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The first total synthesis of prianosin B

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ABSTRACT

The first asymmetric total synthesis of prianosin B (**1**) is described. Formation of the 16,17-dehydropyrroloiminoquinone skeleton from the pyrroloiminoquinone unit is a key step in this synthesis. Thus, the detosylation and dehydrogenation reactions of the pyrroloiminoquinone unit are caused by the presence of a catalytic amount of NaN_3.

1. Introduction

Pyrroloiminoquinone alkaloids, isolated from marine sponges, such as discorhabdins,[1] prianosins,[1b,e] and epinardins,[2] are very attractive compounds because they have potent, diverse cytotoxic and antitumor activities.[3] They have a unique structure with azacarbocyclic spirocyclohexadienone and pyrroloiminoquinone unit. Many studies have been reported for the syntheses of members of such families.[4] Although Kobayashi et al. also reported one of such family, prianosin B (**1**),[1e] which has the 16,17-dehydropyrroloiminoquinone structure, 20 years ago, its synthesis has not been reported yet (Fig. 1).

For the synthesis of prianosin B (**1**), the construction of the 16,17-dehydropyrroloiminoquinone structure is an important issue. Yamamura et al. described the total synthesis of makaluvamine B having a 16,17-dehydropyrroloiminoquinone unit.[5] They formed

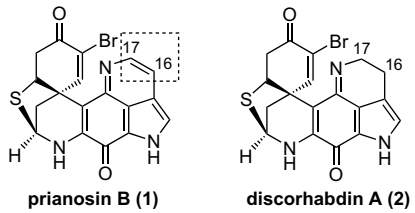
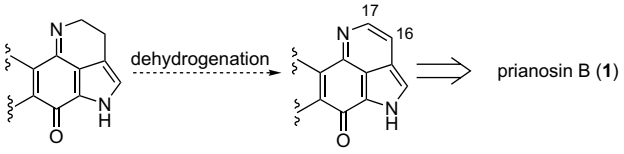


Figure 1. Structures of prianosin B (**1**) and discorhabdin A (**2**).

the unit by dehydrogenation of the pyrroloiminoquinone moiety using Pd/C. White et al. also reported the novel dehydrogenation of the pyrroloiminoquinone unit by using NaN_3.[4h] However, to the best of our knowledge, no systematic research about the dehydrogenation of pyrroloiminoquinones has been carried out to synthesize the prianosins and discorhabdins with the 16,17-dehydropyrroloiminoquinone structure.

Recently, we have succeeded in the first total synthesis of the sulfur-containing discorhabdin, discorhabdin A (**2**).[4s–v] We



Scheme 1. Strategy.

postulated that prianosins and discorhabdins with the 16,17-dehydropyrroloiminoquinone moiety can be synthesized by dehydrogenation of the pyrroloiminoquinone of the discorhabdin A intermediate (Scheme 1; for the structure of discorhabdin A intermediate, *N*,*O*-acetal intermediate, see Scheme 5). We now describe our study for the construction of the 16,17-dehydropyrroloiminoquinone skeleton and the first total synthesis of prianosin B (**1**).

2. Results and discussion

We first examined the dehydrogenation reaction of the simple spirodienone **3** with various oxidants as the model reaction. Spirodienone **3** was prepared from tyramine in 2 steps by

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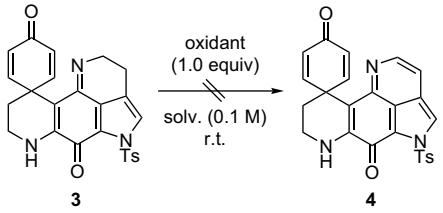
Table 1
Model study using various oxidants

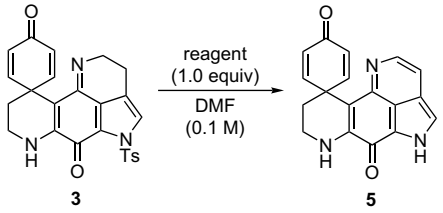


Run	Oxidant	Solvent	Result
1	DDQ	DMF	Decomposition
2	CAN	DMF	N.R.
3	MnO_2	DMF	N.R.
4	Pd/C	MeOH	N.R.

condensation with iminoquinone and successive spiro-cyclization with phenyliodine(III) bis(trifluoroacetate) (PIFA).[6] Reactions with oxidants, such as DDQ, CAN, MnO_2, and Pd/C (Yamamura's conditions),[5] gave poor results (Table 1).

