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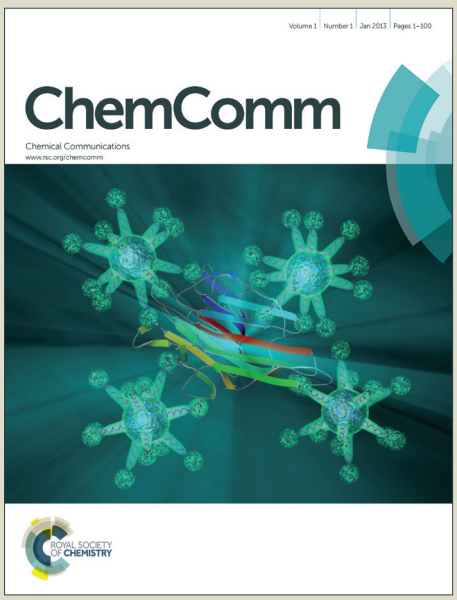

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Synthetic Studies toward Penitrem E: Enantiocontrolled Construction of B–E Rings

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Enantiocontrolled construction of B–E rings of penitrem E was accomplished from 4-iodoindole in 13 steps with an overall yield of 1.7%. Diastereoselective Tf_2NH-catalyzed (2 + 2)-cycloaddition between silyl enol ether and methyl acrylate furnished a tetracyclic product possessing the characteristic cyclobutane ring bearing a hydroxyl group.

A family of indole diterpene alkaloids has attracted a great deal of interest from the synthetic community because of their biological activity and unique structure. Penitrems, isolated from *Penicillium cyclopium* and *Penicillium crustosum* by the Wilson and Steyn groups, possess strong neurotoxicity[1] (Fig. 1). Compared with the structurally related indole diterpenes, such as paspalicine,[2] paspalinine,[2c,2d,3] and paspaline,[2a,2b,4] penitrems have a characteristic cyclobutane ring (B ring) and an eight-membered cyclic ether (A ring). Due to its highly fused cyclic structure, only Smith et al. have so far achieved the enantiocontrolled total synthesis of (–)-penitrem D (**2**) via [2 + 2]-photo-cycloaddition for the formation of the B ring.[5] Curran et al. also reported construction of B–D rings of penitrem D (**2**) using a SmI_2-mediated intermolecular radical cascade reaction.[6] On the other hand, synthetic studies toward penitrems A (**1**) and E (**3**) having a hydroxyl group at the bridgehead of the B and C rings have not yet been reported. Recently, we developed a bis(triflic imide) (Tf_2NH)-catalyzed smooth (2 + 2)-cycloaddition reaction of silyl enol ether to provide a fused-cyclobutane ring bearing a silyloxy group at the bridgehead position (Scheme 1).[7] The major diastereomer of the bicyclic compounds has the opposite relative configuration at the α-position of the methyl ester to those of the B/C ring in penitrems A and E; however, we anticipated that the stereochemistry of this position could be isomerized and initiated synthetic studies toward penitrem E utilizing our (2 + 2)-cycloaddition. Herein, we describe a novel strategy for an enantiocontrolled synthesis of the left segment **4** including B–E rings of penitrem E (**3**) featuring a palladium-catalyzed Catellani reaction[8] and Tf_2NH-catalyzed (2 + 2)-cycloaddition reaction.[7]

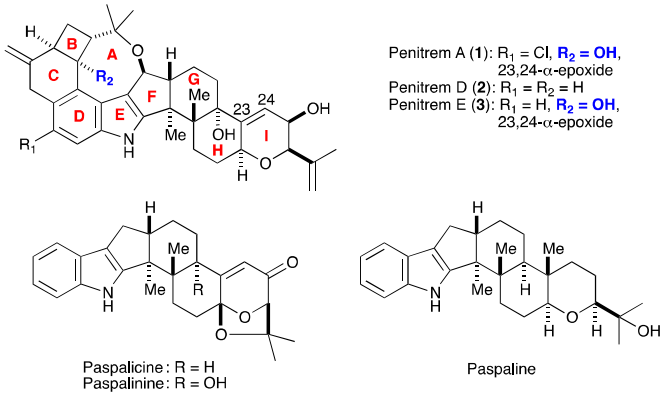
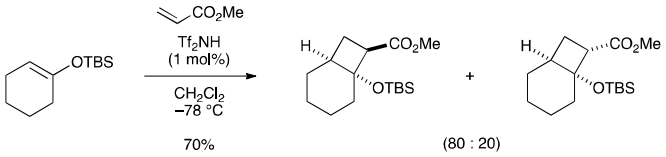


