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The *N*-Acyliminium Pictet–Spengler Condensation as a Multicomponent Combinatorial Reaction on Solid Phase and Its Application to the Synthesis of Demethoxyfumitremorgin C Analogues

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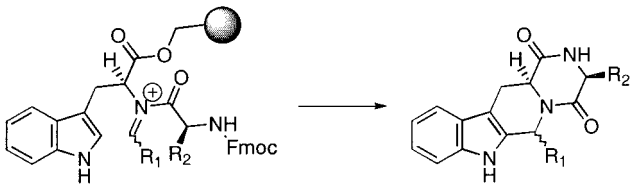
ABSTRACT



L-Tryptophan immobilized on polystyrene–Wang resin was sequentially reacted with an aldehyde and Fmoc-amino acid chloride. This generates a transient *N*-acyliminium species which undergoes Pictet–Spengler condensation to give a mixture of cis and trans tetrahydro-*β*-carbolines. Removal of the Fmoc protecting group, with concomitant diketopiperazine formation, results in cyclative cleavage of the desired products from the resin.

Small molecules that block eukaryotic cell cycle progression are attracting much attention[1] as mechanistic probes and potential therapeutic agents. Recently, a series of prenylated indole alkaloids was isolated[2] that cause cell cycle arrest[3] at the G_2/M transition. The most active of these fungal natural products, demethoxyfumitremorgin C (**1**), contains a tetrahydro-*β*-carboline and diketopiperazine ring embedded within. Both structural motifs are popular templates for drug discovery and have been used as scaffolds for combinatorial libraries.[4] We have previously devised[5] a concise three-step total synthesis of demethoxyfumitremorgin C. Here, we report the adaptation of our route to the solid phase,[6] thus adding the *N*-acyliminium Pictet−Spengler condensation[7−9] to the repertoire of multicomponent reactions[10] carried out under such conditions.

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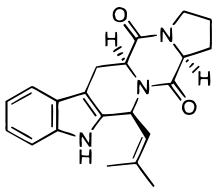

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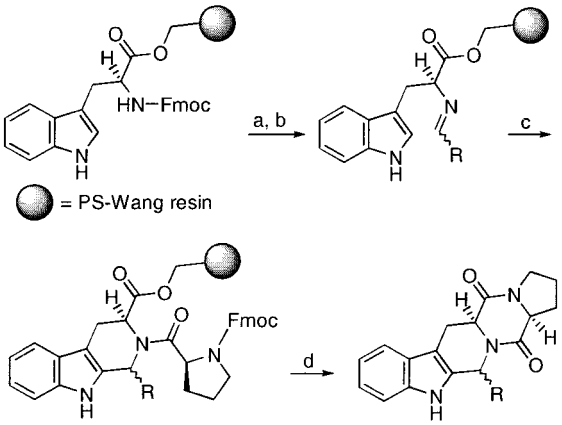
For the solid-phase synthesis of **1** (Scheme 1), commercially available Fmoc-L-tryptophan[11] immobilized on the

Scheme 1[a]



[a]Reagents: (a) 20% piperidine, CH_2Cl_2; (b) R_1-CHO, $HC(OMe)_3$, CH_2Cl_2; (c) Fmoc-L-ProCl, pyridine, CH_2Cl_2; (d) 20% piperidine, CH_2Cl_2;

polystyrene−Wang resin was deprotected, and the free amine reacted with senecialdehyde and trimethyl orthoformate.[12] Treatment of the resulting imine with Fmoc-L-proline acid chloride[13] induced *N*-acyliminium Pictet−Spengler reaction. Fmoc deprotection by piperidine, with concomitant cyclative resin cleavage by diketopiperazine ring closure, afforded natural product **1** and its *trans* epimer (Table 1, entry 1).