We next tried to use some nucleophiles (Table 2) because White et al. reported that the dehydrogenation and detosylation of the pyrroloiminoquinone system were accomplished using sodium azide as a nucleophile. We first examined nucleophiles other than sodium azide, which has toxicity. The soft nucleophiles (runs 1–6) gave poor results. According to Joule's report, we next used a hard nucleophile, ammonium chloride in methanol (run 7).[7] However, the reaction did not produce the aromatized product at all. Although the reaction of spirodienone **3** and the hard nucleophile CsF in DMF gave the aromatized compound **5**, the yields were low despite using both quantitative and catalytic amount of CsF (runs 8 and 9). Other fluoro reagents (KF, TBAF) did not give the aromatized system (runs 10 and 11). Other hard nucleophiles, *t*-BuOK and AcONa, also did not give compound **5** (runs 12 and 13). We next examined the medium nucleophile, bromo anion. As a result, the reaction with the bromo anion only produced a trace of **5**. The bromo anion with pyridine as an additive produced **5** in a low yield (runs 14–16). However, the reaction with a large amount (36 equiv) of NaN_3 (White's conditions) produced the aromatized system in an acceptable yield (39%) (run 17).

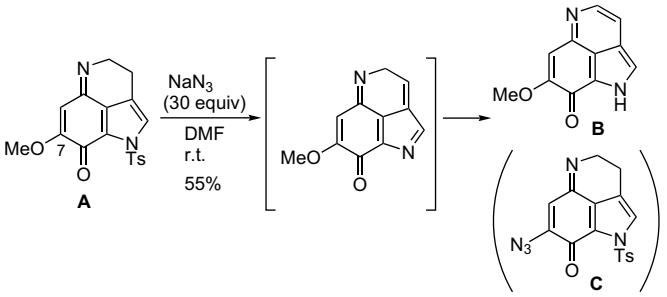
Table 2
Model study using various nucleophiles



Run	Reagent	Additive	T (°C)	t (h)	Result
1	LiI	None	rt	24	Trace
2	KI	18-Crown-6	rt to 70	24	Trace
3	KSCN	None	rt	24	Trace
4	PPh_3	None	rt	24	N.R.
5	KSAc	None	rt	—	Decomposition
6	TMSCN	None	70	2	Decomposition
7[a]	NH_4Cl	None	70	—	Decomposition
8	CsF	None	70	5	33%
9[b]	CsF (0.1 equiv)	None	70	5	25%
10	KF	None	rt	—	Decomposition
11	TBAF	None	70	24	Trace
12	*t*-BuOK	None	rt	—	Decomposition
13	AcONa	None	rt	—	Decomposition
14	TMSBr	None	rt	24	Trace
15	TMSBr	Pyridine	rt	3	15%
16	Pyridine	None	rt to 70	24	Trace
17[b]	NaN_3 (36 equiv)	None	rt	8	39%
18[b]	NaN_3 (36 equiv)	None	70	1	45%
19	NaN_3 (1.0 equiv)	None	70	1	53%
20[b]	NaN_3 (0.1 equiv)	None	70	1	66%

[a] MeOH was used as a solvent.
[b] The equivalent amount of reagent used is in parenthesis after the reagent.

By the way, White et al. aimed to get azide compound **C** by the addition elimination reaction of the methoxy group at C7 by azide substituent. However, treatment of *N*-tosyl-7-methoxyiminoquinone **A** with a large amount of sodium azide (36 equiv) produced the unexpected aromatized product **B** by deprotection of the *N*-tosyl residue and dehydrogenation (Scheme 2).[4h] The reaction looks to have a potential entry to the fully unsaturated pyrroloiminoquinone nucleus. However, they did not examine this interesting reaction any more, for example, adaptation to other substrates, reaction optimization, and reaction mechanism.

