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Total Synthesis

Total Synthesis of Proposed Structure of Yuremamine and All Diastereomers Using [3+2]-Cycloaddition of Platinum-Containing Azomethine Ylide

Tomoya Ohyama,[a] Masako Uchida,[a] Hiroyuki Kusama,[b] and Nobuharu Iwasawa*[a]

Abstract: Total synthesis of the proposed structure of yuremamine has been achieved for the first time based on the intermolecular [3+2]-cycloaddition reaction of the platinum-containing azomethine ylide. All the possible diastereomers of yuremamine were also synthesized via the common intermediate. Through these syntheses, it was confirmed that the proposed structure of yuremamine and the diastereomers differ from the natural product.

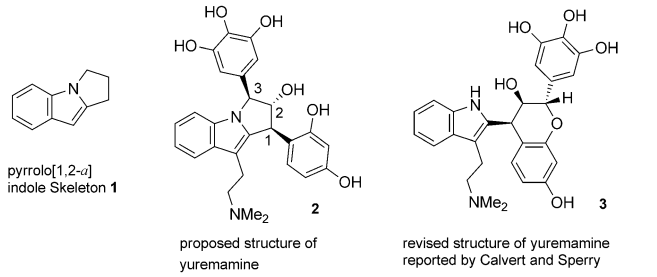
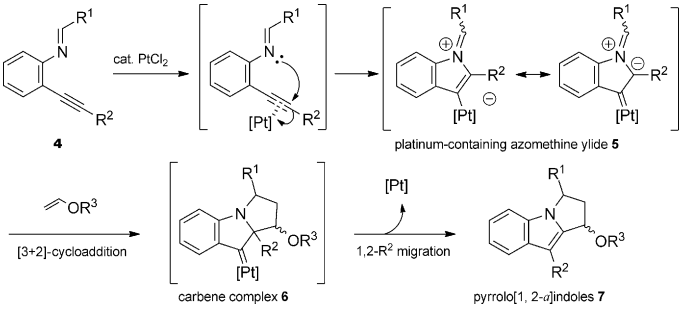


Figure 1. Proposed and revised structures of yuremamine.

Yuremamine was isolated from the root bark of *Mimosa tenuiflora* and was reported to have pyrrolo[1,2-*a*]indole skeleton **1**,[1] which is commonly seen in biologically active compounds such as mitomycins, flinderoles, isoborreverins, and PKC inhibitor JTT-010.[2] We have been carrying out research on the total synthesis of this natural product based on the [3+2]-cycloaddition of platinum-containing azomethine ylides generated from *o*-alkynylanilines with a catalytic amount of platinum(II) chloride, which was developed in our laboratory.[3] In this study, we report the synthesis of the proposed structure of yuremamine **2**, along with its three diastereoisomers, and this resulted in the conclusion that the proposed structure of yuremamine differs from the natural product. Quite recently, Calvert and Sperry reported the structural revision of this natural product based on their bioinspired synthetic study,[4] which also coincides with our conclusion (Figure 1).

We previously reported an efficient method for the construction of the pyrrolo[1,2-*a*]indole skeleton through the intermolecular [3+2]-cycloaddition of platinum-containing azomethine ylides (Scheme 1).[3,5] Treatment of the imine derivatives **4** derived from *o*-alkynylanilines with a catalytic amount of platinum(II) chloride promotes nucleophilic attack of the imino nitrogen to the alkyne moiety, generating the platinum-containing azomethine ylides **5**. The electron-withdrawing nature of the platinum–carbene moiety of **5** decreases the LUMO level of the ylide and promotes [3+2]-cycloaddition with electron-rich alkenes to afford the tricyclic carbene complex intermediate **6**, and finally, 1,2-migration of the substituent R^2 takes place to give the pyrrolo[1,2-*a*]indole derivatives **7** with regeneration of the platinum catalyst. This reaction can be applied to a broad range of substrates and is expected to be useful for the synthesis of biologically active compounds bearing the pyrrolo[1,2-*a*]indole skeleton.



Scheme 1. [3+2] cycloaddition reaction of platinum-containing azomethine ylides.

