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Solid-phase synthesis of 5-(3-indolyl)oxazoles that inhibit lipid peroxidation

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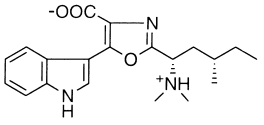
Abstract

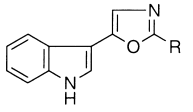
A series of 5-(3-indolyl)oxazoles were prepared by solid-support synthesis. Oxidative cyclization of an immobilized dipeptide containing tryptophan gave these oxazoles efficiently.

Keywords: alkaloid; indoles; oxazoles; solid-phase synthesis.

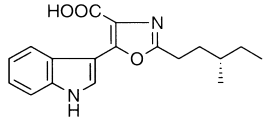
Martefragin A (**1**) was isolated a few years ago from the sea alga *Martensia fragilis* Harvey, and has been shown to have a fully substituted oxazole ring and two stereogenic centers at the side chain.[1] Martefragin A (**1**) has been reported to be a strong inhibitor of lipid peroxidation (ca. 100 times more potent than α-tocopherol) (Fig. 1).



Martefragin A (**1**)



Pimprinine (**2**, R = CH_3)
Pimprinethine (**3**, R = CH_2CH_3)
Pimprinaphine (**4**, R = CH_2Ph)
WS-30581 A (**5**, R = $CH_2CH_2CH_3$)
WS-30581 B (**6**, R = $CH_2CH_2CH_2CH_3$)



Deaminomartefragin (**7**)

Figure 1. 5-(3-Indolyl)oxazole alkaloids

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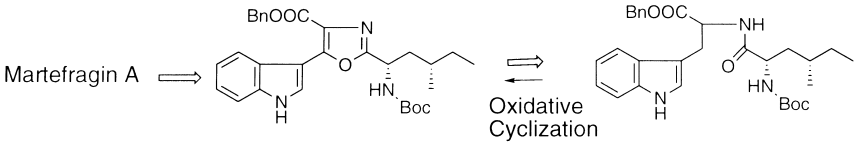
Several other 5-(3-indolyl)oxazoles have been isolated, and they have also shown interesting biological activities. Pimprinine (**2**), which has the simplest structure in this group, was isolated from *Streptoverficillium clivareticuli* and other microorganisms.[2] Pimprinine (**2**) inhibits monoamine oxidase (MAO) and has an anti-epileptic effect.[3] WS-30581 A (**5**) and B (**6**) were also isolated from *Streptoverficillium*, and are reported to have potent inhibitory effects on platelet aggregation.[4,5] The synthesis of **2**, **3** and **4** has been reported by Joshi and other groups.[2b,6]

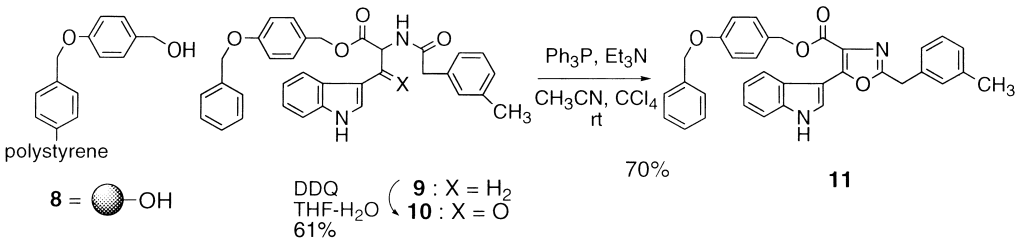
We previously reported the first total synthesis of martefragin A and three possible stereoisomers to confirm its structure, including the absolute configurations of the stereocenters.[7] During these synthetic studies, we found that deaminomartefragin (**7**), a simpler analog of **1**, showed stronger activity than the mother compound itself. Therefore, we became interested in the biological activities of compounds with an indolyloxazole skeleton. Recently, the usefulness of a solid-phase synthesis for exploring the biological activities of compounds with a common skeleton has been well developed.[8] Therefore, we used a solid-phase synthesis to obtain versatile derivatives with the 5-(3-indolyl)oxazole skeleton.

In our synthesis of martefragin A, outlined in Scheme 1,[7] the characteristic heterocyclic ring system was constructed by oxidative cyclization of a dipeptide containing tryptophan, using dichlorodicyanoquinone (DDQ).[3b] Although DDQ oxidation was recently used in a solid-phase synthesis to cleave a benzyl-type linker,[9] considering the ease of severing the linkage between the product and a resin, we chose Wang resin **8** as a solid support. We first studied the selective oxidation of the side chain of **9** without cleavage of the 4-(benzyloxy)benzyl protecting group.



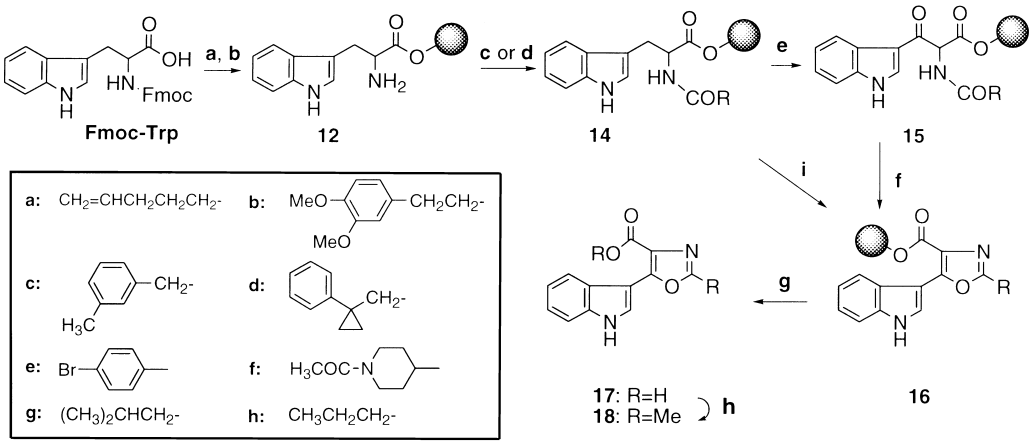
Scheme 1.

