67 *cis*:*trans* mixture as a white solid; mp 124–127 °C; R_f (10% EtOAc/hexane) 0.6; ν_{max} (neat) 2922, 2850, 1748, 1448, 1351, 1219, 1105, 1024, 900, 800, 718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.71 and 7.36 (each d, due to geometrical isomer 1H, J=12.8 Hz and

7.0 Hz), 6.26 and 5.71 (each d, due to geometrical isomer, 1H, J=12.8 Hz and 6.8 Hz), 3.88 and 3.86 (each s, due to geometrical isomer, 3H), 2.23 and 2.11 (each s, due to geometrical isomer 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 167.5, 154.2, 153.9, 142.0, 136.4, 135.7, 135.6, 135.3, 121.2, 121.0, 119.2, 119.0, 117.2, 117.0, 112.9, 110.8, 60.6, 20.9, 20.8; HRMS (ESI): MH^+, found 426.8181. $C_{11}H_{10}Br_3O_3$ requires 426.8180.

4.11. Syntheses of enamides 8 and 4

To a solution of compound **28** (856 mg, 2.0 mmol) in anhydrous THF (10 mL) were added prolinamide **25** (128 mg, 1.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol) and K_3PO_4 (637 mg, 3.0 mmol). Resultant reaction solution was stirred at 70–80 °C for 13 h. After that reaction solution was cooled up to room temperature and filtered through a small silica gel pad and eluted with CH_2Cl_2. Filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (20–60% EtOAc/hexane) to give *Z*-enamide **8** (75 mg, 15%) as a light yellow liquid and *E*-enamide **4**[6] (197 mg, 40%) as a white solid.

*4.11.1. Data for Z-enamide **8**.* R_f (60% EtOAc/hexane) 0.8; $[\alpha]_D^{22}$ −16.8 (*c* 0.95, $CHCl_3$); ν_{max} (neat) 3315, 3067, 2936, 2850, 1699, 1653, 1478, 1022, 928, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, 1H, J=11.3 Hz), 7.82 (s, 1H), 7.02 (dd, 1H, J=9.3 Hz, 12.1 Hz), 5.57 (d, 1H, J=9.5 Hz), 3.88 (s, 3H), 2.99 (t, 1H, J=7.2 Hz), 2.95 (dd, 1H, J=4.9 Hz, 10.4 Hz), 2.32–2.27 (m, 1H), 2.29 (s, 3H), 2.24–2.16 (m, 1H), 1.90–1.84 (m, 1H), 1.77–1.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 154.3, 137.2, 135.6, 123.9, 121.0, 119.3, 117.3, 108.8, 68.7, 60.6, 56.7, 42.1, 31.2, 24.6; HRMS (ESI): MH^+, found 494.8918. $C_{15}H_{18}Br_3N_2O_2$ requires 494.8918.

*4.11.2. Data for E-enamide **4**.* Mp 132–134 °C; R_f (60% EtOAc/hexane) 0.6; $[\alpha]_D^{22}$ −65.0 (*c* 1.0, CH_2Cl_2) [lit.[6] $[\alpha]_D^{23}$ −9.8 (*c* 0.01, CH_2Cl_2)]; ν_{max} (neat) 3268, 2971, 2842, 2779, 1669, 1641, 1476, 1346, 1211, 1043, 978, 890, 716 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (d, 1H, J=11.3 Hz), 7.78 (s, 1H), 7.42 (dd, 1H, J=11.6 Hz, 14.7 Hz), 6.06 (d, 1H, J=15.0 Hz), 3.87 (s, 3H), 3.20–3.17 (m, 1H), 3.02 (dd, 1H, J=5.2 Hz, 10.4 Hz), 2.45 (s, 3H), 2.43–2.40 (m, 1H), 2.32–2.24 (m, 1H), 1.97–1.91 (m, 1H), 1.85–1.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 154.1, 137.5, 135.7, 129.7, 120.8, 118.7, 115.9, 110.4, 68.8, 60.6, 56.8, 42.2, 31.1, 24.6; HRMS (ESI): MH^+, found 494.8927. $C_{15}H_{18}Br_3N_2O_2$ requires 494.8918.