We then decided to apply our method to the total synthesis of the proposed structure of yuremamine.[6] The synthetic plan is shown in Scheme 2. The basic core skeleton of **2** would be constructed by platinum-catalyzed [3+2]-cycloaddition of imine **8** and vinyl ether and the cycloadduct **9** would be easily converted into the corresponding ketone **10**. Stereoselective α-oxygenation of the carbonyl moiety and introduction of a resorcinol unit followed by stereoselective reduction of the re-

[a] *T. Ohyama, M. Uchida, Prof. Dr. N. Iwasawa*
Department of Chemistry
Tokyo Institute of Technology
2-12-1, O-okayama, Meguro-ku, Tokyo, 152-8551 (Japan)
E-mail: niwasawa@chem.titech.ac.jp

[b] *Prof.Dr. H. Kusama*
Department of Chemistry, Faculty of Science
Gakushuin University
1-5-1 Mejiro, Toshima-ku, Tokyo 171-8588 (Japan)

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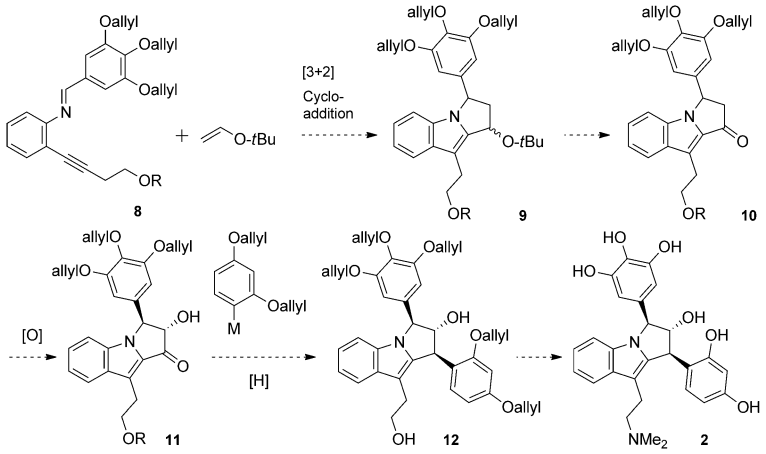
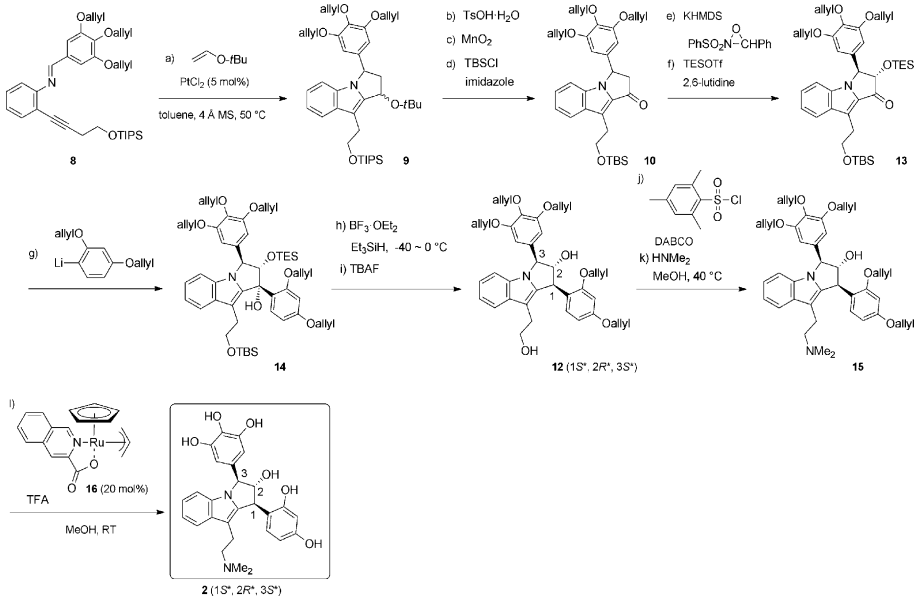


Scheme 2. Synthetic plan.



Scheme 3. Total Synthesis of the proposed structure of yuremamine : a) $PtCl_2$ (5 mol%), *t*Bu vinyl ether (9.0 equiv), toluene, 4 Å MS, 50 °C, 5 h, 84% (dr = 7 :3) (2 steps from 2-(4-triisopropylsiloxybut-1-ynyl)aniline); b) TsOH·H_2O (1.7 equiv), acetone/water = 2:1, RT, 1 day; c) MnO_2 (20 equiv), CH_2Cl_2, RT, 2 days; d) TBSCl (3.0 equiv), imidazole (5.0 equiv), DMF, RT, 2 h, 55% (3 steps); e) KHMDS (1.5 equiv), Davis' oxaziridine (1.2 equiv), THF, −100 °C, 1 h; f) TESOTf (1.5 equiv), 2,6-lutidine (5.0 equiv), CH_2Cl_2, −78 °C, 1 h, 68% (2 steps); g) 1-bromo-2,4-bis(prop-2-en-1-yloxy)benzene (3.0 equiv), *n*BuLi (3.0 equiv), THF, −100 °C, 1 h, 89% (dr = 88:12); h) BF_3·OEt_2 (1.1 equiv), Et_3SiH (30 equiv), CH_2Cl_2, −40 °C ~ 0 °C, 2 h; i) TBAF (12 equiv), THF, RT, 1 day, 91% (d.r. = 87:13 (2 steps); j) 2-mesitylenesulfonyl chloride (1.1 equiv), 1,4-diazabicyclo[2.2.2]octane (DABCO) (2.2 equiv), CH_2Cl_2, 0 °C, 1 h; k) $HNMe_2$ (2.0 M MeOH solution), MeOH, 40 °C, 2 h, 25% (2 steps); l) Ru catalyst (20 mol%), TFA (10 equiv), MeOH, RT, 1 day, 65% (yield determined from H^1 NMR spectroscopy).

