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# $Cu(OTf)_2$ catalysed [6+2] cycloaddition reaction for the synthesis of highly substituted pyrrolo[1,2-*a*]indoles: rapid construction of the yuremamine core†‡

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**Lewis acid catalysed [6+2] cycloaddition reaction for the synthesis of pyrrolo[1,2-*a*]indoles generating three contiguous stereocenters in a highly regio- and diastereoselective manner has been developed and further applied for the construction of the fully functionalized tricyclic core of yuremamine.**

Pyrrolo[1,2-*a*]indoles, the tricyclic indole derivatives, represent key structural motifs in a variety of biologically active natural products and pharmaceutical compounds.[1] For example, mitomycin C **1** exhibits potent antibacterial and antitumoural activity, which is now used as an anticancer drug in the treatment of certain cancers.[2] Another indole alkaloid flinderole **2** containing this moiety has shown selective antimalarial properties.[3] Recently another pyrroloindole natural product isatisine A **3** has generated much interest among synthetic chemists.[4] In 2005, a new member of pyrrolo[1,2-*a*]indole alkaloids, yuremamine **4**, was isolated from the stem bark of *Mimosa hostilis* and was found to have hallucinogenic and psychoactive effects (Fig. 1).[5]

The structural features of **4** include a fused tricyclic framework containing a densely substituted pyrrolidine subunit, containing two phenyl ring substitutions. The challenging structural and stereochemical features of these natural products combined with their interesting biological activities have fuelled several synthetic projects and many reports directed toward the synthesis of pyrrolo[1,2-*a*]indoles have appeared so far.[6] The preliminary reports from the groups led by Kerr,[7a] France,[7b] Shi[7c] and Chen[7d] have focused on the synthesis of the pyrroloindole core present in **4**. A total synthesis of yuremamine has not been achieved so far. Generation of three contiguous stereocenters with the required stereochemistry has been a major impediment in the synthesis of yuremamine.

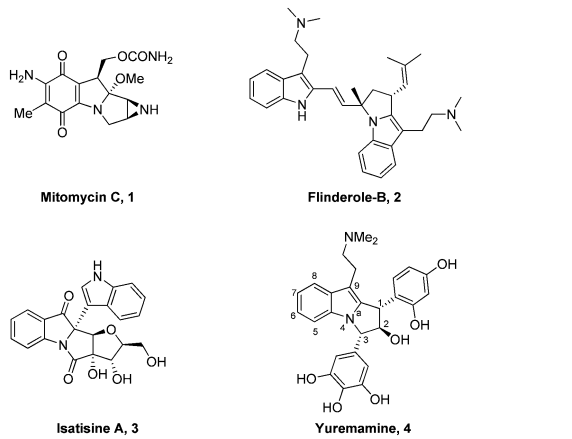


**Fig. 1** Selected examples of natural products that contain the pyrrolo[1,2-*a*]-indole framework.

All the strategies for synthesis of pyrrolo[1,2-*a*]indoles developed to date have focused on generating one or two stereocenters, however to the best of our knowledge there is no report in the literature on synthesis of pyrrolo[1,2-*a*]indoles generating three contiguous stereocenters as required in yuremamine. You *et al.*[7e] in their approach towards the total synthesis of **4** have developed an elegant route for the synthesis of the diastereomer of pentamethyl yuremamine.

In this communication, we report our progress towards the synthesis of **4**, which has resulted in the discovery of [6+2] cycloaddition reaction between a suitably substituted secondary benzylic alcohol and an α,β-unsaturated ester for the one pot formation of pyrrolo[1,2-*a*]indoles with generation of three contiguous stereocenters in a highly regio- and diastereoselective manner.

