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Novel cyclo-dimerization of 1-*tert*-butoxycarbonyl-3-alkenylindole derivatives

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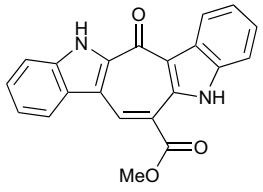
Abstract—Reaction of 1-*tert*-butoxycarbonyl-3-cyclopentylidenemethyl-1*H*-indole with an excess of trifluoroacetic acid in dichloromethane at room temperature gave a cyclic dimer, 13-cyclopentyl-6,7,12,13-tetrahydrospiro[5*H*-cyclohepta[1,2-*b*:4,5-*b*′]diindole-6,1′-cyclopentane] in 73% yield as the sole product through a novel cyclo-dimerization process. Structure of the cyclic dimer derived from 5-bromo-1-*t*-butoxycarbonyl-3-cyclopentylidenemethyl-1*H*-indole was elucidated by X-ray crystallographic analysis.

1. Introduction

A number of bisindole alkaloids have been isolated from various genera of marine sponges, and they have become an important focus of scientific attention because of the high degree of their biological activity and their unique structure.[1,2] Of remarkable importance is the fact that bisindoles often exhibit more potent biological activity than the monomeric units.[3] For these reasons, over the past several years, some efforts have been devoted towards the development of new synthetic methods for this type of natural products.[4] Among them, bisindole alkaloid caulersin **1**, isolated from an alga *Caulerpa serrulata* in 1997, has been known as the first member constructed from the unique cyclohepta[1,2-*b*:4,5-*b*′]diindole skeleton (Fig. 1).[5] Total synthesis of **1** was achieved through several steps of reactions involving cyclization for the construction of the central seven-membered ring system by Fresneda et al.[6] and Bergman and co-workers.[7] In this paper, we would like to present a novel cyclo-dimerization of 1-*tert*-butoxycarbonyl-3-alkenylindole derivatives by treatment with an excess of trifluoroacetic acid (TFA) to give cyclohepta[1,2-*b*:4,5-*b*′]diindoles.



1 Caulersin

Figure 1. Structure of caulersin.

2. Results and discussion

In the course of our continuous research[8] for synthesis of bioactive imidazole–indole alkaloids such as tubastrindoles[9] and cycloaplysinopsins,[10] we prepared a 2′,2′-disubstituted 1-*tert*-butoxycarbonyl-3-alkenyl-1*H*-indole as a model monomer from 1-Boc-3-formylindole **2**[11] by treating with cyclopentyltriphenylphosphonium bromide as shown in Scheme 1.[12] The alkenylindole **3a** was then treated with an excess of TFA in dichloromethane (DCM) for removing the Boc group;[13] however, the unexpected cyclodimer **4a** was obtained in 73% yield after chromatographic purification (Scheme 1).[14] The cyclodimer **4a** gave an M^+ peak in its HREIMS at *m*/*z* 394.2405, which corresponded to the molecular formula $C_{28}H_{30}N_2$. Two broad peaks at 7.75 and 7.81 ppm in the ^1H NMR spectrum, and a strong absorption band at 3438 cm^{-1} in the IR spectrum suggested the presence of the two NH protons of the indole rings. In the

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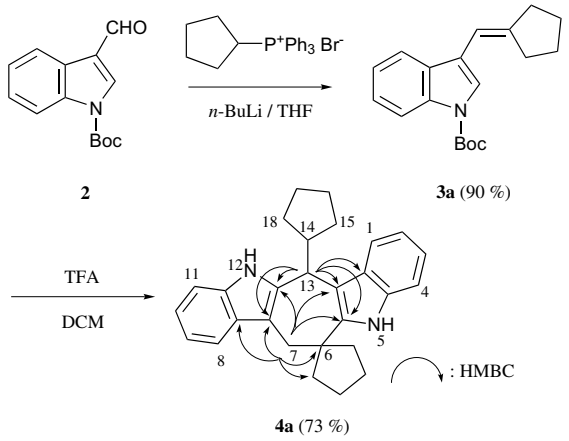
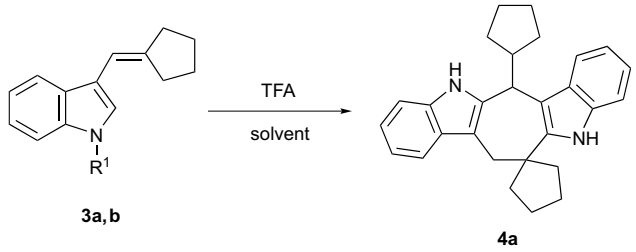


2 **3a** (90 %) **4a** (73 %)

Scheme 1.