sulting tertiary hydroxy group would give rise to diol **12**. Finally, substitution of the primary hydroxy group with a dimethylamino group and deprotection of the five protecting groups on the phenolic oxygen atoms would complete the synthesis of the target compound **2**.

According to the above synthetic plan, we first examined the construction of the pyrrolo[1,2-*a*]indole skeleton (Scheme 3). The substrate for the [3+2]-cycloaddition reaction, *N*-[2-(4-triisopropylsiloxybut-1-ynyl)phenyl]imine derivative **8** with its phenolic hydroxy groups protected as allyl ether, was easily prepared as follows: Sonogashira coupling of the commercially available *o*-iodoaniline with 4-triisopropylsiloxybut-1-yne followed by condensation of the resulting aniline with 3,4,5-triallyloxybenzaldehyde afforded **8**, which was directly used for the [3+2]-cycloaddition reaction without purification. Treatment of the crude imine **8** with a catalytic amount of platinum(II) chloride in the presence of *tert*-butyl vinyl ether at 50 °C gave the desired tricyclic indole derivative **9** in 84% yield as a diastereomeric mixture (d.r. = 7:3). Removal of the *tert*-butyl group under acidic conditions together with deprotection of the triisopropylsilyl (TIPS) ether and MnO_2 oxidation of the resulting secondary alcohol followed by reprotection of the primary hydroxy group with *tert*-butyldimethylsilyl chloride (TBSCl) gave ketone **10** in 55% yield in 3 steps. α-Oxygenation of the ketone with Davis' oxaziridine[7] proceeded stereoselectively to give secondary alcohol **11** as a single diastereomer and the resultant hydroxy group was protected using triethylsilyl trifluoromethanesulfonate (TESOTf). Introduction of the allyl-protected resorcinol unit to the ketone **13** smoothly proceeded to give the adduct **14** as a diastereomeric mixture, and then the stereoselective removal of the resulting tertiary hydroxy group was examined. After several experiments, it was found that treatment of **14** with an excess amount of triethylsilane in the presence of BF_3·OEt_2 at −40 °C to 0 °C efficiently promoted the desired reaction and the corresponding diol **12** was obtained in high yield with good stereoselectivity (d.r. = 87:13) after removal of the silyl group by *tetra*-*n*-butylammonium fluoride (TBAF). The two diastereomers were easily separated by silica-gel chromatography and the relative stereochemistry of the major isomer **12** was unambiguously determined to be the same as that of the target compound **2** by X-ray crystallographic analysis (see the Supporting Information). Then the primary hydroxy group of

the major isomer **12** was selectively converted into a sulfonate ester and a substitution reaction with dimethylamine gave dimethylamino derivative **15**. Judging from the ^{1}H NMR spectra of the crude materials, this transformation proceeded in good yield (ca. 70%), however, the product **15** was rather unstable under purification conditions and the yield after silica-gel chromatography was 25% over 2 steps from **12**. Removal of the five allyl groups was also problematic because the highly oxygenated aromatic moieties of **2** were unstable toward oxygen and basic conditions. After several examinations, we finally found that the use of Kitamura's ruthenium catalyst **16** under acidic conditions[8,9] cleanly deprotected the allyl groups. The product **2** was too labile to be isolated and decomposed even under the reported isolation procedure of the natural product.[10] Only Diol-silica gel chromatography allowed the isolation of **2** in nearly pure form in our hands. However, ^{1}H- and ^{13}C-NMR spectra of the synthetic sample were apparently different from the reported data (Figure 2),[11] suggesting the proposed structure of yuremamine was not correct. At this stage, we thought of the possibility that the reported relative stereochemistry on the three contiguous stereogenic centers might be assigned wrongly.