According to our retrosynthetic analysis it was envisioned that a [6+2] cycloaddition using suitably substituted indole derivative **5** as a dipolarophile and cinnamate **6** as a dienophile would lead to one pot construction of the yuremamine core, which on further functional group transformation could be converted to yuremamine **4**. Compound **5** could be generated

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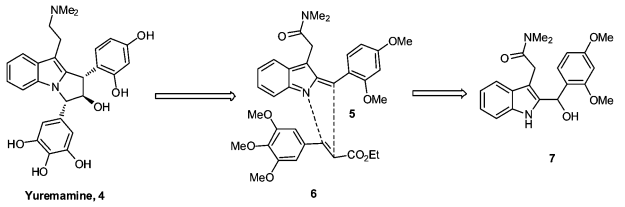
† This work is dedicated to Prof. Goverdhan Mehta on the occasion of his 70th birthday.

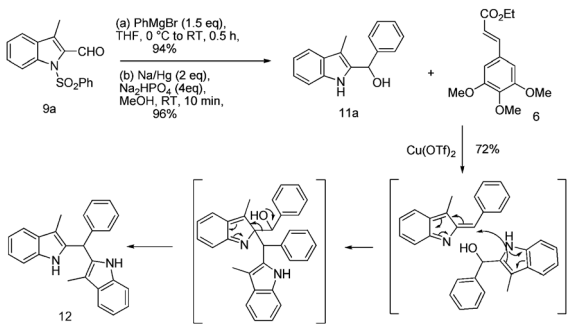
‡ Electronic supplementary information (ESI) available: CCDC 917193 and 917194. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc40617b




**Scheme 1** Retrosynthetic analysis for yuremamine.

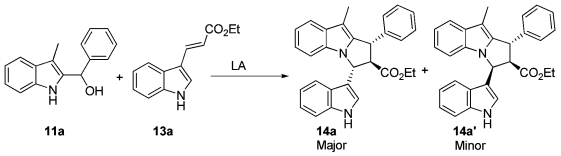
*in situ* from alcohol **7** (Scheme 1). The basis for our initial expectation regarding the stereochemistry of the cyclization step was based on the assumption that the ester group of cinnamate **6** and the 2,4-dimethoxyphenyl ring would be *trans* to each other to avoid steric interaction and generate a thermodynamically more stable product.

To quickly check our strategy, we designed a model system to check whether the cycloaddition of **5** and **6** is viable. The synthesis was initiated (Scheme 2) by treatment of indole aldehyde **9a**[3d] with PhMgBr followed by deprotection of the phenylsulfonyl group in **10a** using Na/Hg to deliver alcohol **11a** in 96% yield. Having the key intermediate **11a** in hand, the stage was set for the key [6+2] cycloaddition reaction. To our disappointment reaction of alcohol **11a** with ethyl 3,4,5-trimethoxy cinnamate **6** under various Lewis acid conditions could not produce the desired cycloadduct; instead it resulted in the formation of the unexpected product **12**, through retro-aldol type reaction as shown in Scheme 2. The structure of compound **12** was deduced from its spectral data and was further confirmed by matching the spectral data with the literature report.[8] Even other cinnamates such as ethyl cinnamate, *p*-methoxy ethyl cinnamate and *p*-bromo ethyl cinnamate failed to undergo [6+2] cycloaddition reaction. Interestingly after screening various catalysts (Table 1), we were gratified to discover that reaction of alcohol **11a** with the comparatively more reactive ester **13a** underwent smooth cyclization using 5 mol% $Cu(OTf)_2$ in $CH_2Cl_2$ at 0 °C to give pyrroloindole **14a** in 90% yield and with excellent regio- and diastereoselectivity. Other Lewis acids gave poor diastereoselectivity (Table 1). The structures of the compounds **14a** and **14a′** were deduced from their spectral data ($^1H$, $^{13}C$, HRMS and NOESY). Formation of **14a′** suggests that the reaction is going through a stepwise mechanism (see ESI‡). The reaction was equally efficient with protected and free NH of indole ester **13a**. Under optimized