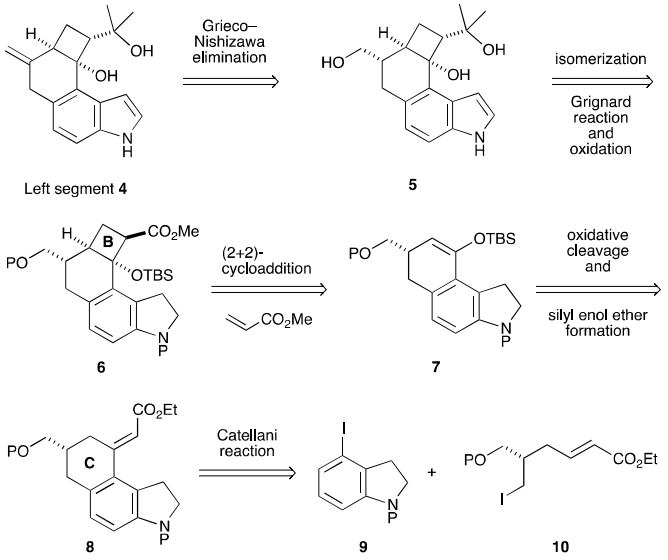
Fig. 1 Penitrems and related alkaloids.



Scheme 1 Tf_2NH-catalyzed (2 + 2)-cycloaddition of silyl enol ether and methyl acrylate.[7c]

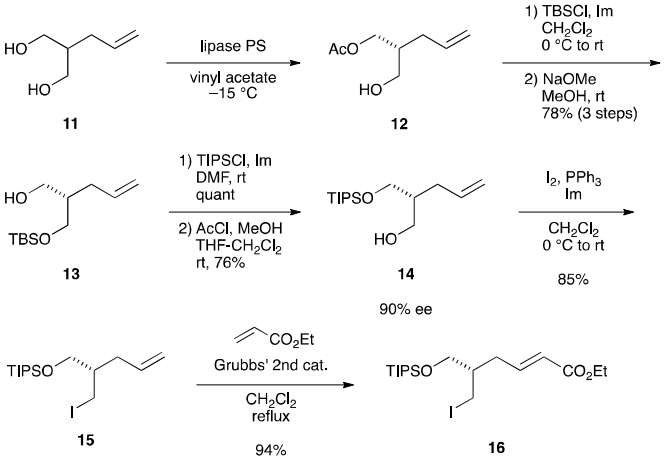
The retrosynthetic sequence in Scheme 2 demonstrates a stereocontrolled construction of the B and C rings, having a hydroxy group at the bridgehead position. To control the facial selectivity in the C–C bond formation of a silyl enol ether and methyl acrylate, we planned to use the stereochemistry of a hydroxymethyl moiety, which is a synthetic equivalent of *exo*-methylene according to Smith's synthesis[5] utilizing Grieco–Nishizawa elimination.[9] The tertiary alcohol attached to the B ring would be derived from ester **6** and two equivalents of methyl Grignard reagent, and the indole

could be synthesized from the protected indoline through deprotection and subsequent oxidation. The cyclobutane ring bearing the hydroxyl group would be constructed by the Tf_2NH-catalyzed (2 + 2)-cycloaddition of silyl enol ether **7** and methyl acrylate.[7] In this reaction, we expected that the hydroxymethyl side chain in the C ring should control the facial selectivity. Silyl enol ether **7** would be derived from the corresponding ketone, which should be prepared from unsaturated ester **8** through oxidative cleavage of the C=C. We planned to construct the C ring from 4-iodoindoline derivative **9** and optically active ε-iodo-unsaturated ester **10** by Catellani reaction,[8] a one-pot palladium-catalyzed ring formation in the presence of norbornene.