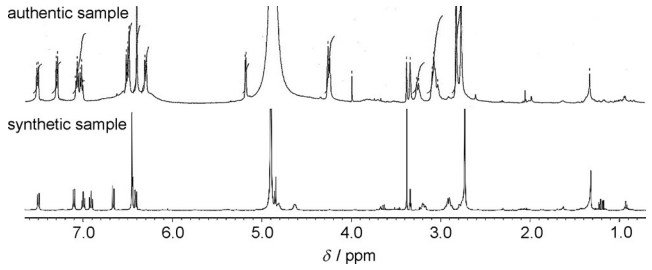


Figure 2. Comparison of 1H NMR spectra measured in [D_4]MeOH (the authentic sample of yuremamine (above) and the synthetic sample **2** (below)).

We then tried to synthesize the other possible diastereomers starting from the synthetic intermediate **12** shown in Scheme 3. Selective oxidation of the secondary alcohol of **12** under Pfitzner–Moffart conditions proceeded with epimerization to give ketone **17** as a mixture of two diastereomers.[12] Fortunately, comparable amounts of all the other three stereoisomers of the starting alcohol **12** were obtained by the reduction of this diastereomer mixture with $NaBH_4$ (Scheme 4).[13,14] These stereoisomers were separable by silica-gel chromatography and subsequent amination reactions were carried out independently.

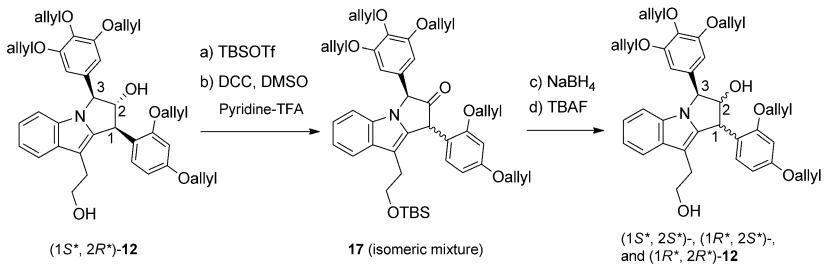
Introduction of the dimethylamino group was accomplished through an almost identical procedure (Scheme 5),[15] and X-ray crystallographic analyses of the remaining three stereoisomers were successfully achieved to assign the relative stereochemistry unambiguously (see the Supporting Information).

Removal of the allyl groups of (1*R**,2*S**)-**15** and (1*R**,2*R**)-**15** smoothly proceeded again with Kitamura's ruthenium catalyst, although the deprotected (1*R**,2*S**)-**2** and (1*R**,2*R**)-**2** were not isolated in completely pure form owing to their instability (Scheme 6).[14]

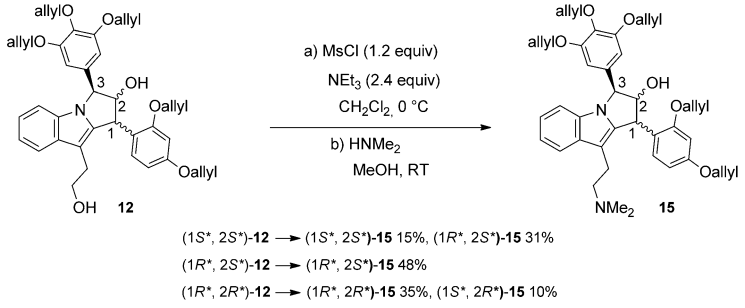
Deprotection of (1*S**,2*S**)-**15** was more problematic and was achieved only with phenylsilane and a catalytic amount of $[Pd(PPh_3)_4]$.[16] The obtained product (1*S**,2*S**)-**2** was exceptionally unstable and the NMR spectrum was as a mixture of several unidentified products (Scheme 7).

Disappointingly, the ^{1}H NMR spectra of the synthesized three stereoisomers were not consistent with the reported data either. Thus we concluded that the structure of yuremamine is different from the initially reported one, which is consistent with the recent report on the structural revision by Calvert and Sperry.[4]

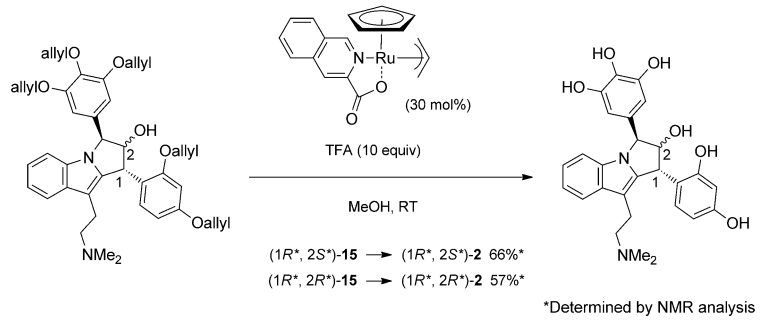
In conclusion, the total synthesis of the proposed structure of yuremamine was achieved in 14 steps from a commercially available material based on the [3+2]-cycloaddition reaction of the platinum-containing azomethine ylide. The spectral data of the synthetic sample along with its diastereomers were different from the reported one, supporting the recent report by Calvert and Sperry that yuremamine has a flavonoidal skeleton. We believe that this synthetic study demonstrates the utility of our methodology for syntheses of highly-functionalized pyrrolo[1,2-*a*]indole derivatives.