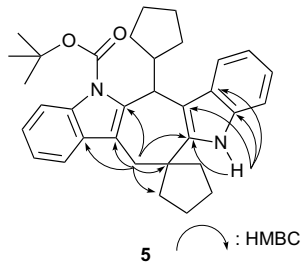
Table 1. Cyclo-dimerization of **3a**,**b**



3a,**b** **4a**

Entry	R^1	Substrate	Solvent	Yield (%)
1	Boc	**3a**	DCM	73
2	Boc	**3a**	$CHCl_3$	71
3	Boc	**3a**	PhMe	36[a]
4	Boc	**3a**	THF	NR[b]
5	H	**3b**	DCM	CM[c]

[a] By-product **5** was also obtained (15%) and shown in Figure 2.
[b] No reaction, recovery of **3a**.
[c] A complex mixture was obtained.



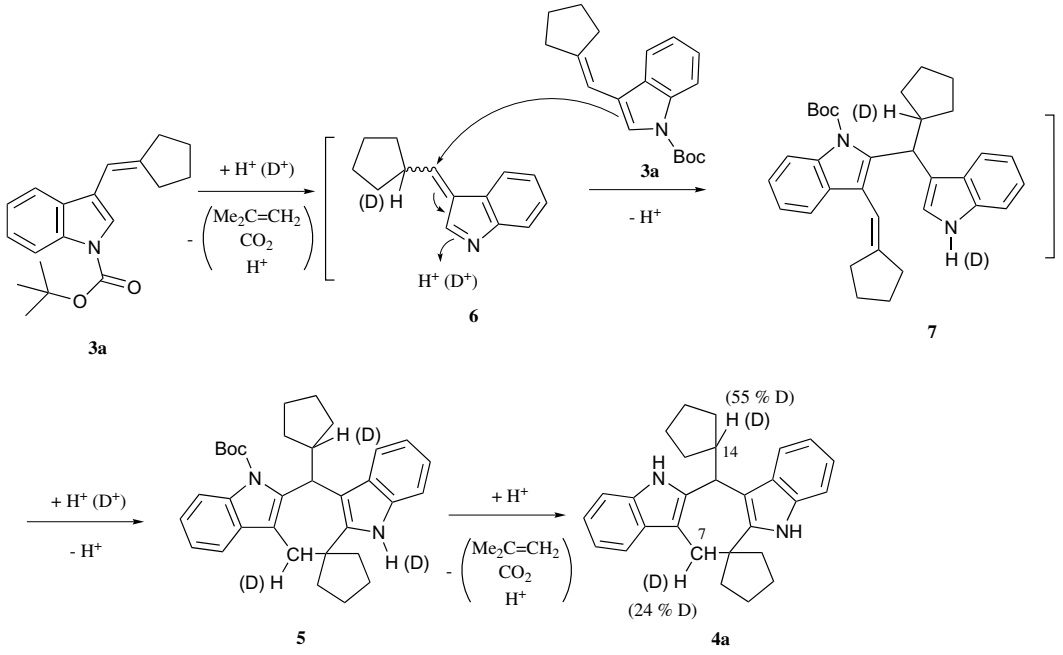
5

Figure 2. Structure and selected HMBC correlations of the by-product **5**.

^1H–^1H COSY spectrum, CH(13)–CH(14)–CH_2(15, 18) and one CH_2(7) attached to two quaternary carbons were revealed. These spectral data and HMBC experiment led to the indicated structure of the obtained product **4a** to have a seven-membered ring between two indole moieties as depicted in Scheme 1.[15]

In general, 3-alkenylindoles have been well known as substrates for [4+2] cycloaddition reaction to six-membered ring systems[16,17] and dimerization reactions to cyclopent[*b*]indole compounds having a five-membered ring systems,[18] respectively. To our best knowledge, the present reaction is the first example of cyclo-dimerization reaction from 3-alkenylindoles to construct a seven-membered ring skeleton such as the cyclohepta-[1,2-*b*:4,5-*b*′]diindole.

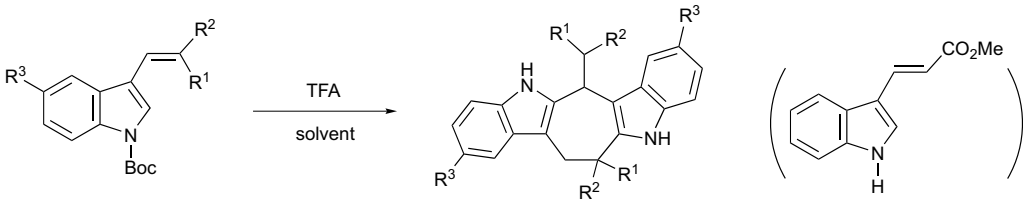
Then, we examined the reaction solvents for preparing the cyclodimer (Table 1). It was found that the reaction of **3a** in DCM gave the best result (73%; entry 1). The reaction in toluene gave **4a** in only 36% yield together with a by-product **5** (15% yield, entry 3), whose structure was determined by HMBC experiment as shown in Figure 2. Isolation of the mono-Boc compound **5** might



3a **6** **7** **5** **4a**

Scheme 2. The proposed reaction mechanism of cyclo-dimerization.