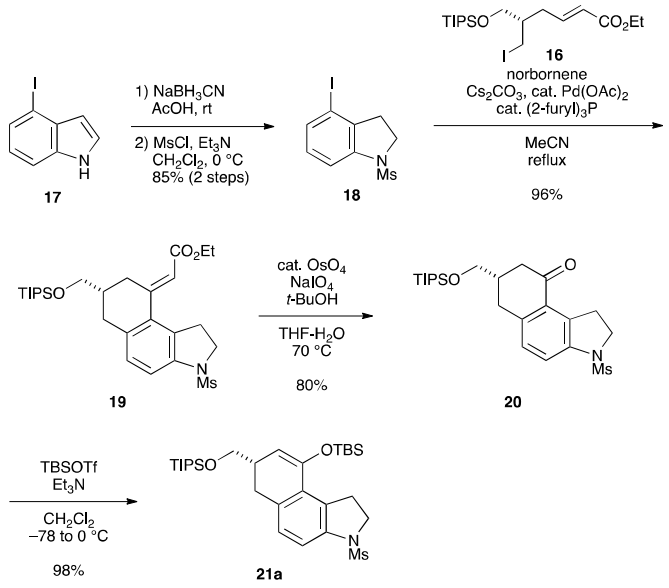
Scheme 2 Retrosynthetic analysis of left segment **4**.

First, we prepared optically active ester **16** from readily available 1,3-diol **11**,[10] a coupling partner for Catellani reaction (Scheme 3). The synthesis commenced with lipase-mediated desymmetrization of *meso*-1,3-diol **11** at −15 °C to give monoacetate **12**.[11] Manipulation of oxygen functionalities provided mono-TIPS ether **14** in 90% ee.[12] Appel iodination[13] of the alcohol and subsequent olefin cross metathesis with ethyl acrylate yielded ester **16**.



Scheme 3 Preparation of unsaturated ester **16**.

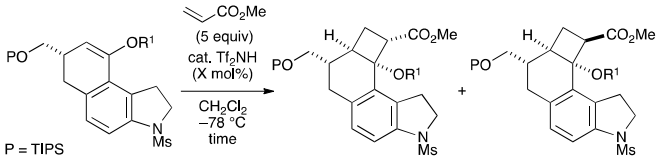
With the ε-iodo-unsaturated ester **16** in hand, we then examined Catellani reaction for the construction of the C ring[14] (Scheme 4). The known 4-iodoindole (**17**)[15] was converted to the corresponding *N*-mesyl-4-iodoindoline (**18**) in a two-step sequence. Gratifyingly, subjection of the indoline **18** and the optically active ester **16** to the standard Catellani conditions[8] provided the desired tricyclic compound **19**[16] in 96% yield. Oxidative cleavage of the trisubstituted electron-deficient olefin was effected by the combination of OsO_4 and $NaIO_4$[17] to give tetralone **20** in good yield,[18] which was converted to TBS enol ether **21a** for the construction of the cyclobutane ring.



Scheme 4 Synthesis of C ring by Catellani reaction.

Having synthesized the requisite silyl enol ether, we then investigated construction of the B ring using Tf_2NH-catalyzed (2 + 2)-cycloaddition (Table 1). An aliquot of 80 mM solution of Tf_2NH in toluene was added to a mixture of **21a** and excess methyl acrylate (5 equiv) in CH_2Cl_2 at −78 °C. After 3 days, the reaction was quenched with Et_3N, and the mixture was concentrated in vacuo, which was then purified to provide a mixture of cyclobutane *cis*-**22a** and *trans*-**22a**. Interestingly, unlike the previous report using the simple substrate (Scheme 1), the reaction of **21a** gave the desired

Table 1 Substituent effects on Tf_2NH-catalyzed (2 + 2)-cycloaddition.