**Scheme 2** Model study for [6+2] cycloaddition reaction.

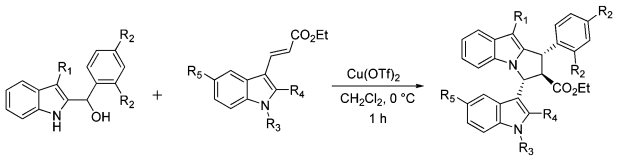
**Table 1** Optimization of [6+2] cycloaddition reaction




| Entry | Catalyst | Solvent | Yield % | dr ratio[a] |
|---|---|---|---|---|
| 1 | $TiCl_4$ | $CH_2Cl_2$ | 82 | 11 : 1 |
| 2 | $BF_3{\cdot}OEt_2$ | $CH_2Cl_2$ | 77 | 14 : 1 |
| 3 | *p*-TSA | $CH_2Cl_2$ | 76 | 25 : 2 |
| 4 | CSA | $CH_2Cl_2$ | 91 | 25 : 1 |
| 5 | $CF_3CO_2H$ | $CH_2Cl_2$ | 83 | 9 : 1 |
| 6 | $CH_3CO_2H$ | $CH_2Cl_2$ | N.R. | N.A. |
| 7 | $FeCl_3$ | $CH_2Cl_2$ | 86 | 4 : 1 |
| 8 | $AlCl_3$ | $CH_2Cl_2$ | 83 | 3 : 1 |
| 9 | $ZnCl_2$ | $CH_2Cl_2$ | 93 | 7 : 1 |
| 10 | $Cu(OTf)_2$ | $CH_2Cl_2$ | 82 | 30 : 1 |
| 11 | $Yb(OTf)_3$ | $CH_2Cl_2$ | 77 | 3 : 1 |
| 12 | $Sn(OTf)_2$ | $CH_2Cl_2$ | 89 | 7 : 1 |
| 13 | $Sc(OTf)_3$ | $CH_2Cl_2$ | 82 | 5 : 1 |
| 14 | $Fe(OTf)_3$ | $CH_2Cl_2$ | 56 | 6 : 1 |
| 15 | $Cu(OTf)_2$ | $CHCl_3$ | 62 | 20 : 1 |
| 16 | $Cu(OTf)_2$ | $CCl_4$ | 81 | 20 : 1 |
| 17 | $Cu(OTf)_2$ | DCE | 54 | 4 : 1 |
| 18 | $Cu(OTf)_2$ | Benzene | 74 | 15 : 1 |

[a] Diastereoselectivities determined from $^1H$ NMR of the crude reaction mixture.

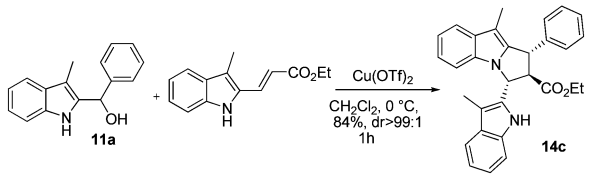
**Table 2** Substrate scope of the [6+2] cycloaddition reaction




| Entry | Substrate (**11**) ($R_1/R_2$) | Substrate (**13**) ($R_3/R_4/R_5$) | Product (**14**) | Yield (%) | dr[b] |
|---|---|---|---|---|---|
| 1 | **11a** (Me/H) | **13a** (H/H/H) | **14a** | 90 | 30 : 1 |
| 2 | **11a** (Me/H) | **13c** (H/Me/H) | **14b** | 85 | 10 : 1 |
| 3 | **11a** (Me/H) | **13d** (Me/H/H) | **14d** | 89 | 99 : 1 |
| 4 | **11a** (Me/H) | **13e** (Me/H/Br) | **14e** | 86 | 99 : 1 |
| 5 | **11b** (Me/OMe) | **13d** (Me/H/H) | **14f** | 91 | 99 : 1 |
| 6 | **11b** (Me/OMe) | **13e** (Me/H/Br) | **14g** | 85 | 99 : 1 |
| 7 | **11c** ($CH_2CH_2OTBS$/H) | **13d** (Me/H/H) | **14h** | 89 | 99 : 1 |
| 8 | **11c** ($CH_2CH_2OTBS$/H) | **13e** (Me/H/Br) | **14i** | 90 | 99 : 1 |
| 9 | **11d** ($CH_2CH_2OTBS$/OMe) | **13d** (Me/H/H) | **14j** | 91 | 99 : 1 |
| 10 | **11d** ($CH_2CH_2OTBS$/OMe) | **13e** (Me/H/Br) | **14k** | 92 | 99 : 1 |