Table 2. Cyclo-dimerization of **3c–j**



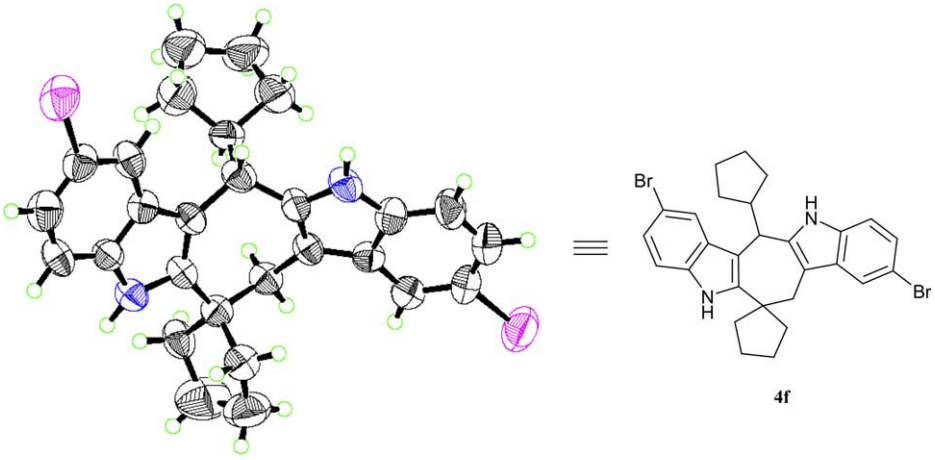
3c-j **4b-g** **8**

Entry	R^1		R^2	R^3	Substrate	Solvent	Product	Yield (%)
1		$-(CH_2)_5-$		H	**3c**	DCM	**4b**	49
2		$-(CH_2)_5-$		H	**3c**	$CHCl_3$	**4b**	46
3	Me		Me	H	**3d**	DCM	**4c**	58
4	Me		Me	H	**3d**	$CHCl_3$	**4c**	24
5	Ph		Ph	H	**3e**	DCM	—	CM[a]
6	H		H	H	**3f**	DCM	—	CM[a]
7	H		Ph	H	**3g**	DCM	**4d/4e**[b]	77[c]
8		$-(CH_2)_4-$		Br	**3h**	DCM	**4f**	82
9		$-(CH_2)_4-$		MeO	**3i**	DCM	**4g**	59
10	H		CO_2Me	H	**3j**	DCM	**8**	76

[a] A complex mixture was obtained.
[b] A mixture of *syn* and *anti* products was obtained (1:2).
[c] Total yield of **4d** and **4e**.

suggest that removal of the remaining second Boc group from the relatively hindered 12-position by action of TFA should be the final step of this cyclo-dimerization process. On the other hand, treatment of **3a** with TFA in THF gave no reaction (entry 4). Treatment of *N*-unsubstituted 3-cyclopentylidenemethylindole **3b** under the same reaction conditions as entry 1 afforded only a complex mixture and no cyclodimer **4a** (entry 5), and this result suggested that the presence of a Boc group at the 1-position should be an important factor to promote the present cyclo-dimerization reaction. Furthermore, reaction with CF_3CO_2D instead of TFA was performed, and it was found that deuterium was incorporated at the 14-position (55%) and the 7-position (24%) in the product **4a**, respectively. From these facts, we propose a reaction mechanism as shown in Scheme 2. Removal of the 1-Boc group may be the first step of this reaction to give the active intermediate **6**, then the dimer **7** might be provided by the reaction of **6** with the 1-Boc indole **3a**. The mono-*N*-Boc-cyclohepta[1,2-*b*:4,5-*b*′]diindole **5** is furnished by the '7-*endo*'-type ring closure of **7** followed by aromatization.

Next, we prepared several 1-Boc-3-alkenylindole derivatives,[19] and the results of their reaction with TFA are summarized in Table 2. The reaction of **3c** and **3d** in DCM proceeded better than in $CHCl_3$ to give the corresponding cyclodimers **4b** and **4c** (entries 1–4). Unfortunately, treatment of 2′,2′-diphenylated and unsubstituted alkenylindoles **3e** and **3f** gave only complex mixtures (entries 5 and 6); however, use of the 2′-monophenylated compound **3g** provided a mixture of *syn* and *anti* 13-benzyl-6-phenylcyclohepta[1,2-*b*:4,5-*b*′]-diindoles (**4d** and **4e**) in 77% yield (entry 7). Although formation of a cyclic dimer, cyclopent[*b*]indole, was