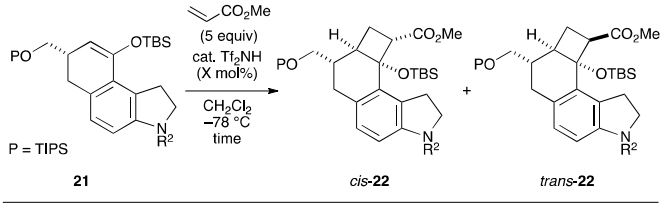


entry	R^1	substrate	X	time (d)	**22** (%)[a]	*cis*-**22**: *trans*-**22**	**21** (%)	**20** (%)
1	TBS	**21a**	5	3	43 (**22a**)	2.1: 1.0[b]	3[b]	27[b]
2	TBS	**21a**	3	7	54 (**22a**)	2.0: 1.0[f]	-[c]	30[b]
3	TMS	**21b**	5	3	-[d]	-[e]	19[b]	53[b]
4	TES	**21c**	5	3	-[d]	-[e]	65[b]	18[b]

[a] Combined yield of *cis*- and *trans*-isomers. [b] Isolated yield. [c] Not detected. [d] Not isolated. [e] Not determined. [f] Calculated by ^1H NMR.

diastereomer *cis*-**22a**[19] as a major product even under the previously established conditions[7] (Table 1, entry 1). Reduction of the catalytic amount of the triflic imide required a prolonged reaction time but gave **22a** in better yield with concomitant generation of tetralone **20** (Table 1, entry 2). TMS enol ether **21b** was more prone to form tetralone **20**, and none of the desired cyclobutane was isolated (Table 1, entry 3). On the other hand, TES enol ether **21c** was robust but less reactive under the conditions, resulting in recovery of 65% of the starting material **21c** (Table 1, entry 4). We also found that the choice of a protecting group on the nitrogen was also important for the diastereoselectivity. Thus, tosyl amide **21d** and Cbz carbamate **21e** were converted to the corresponding products **22b** (*cis*-**22b**: *trans*-**22b** = 1.1: 1.0) and **22c** (*cis*-**22c**: *trans*-**22c** = 2.4: 1.0), (Table 2, entries 1 and 2).[20]

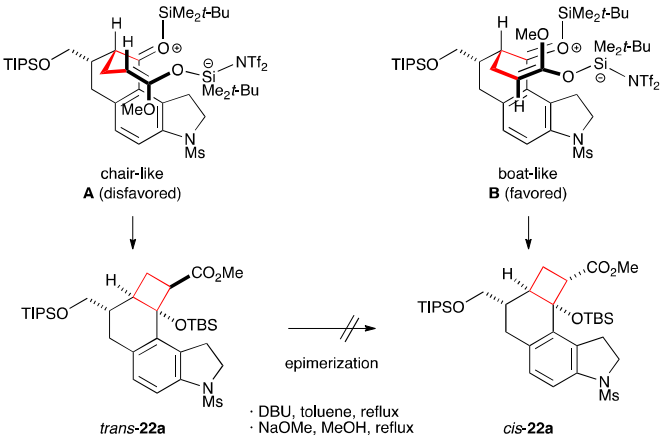
Table 2 Effects of protective group on indoline nitrogen.



entry	R^2	substrate	X	time (d)	**22** (%)[a]	*cis*-**22**: *trans*-**22**	**21** (%)	**20** (%)
1	Ts	**21d**	5	3	56 (**22b**)	1.1: 1.0[d]	-[c]	20[b]
2	Cbz	**21e**	5	3	46 (**22c**)	2.4: 1.0[d]	4[b]	20[b]