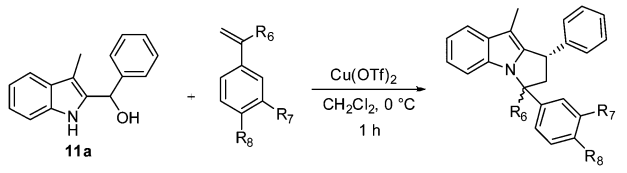
[b] Diastereoselectivities determined from $^1H$ NMR of the crude reaction mixture.

conditions we next examined the substrate scope of this reaction and the results are shown in Table 2 and Scheme 3. Several differently substituted pyrroloindoles **14a–14n** were prepared in a highly regio- and diastereoselective manner and in excellent yields. It is worth mentioning that the scope of the reaction was not limited to only the indole esters like **13a–13d**, even styrene derivatives underwent smooth cyclization to generate the pyrroloindole derivatives (Table 3) in excellent yields, but the diastereoselectivity was poor for these substrates, which confirms the role of the ester group in controlling the stereochemistry. Relative stereochemistry of the three contiguous



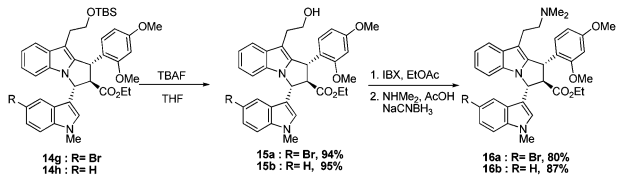

**Scheme 3** Substrate scope of the [6+2] cycloaddition reaction.

**Table 3** Substrate scope of the [6+2] cycloaddition reaction




| Entry | Substrate | Substrate (**13**) ($R_6/R_7/R_8$) | Product (**14**) | Yield (%) | dr[a] |
|---|---|---|---|---|---|
| 1 | **11a** | **13e** (Me/OMe/Me) | **14l** | 87 | 10 : 7 |
| 2 | **11a** | **13f** ($CH(Me)_2$/H/OMe) | **14m** | 86 | 5 : 3 |
| 3 | **11a** | **13g** (Me/OMe/OMe) | **14n** | 83 | 5 : 2 |

[a] Diastereoselectivities determined from $^1$H NMR of the crude reaction mixture.




**Scheme 4** Synthesis of a yuremamine analogue.

stereocenters was unambiguously established by single crystal X-ray analysis of compounds **14b** and **14e**.[9]

As a demonstration, the side chain at the 3-position of indole derivatives **14g** and **14h** was converted to corresponding dimethylamine derivatives **16a** and **16b** as present in yuremamine. Desilylation of compounds **14g** and **14h** using TBAF/THF followed by oxidation and reductive amination of the resultant aldehyde generated the dimethylamine derivatives **16a** and **16b** (Scheme 4).

In summary, a novel approach for the synthesis of highly substituted pyrrolo[1,2-*a*]indoles has been developed that results in direct construction of the yuremamine core system in a highly regio- and diastereoselective manner from readily available starting materials. In a single transformation, three stereochemical issues ($C_1$, $C_2$ and $C_3$) have been addressed effectively while assembling the core system of **4**.

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