4.12. Synthesis of 1,3,5-tribromo-2-ethynyl-4-methoxybenzene 29

To a solution of aldehyde **26** (318 mg, 0.85 mmol) in anhydrous MeOH (13 mL) were added K_2CO_3 (236 mg, 1.71 mmol) and dimethyl-1-diazo-2-oxopropylphosphonate (197 mg, 1.02 mmol). The resultant solution was stirred at room temperature for 16 h and then reaction solution was diluted with Et_2O (25 mL), washed with 5% aqueous $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (0.6% EtOAc/Hexane) to give **29** (280 mg, 89%) as a white solid; mp 99–101 °C; R_f (10% EtOAc/hexane) 0.7; ν_{max} (neat) 3272, 3070, 2937, 2109, 1447, 1413, 1349, 1023, 856, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 3.87 (s, 3H), 3.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 135.4, 126.9, 123.1, 121.5, 119.2, 87.6 80.6, 60.7; HRMS (ESI): MH^+, found 366.7954. $C_9H_6Br_3O$ requires 366.7969.

4.13. Synthesis of 1,3,5-tribromo-2-methoxy-4-vinylbenzene 30

To a cooled (0 °C) suspension of CH_3PPh_3Br (1.81 g, 5.1 mmol) in anhydrous THF (10 mL) was added potassium *tert*-butoxide ($KOBu^t$, 583 mg, 5.2 mmol). The resultant reaction solution was stirred at 0 °C for 30 min and at room temperature for 1 h. After that a solution of aldehyde **26** (948 mg, 2.5 mmol) in anhydrous THF (8 mL) was added dropwise via cannula at 0 °C. Reaction solution was allowed to warm to room temperature and stirred overnight. Reaction solution was filtered through Celite pad, filtrate washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (Hexane only) to give **30** (582.6 mg, 62%) as a white crystalline solid; mp 53–55 °C; R_f (10% EtOAc/hexane) 0.5; ν_{max} (neat) 3068, 2938, 2839, 1449, 1400, 1323, 1251, 1004, 913, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.52 (dd, 1H, J=11.4 Hz, 17.7 Hz), 5.67 (d, 1H, J=11.4 Hz), 5.58 (d, 1H, J=17.7 Hz), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 139.6, 135.5, 134.9, 123.1, 120.1, 118.0, 116.6, 60.5; HRMS (ESI): MH^+, found 368.8205. $C_9H_8Br_3O$ requires 368.8125.

4.14. Synthesis of (*S*)-1-methyl-*N*-vinylpyrrolidine-2-carboxamide 31

To a solution of prolinamide **25**[26] (64 mg, 0.5 mmol) in vinyl acetate (1 mL) were added $Pd(OAc)_2$ (11.3 mg, 0.05 mmol) and K_3PO_4 (106 mg, 0.5 mmol). Resultant reaction solution was stirred at room temperature for 36 h. After that all volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (20–80% EtOAc/hexane) to give **31** (12.5 mg, 16%; 37% based on recovered starting material) as a colorless viscous liquid; R_f (30% EtOAc/hexane) 0.6; $[\alpha]_D^{20}$ −89.1 (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3307, 2940, 2805, 1730, 1666, 1639, 1494, 1371, 1238, 1045, 857 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 and 9.09 (each br s, due to geometrical isomer, 1H), 6.98–6.84 (m, 1H), 5.42 and 5.16 (each *q*, due to geometrical isomer, 1H, J=6.5 Hz), 4.66 (dd, 1H, J=8.8 Hz, 15.9 Hz), 4.43 (t, 1H, J=7.7 Hz), 3.15–3.11 and 3.04–3.02 (each m, due to geometrical isomer, 1H), 2.97–2.91 and 2.77–2.72 (each m, due to geometrical isomer, 1H), 2.60 and 2.45 (each s, due to geometrical isomer, 3H), 2.11–2.07 (m, 2H), 2.04 and 2.01 (each s, due to geometrical isomer, 3H), 1.87–1.67 (m, 3H), 1.48 and 1.40 (each d, due to geometrical isomer, 3H, J=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.9, 170.3 and 169.8 (due to geometrical isomer), 128.8 and 128.6 (due to geometrical isomer), 95.6 and 95.5 (due to geometrical isomer), 73.5, 72.7, 71.7 and 71.6 (due to geometrical isomer), 56.2 and 56.0 (due to geometrical isomer), 36.4, 35.6, 35.5 and 34.6 (due to geometrical isomer), 23.4, 23.2 and 21.5 (due to geometrical isomer), 17.3 and 16.3 (due to geometrical isomer); HRMS (APCI): MH^+, found 155.1175. $C_8H_{15}N_2O$ requires 155.1184.

Acknowledgements

F.A.K. gratefully acknowledges Council of Scientific and Industrial Research (CSIR) for financial support. S.A. and S.C. thank CSIR for the fellowship.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.04.091.

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