Compound **9** was prepared from Fmoc–tryptophan in three steps: (i) 4-(benzyloxy)benzyl alcohol, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·HCl (EDCI), DMAP, rt; (ii) 20% piperidine/DMF, rt; and (iii) (3-methylphenyl)acetic acid, Ph_3P, NCS, pyridine, CH_2Cl_2, 89% overall yield (Scheme 2). When **9** was treated with 2.2 equiv. DDQ in 10% aq. THF at rt for 20 min, ketoester **10** was obtained in 61% yield, which was converted to oxazole **11** under the mild conditions (70%). No reaction was observed when other reagents, such as chloranil, ceric ammonium nitrate, or iodine[10] were employed. Then we started to investigate a solid-phase synthesis of 5-(3-indolyl)oxazoles.



Scheme 2.

Fmoc–tryptophan was condensed with Wang resin **8** by a standard technique [1,3-diisopropylcarbodiimide (DIC), DMAP, DMF, rt, 59 h], and the Fmoc group was then removed by a 20% piperidine/DMF mixture (rt, 20 min). Immobilized tryptophan **12** was condensed with a variety of carboxylic acids **13a–f** (Ph_3P, NCS, pyridine, CH_2Cl_2, rt, 15 min) or carboxylic acid anhydrides **13g,h** (pyridine, rt, 2 h). Washing the resin afforded *N*-acyltryptophan resin **14a–h** (Scheme 3). The crucial oxidation of immobilized *N*-acyltryptophan was carried out as follows: A mixture of *N*-acyltryptophan resin **14a–h** (0.16 mmol) and DDQ (2 equiv.) in 10% aq. THF (3 mL) was stirred at rt for 20 min. The resin was washed with DMF–5% aq. ascorbic acid, DMF, DMF–aq. $NaHCO_3$. Further washing with CH_2Cl_2, then EtOH (three cycles), and finally CH_2Cl_2 afforded **15a–h**. Compounds **15a–h** were then reacted with triethylamine (20 equiv.), CCl_4 (1.5 mL), and PPh_3 (20 equiv.) in acetonitrile (1.5 mL) at rt for 2 h to give **16a–h**. The resin was washed several times with DMF. Further washings with CH_2Cl_2 and EtOH (three cycles), and CH_2Cl_2, followed by cleavage of the resin with 20% TFA–CH_2Cl_2 (rt, 1.5 h) gave carboxylic acids **17a–h**. The carboxylic acids were treated with TMS–diazomethane to give crude **18a–h**, which were purified by column chromatography.



Scheme 3. *Reagents and conditions*: (a) **8**, DIC (5 equiv.), DMAP (0.5 equiv.), DMF, rt, 20 h; (b) 20% piperidine/DMF, rt, 2 h; (c) RCOOH **13a–h** (5 equiv.), DIC (5 equiv.), DMF, rt, 20 h; (d) $(RCO)_2O$ **13g,h** (5 equiv.), pyridine, rt, 20 h; (e) DDQ (2 equiv.), THF:H_2O (9:1), rt, 20 min; (f) Ph_3P (20 equiv.), Et_3N (20 equiv.), CCl_4, CH_3CN, rt, 2 h; (g) 20% TFA/CH_2Cl_2, rt, 20 min; (h) $TMSCHN_2$, ether; (i) DDQ (10 equiv.), THF, rt, 2 h

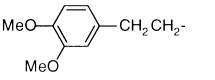
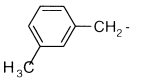
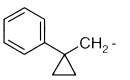
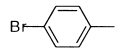
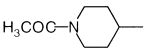
As shown in Table 1, **18a–h** were obtained from Fmoc–tryptophan in seven steps in 9.4 to 41.6% yield. These yields were calculated based on initial loading level of the Wang resin, 0.8 mmol/g. All the products were identical in all respects to authentic material prepared using a conventional synthesis.

Single-step conversion of **14** to **16** was also achieved by using 10 equiv. DDQ, although the yields of **16** were slightly lower than those of the two-step conversion.

Preliminary tests of inhibitory activity against lipid peroxidation using rat liver microsome showed that **17c** was the most potent inhibitor among the compounds obtained by this method.

In conclusion, we have developed a simple and mild procedure for the solid-phase synthesis of 5-(3-indolyl)oxazoles, using DDQ oxidation of a tryptophan dipeptide. This has since been shown to be a general method for preparing a series of related analogs for biological testing, as will be reported elsewhere.

Table 1
Yields of 5-(3-indolyl)oxazoles by solid-phase synthesis

RCOOH or $(RCO)_2O$ R =		**18**, Isolated Yield, %[a]	RCOOH or $(RCO)_2O$ R =		**18**, Isolated Yield, %[a]
$CH_2=CHCH_2CH_2CH_2$-	**13a**	41.6		**13b**	15.0
	**13c**	9.4		**13d**	31.8
	**13e**	19.5		**13f**	13.7
$(CH_3)_2CHCH_2$-	**13g**	15.5	$CH_3CH_2CH_2$-	**13h**	9.7

a These yields were caluculated based on initial loading level of the Wang resine, 0.8 mmol/g.

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