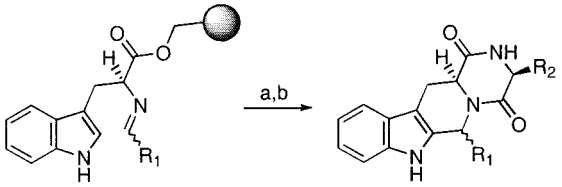
Table 1. Synthesis of Demethoxyfumitremorgin C Analogues

entry	R	yield, %[a]	*cis*/*trans* ratio[b]
1	Me_2C=CH	49	53/47
2	Me_2CHCH_2	61	24/76
3	cyclohexyl	73	14/86
4	PhCH=CH	61	59/41
5	Ph	76	46/54
6	*p*-MeO-C_6H_4	75	56/44
7	*p*-NO_2-C_6H_4	61	44/56

[a] Isolated overall yield after chromatography, based on the loading of Wang resin. [b] Determined as explained in footnote 14.

The *cis*−*trans* ratio[14] and overall yield of tetrahydro-*β*-carbolines[15] was comparable to those of our solution-phase synthesis.

Scheme 2[a]



[a]Reagents: (a) Fmoc--L-aa-COCl, pyridine, CH_2Cl_2; (b) 20% piperidine, CH_2Cl_2;

As shown in Table 1, the solid-phase *N*-acyliminium Pictet−Spengler condensation is tolerant of a variety of aldehydes. Besides other saturated and unsaturated aliphatic examples (entries 2−4), both electron-deficient and electron-rich aromatic aldehydes (entries 5−7) are compatible with this process, facilitating preparation of a broad range of demethoxyfumitremorgin C analogues.

The final diketopiperazine ring-forming cyclative cleavage ensures a high purity of the desired compounds. Although use of the secondary amino acid L-proline is expected to favor diketopiperazine formation, it is not essential. We have also prepared demethoxyfumitremorgin C analogues where the proline unit has been replaced by other amino acids (Scheme 2, Table 2).[16,17]

Table 2. Synthesis of Demethoxyfumitremorgin C Analogues Lacking the Proline Ring

entry	R_1	R_2	yield, %[a]	*cis*/*trans* ratio[b]
1	cyclohexyl	$PhCH_2$	39	40/60
2	Me_2C=CH	Me_2CHCH_2	36	64/36
3	PhCH=CH	Me_2CHCH_2	54	59/41
4	Ph	$PhCH_2$	85	58/42
5	Ph	Me_2CHCH_2	72	57/43
6	*p*-$MeOC_6H_4$	$PhCH_2$	64	57/43
7	*p*-$MeOC_6H_4$	Me_2CHCH_2	57	49/51
8	*p*-$NO_2C_6H_4$	H	74	50/50
9	*p*-$NO_2C_6H_4$	$PhCH_2$	73	50/50
10	*p*-$NO_2C_6H_4$	Me_2CHCH_2	88	55/45

[a] Isolated overall yield after chromatography, based on the loading of Wang resin. [b] Determined as explained in footnote 14.

In summary, the *N*-acyliminium Pictet−Spengler condensation is a useful addition to existing C−C and C−X bond-

(8) Solid-phase tetrahydro-*β*-carboline syntheses via Pictet−Spengler reactions under traditional protic conditions have been reported: (a) Kaljuste, K.; Undén, A. *Tetrahedron Lett.* **1995**, *36*, 9211−9214. (b) Mohan, R.; Chou, Y.-L.; Morrissey, M. M. *Tetrahedron Lett.* **1996**, *37*, 3963−3966. (c) Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041−5044. (d) Mayer, J. P.; Bankaitis-Davis, D.; Zhang, J.; Beaton, G.; Bjergarde, K.; Andersen, C. M.; Goodman, B. A.; Herrera, C. J. *Tetrahedron Lett.* **1996**, *37*, 5633−5636. (e) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−1294. (f) van Loevezijn, A.; van Maarseveen, J. H.; Stegman, K.; Visser, G. M.; Koomen, G.-J. *Tetrahedron Lett.* **1998**, *39*, 4737−4740. (g) Sauerbrei, B.; Jungmann, V.; Waldmann, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 1143−1146.