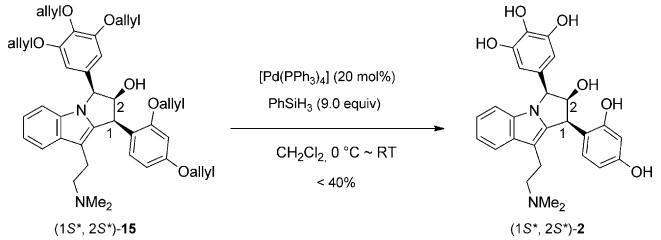
Scheme 4. Synthesis of Stereoisomers of Diol **12**: a) TBSOTf (1.2 equiv), 2,6-lutidine (5.0 equiv), CH_2Cl_2, −78 °C, 76% b) DCC (4.5 equiv), pyridine-TFA (0.75 equiv), DMSO (45 equiv), toluene, RT,1.5 h; c) $NaBH_4$ (3.0 equiv), EtOH,0 °C, 1 h; d) TBAF (12 equiv), THF, RT, 1 day, (1S*, 2S*)-**12** 28%, (1R*, 2S*)-**12** 19%, (1R*, 2R*)-**12** 30% (3 steps).



Scheme 5. Synthesis of diastereomers of the amine **15**.



Scheme 6. Synthesis of (1*R**,2*S**)- and (1*R**,2*R**) −**2**.



Scheme 7. Synthesis of (1*S**,2*S**)-**2**.

Experimental Section

The synthetic procedures and characterization of the compounds studied herein can be found in the Supporting Information. CCDC 1400491 (**14**), 1400492 ((1*R**, 2*S**)-**15**), and 1400493 ((1*S**, 2*S**)-**15**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Acknowledgements

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Keywords: [3+2] cycloaddition · azomethine ylide · platinum · total synthesis · yuremamine

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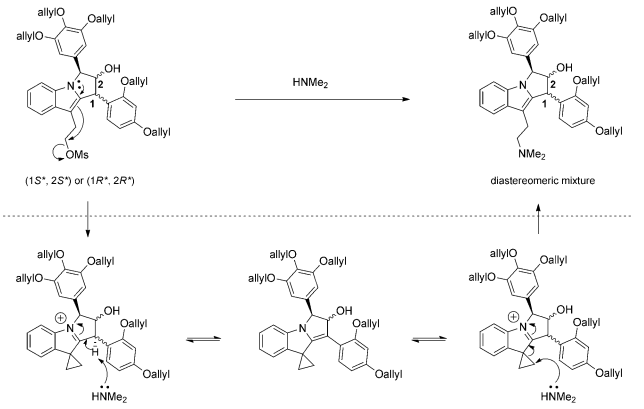
[9] In the absence of acid, the ruthenium catalyst was deactivated due to the basic dimethylamino group of **15**.
[10] The natural yuremamine was isolated by reversed phase HPLC (water:acetonitrile:trifluoroacetic acid = 80:20:0.1),[1] but the synthetic sample **2** decomposed under the same purification conditions.
[11] The spectrum shown above in Figure 2 was kindly provided by Prof. Vepsäläinen.
[12] D. P. Bradshaw, D. W. Jones, F. M. Nongrum, *J. Chem. Soc. Perkin Trans. 1* **1991**, 19 – 23.
[13] In this reaction, it was confirmed that (1*S**)-ketone **17** was selectively reduced to (1*S**,2*S**)-alcohol **12**, while reduction of (1*R**)-ketone gave a mixture of (1*R**,2*R**)- and (1*R**,2*S**)-isomers **12**.
[14] Hereafter, the relative stereochemistry at only C1 and C2 positions is described on the basis of the (3*S**)-isomer for simplicity.
[15] Epimerization occurred during the reaction in case of (1*S**,2*S**)- and (1*R**,2*R**)-isomers **12**, although diastereomers **15** could be separated by silica-gel chromatography. Probably, isomerization took place at the C1 position through the mechanism shown below.



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