4f

Figure 3. ORTEP drawing for **4f**.

known by treatment of methyl 3-(1*H*-indol-3-yl)-2-propenoate **8** with HCl,[20] in our experiment with TFA only removal of the 1-Boc group was observed in the reaction of the corresponding 1-Boc indole **3j** to give the NH indole **8** in 76% yield (entry 10). The cyclo-dimerization reaction of 3-cyclopentylidenemethylindole having bromo and methoxy groups at the 5-position smoothly proceeded to give crystalline cyclodimers **4f** (mp 278–279 °C) and **4g** (mp 139–140 °C) in good to moderate yields (82% and 59%) (entries 8 and 9), and the structure of the former **4f** could be elucidated by X-ray crystallographic analysis as shown in Figure 3.[21]

As a conclusion, we have found a novel cyclo-dimerization of 1-*tert*-butoxycarbonyl-3-alkenylindole derivatives to give the cyclohepta[1,2-*b*:4,5-*b*′]diindoles. Further investigation and applications of this reaction are under way, and the results of these studies will be reported elsewhere in due course.

Acknowledgements

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14. Preparation of **4a** as a typical experiment: TFA (0.3 mL, 3.9 mmol) was added to a stirred solution of **3a** (89 mg, 0.3 mmol) in DCM (3.0 mL) under N_2 at 0 °C. After stirring for 1 h at 0 °C, the cooling bath was removed and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was neutralized by addition of satd $NaHCO_3$ aq and the products were extracted with $CHCl_3$ (30 mL × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated to give an oily residue, which was purified by silica gel column chromatography (*n*-hexane to AcOEt/*n*-hexane = 1/8) to give pure **4a** (43 mg, 73%) as a pale yellow solid. Analytical sample was obtained by recrystallization from isopropyl ether (mp 239–240 °C).
15. Spectral data of **4a**: δ_H (300 MHz, $CDCl_3$): 1.26–2.16 (15H, m, CH_2 in cyclopentyl), 2.22–2.31 (1H, m, CH_2 in cyclopentyl), 2.49–2.57 (1H, m, 14-CH), 3.03 (1H, d, J = 14.7 Hz, 7-CH_2), 3.28 (1H, dd, J = 1.3, 14.7 Hz, 7-CH_2), 4.07 (1H, d, J = 8.8 Hz, 13-CH), 7.07–7.15 (4H, m, Ar–CH), 7.26–7.30 (2H, m, Ar–CH), 7.53 (1H, dd, J = 3.1, 5.9 Hz, Ar–CH), 7.58 (1H, dd, J = 3.0, 6.0 Hz, Ar–CH), 7.75 (1H, br s, NH), 7.81 (1H, br s, NH). δ_C (100 MHz, $CDCl_3$): 24.1 (CH_2), 24.4 (CH_2), 25.3 (CH_2), 25.8 (CH_2), 31.5 (CH_2), 32.39 (CH_2), 32.44 (CH_2), 39.3 (CH_2), 40.8 (CH), 41.0 (CH_2), 47.2 (C), 48.8 (CH), 108.7 (C), 110.1 (CH), 110.5 (CH), 111.9 (C), 117.0 (CH), 118.5 (CH), 118.9 (CH), 119.1 (CH), 120.3 (CH), 121.1 (CH), 128.9 (C), 130.0 (C), 133.9 (C), 134.3 (C), 140.0 (C), 142.2 (C). ν_{max} ($CHCl_3$, cm^{-1}): 3438, 2931, 2930, 1458, 1320. EI MS (*m*/*z*, %): 55 (17), 69 (8), 130 (20), 141 (8), 269 (6), 282 (6), 295 (5), 325 (100), 326 (27), 394 (M^+, 4). HRMS (EI): found M^+ 394.2405, $C_{28}H_{30}N_2$ requires M^+ 394.2409. Anal. Calcd for $C_{28}H_{30}N_2$: C, 85.24; H, 7.66; N, 7.10. Found: C, 84.94; H, 7.88; N, 6.92.
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21. Crystal data of the compound **4f**: The obtained crystal was a 2:3 complex of **4f** and isopropyl ether (recrystallizing solvent). Empirical formula $C_{37}H_{49}Br_2N_2O_{1.5}$, $M = 552.34$, monoclinic, $a = 12.010(2)$, $b = 28.331(2)$, $c = 21.701(1)$ Å, $\beta = 101.03(1)°$; $V = 7247(1)$ Å^3; $Z = 8$, $Dc = 1.29$ g cm^{-3}, λ(Cu Kα) = 1.54178 Å, μ(Cu Kα) = 30.67 cm^{-1}; $F(000) = 2936.00$; $T = 296$ K; $R1 = 0.055$ for 12815 observations, space group $P2_1/n$. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC 257507. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].