(9) For a recent solid-phase synthesis of homoallylic amines via *N*-acyliminium ion reactions, see: Meester, W. J. N.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601−1604.

(10) For a review, see: Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255−270.

forming heterocyclization reactions performed on the solid phase. It brings together three reacting partners—a β-arylamine with an electron-rich aromatic ring such as indole, an aldehyde, and an acylating agent—which are commercially available with a high degree of diversity.

Compared to previous classical protic Pictet−Spengler reactions on the solid phase, our protocol has several noteworthy features. First, the avoidance of acidic conditions allows wide flexibility in the choice of solid-phase linkers. The increased reactivity of the *N*-acyliminum species enables the successful use of normally unreactive aldehydes such as α,β-unsaturated examples. Furthermore, the free secondary amine resulting from the protic Pictet−Spengler reaction is rather hindered. Diversification of this amine by acylation or sulfonylation is troublesome and does not always proceed in high yield. In our case, the functionalization of the tetrahydro-β-carboline occurs as part of the Pictet−Spengler reaction itself.

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(11) Abbreviations: aa = amino acid, Fmoc = (9*H*-fluoren-9-ylmethoxy-)carbonyl, Pro = proline.

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(14) All compounds were characterized spectroscopically (NMR, MS). Assignment of cis/trans products was done by ^{1}H NMR − the cis isomer has a more upfield chemical shift for the C1-methine in the tetrahydro-β-carboline ring. The *cis/trans* ratio was calculated based on the isolated yield, or by NMR peak integration in cases where the two diastereomers were not completely separable by chromatography. In all but two of the entries in Tables 1 and 2, the cis compound is more polar than the trans by TLC.

(15) By NMR, we also detected approximately 10% of an epimeric pair of products, due to racemization of the tryptophan imine.

(16) Workup for solid-phase reactions refers to filtration, washing of the resin [CH_2Cl_2 (x5), DMF (x5), CH_2Cl_2 (x5), 10% MeOH−CH_2Cl_2 (x5), and MeOH (x5)], and drying before use in the next step.

(17) **Typical Experimental Procedure**: Fmoc-L-Trp−Wang resin (Calbiochem-Novabiochem, loading of 0.54 mmol/g) was deprotected with 20% piperidine in DMF (rt, 20 min ×2) and worked up.[16] The resin (ca. 1 g, 0.62 mmol/g) was next shaken with an aldehyde (10 equiv) and trimethyl orthoformate (20 equiv) in CH_2Cl_2 (7 mL/g resin) overnight at rt and worked up. The imine-bearing resin (ca. 0.07−0.1 mmol) was placed in a 20 mL glass vial and swelled by the addition of dry CH_2Cl_2. Solutions of an Fmoc-amino acid chloride (0.4−0.6 M, 10 equiv) and pyridine (4 M, 15 equiv) in CH_2Cl_2 were added. After the vial was agitated at rt for 40−45 h, the resin was filtered through a fritted 2 mL plastic syringe and worked up. The resin was then swollen by addition of CH_2Cl_2 (1.6 mL), followed by piperidine (0.4 mL). After being shaken at rt for 20−30 min, the resin was filtered and washed with CH_2Cl_2 (×10), 10% MeOH−CH_2Cl_2 (×5), and MeOH (×5). The combined filtrates were concentrated, and the residue was purified by preparative TLC (silica). The plate was first developed with 50% ethyl acetate−hexanes and the less polar first band (dibenzofulvene−piperidine adduct) collected to estimate the acylation yield in the *N*-acyliminium Pictet−Spengler reaction. The plate was then redeveloped with a second solvent system, typically 10% MeOH−CH_2Cl_2. Two major bands were seen, corresponding to *cis* and *trans* tetrahydro-β-carboline products, and collected.