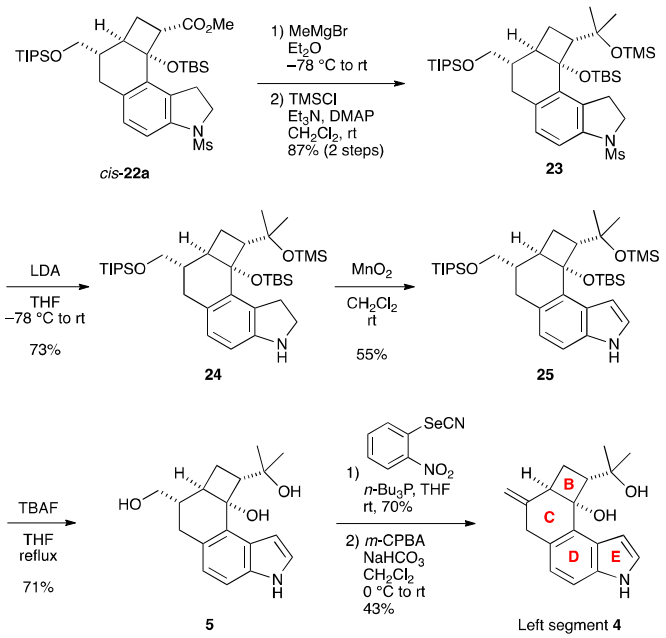
[a] Combined yield of *cis*- and *trans*-isomers. [b] Isolated yield. [c] Not detected. [d] Calculated by ^{1}H NMR.

A plausible mechanism depicted in Scheme 5 would explain the observed diastereoselectivity, which was opposite to that of the former (2 + 2)-cycloaddition.[7] First, Tf_2N–TBS, generated from Tf_2NH, reacted as a Lewis acid to promote Mukaiyama-type Michael addition of the silyl enol ether to methyl acrylate on the less hindered face.[7,21] The possible conformers **A** and **B** in the second aldol reaction provided the corresponding cyclobutanes *trans*-**22a** and *cis*-**22a**. Steric repulsion of the methyl ester and the aromatic ring disfavored chair-like conformer **A**, thus providing *cis*-**22a** (via the favored boat-like conformer **B**) as a major product.[22] We attempted epimerization of *trans*-**22a** to obtain *cis*-**22a**; however, the treatment of the undesired *trans*-**22a** with either DBU in refluxing toluene or NaOMe in refluxing MeOH did not afford the desired *cis*-**22a**.



Scheme 5 A plausible mechanism for the diastereoselectivity in (2 + 2)-cycloaddition.

We then turned our attention toward the synthesis of the left segment **4** (Scheme 6). Addition of excess methyl Grignard reagent followed by protection of the resulting alcohol as its TMS ether provided the trisilylated compound **23**. Deprotection of the mesyl group using LDA smoothly proceeded to give the desired unprotected indoline **24** in high yields,[23] which was then treated with MnO_2 to afford the indole **25**. Synthesis of the left segment **4** was completed in a three-step sequence through Grieco–Nishizawa elimination.[9] Thus, after removal of three silyl groups under basic conditions,[24] the resultant triol **5**, whose structure was confirmed by X-ray crystallographic analysis in Fig. 2,[25] was subjected to selenation followed by oxidative elimination to provide the left segment **4** while leaving the unprotected indole intact.



Scheme 6 Synthesis of the left segment **4**.

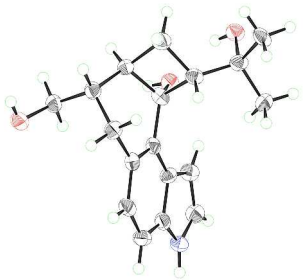


Fig. 2 X-ray crystallographic structure of triol **5**.

In conclusion, we have established an enantiocontrolled construction of B–E rings in penitrem E (**3**). Catellani reaction facilitated the one-step formation of the C ring. The B ring bearing a hydroxyl group was successfully constructed by our Tf_2NH-catalyzed (2 + 2)-cycloaddition, in which the desired diastereomer was obtained as a major product.

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a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (25105705) for K.O., and JSPS predoctoral fellowship and Tohoku University Campus Asia Project for Y.Y.

Notes and references

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† Experimental procedures, compound characterization data, and copies of ^{1}H and ^{13}C-NMR spectra for all new compounds. [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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19 Structure determination of *cis*- and *trans*- isomers was performed by comparison of ^{1}H-NMR spectra of *cis*- and *trans*- isomers of a similar compound. See Supporting Information.

20 The diastereomeric ratio was determined by ^{1}H NMR.

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24 Acidic treatment caused ring opening of the cyclobutane.

25 The data of compound **5** can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (CCDC 1026313).