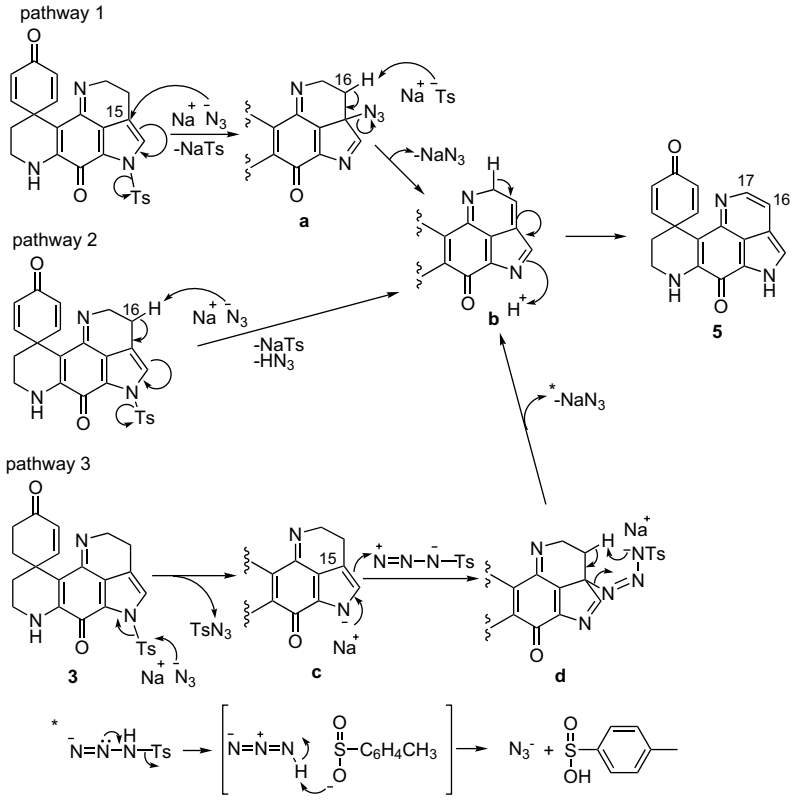


Scheme 2. White's report.

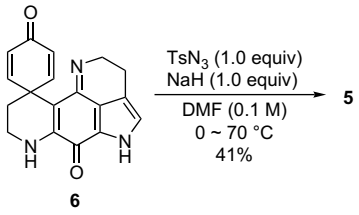
From the encouraging result in run 17 of Table 2, we studied the reaction using NaN_3 in detail (Table 2, runs 18–20). An elevated reaction temperature (70 °C) produced a slightly better result (run 18). The reaction at a much higher temperature caused decomposition of the substrate. As mentioned above, sodium azide has toxicity. We then tried to use small amount of NaN_3. The reaction with 1.0 equiv of NaN_3 produced a better result (run 19), and the use of a catalytic amount of NaN_3 produced the best result (run 20).

A plausible reaction mechanism of the present dehydrogenation reaction of pyrroloiminoquinone using NaN_3 is illustrated in Scheme 3. Three pathways leading to compound **5** are then conceivable. Pathway 1 is nucleophilic attack of N_3^- at 15-position followed by elimination of the *N*-tosyl residue to produce the intermediate **a**. The elimination of N_3^- of the intermediate **a** would then give the intermediate **b** and isomerization to produce **5**. Reproduction of the azide anion during the reaction would make use of the catalytic amount of NaN_3 possible. Pathway 2 is deprotonation at 16-position by N_3^- as a base to give the intermediate **b**. The following manner is the same as pathway 1. But we think that the reproduction of the azide anion during the reaction would not be possible. Pathway 3 is nucleophilic attack of N_3^- to tosyl residue followed by addition of metalo enamine to TsN_3 to produce the intermediate **d**. And dehydrogenation would proceed by the intramolecular elimination via a six-membered transition state to produce the intermediate **b**. The following manner is the same as pathway 1.

For determining the reaction mechanism, two studies were carried out. One was the measurement of the mass spectrum of the reaction mixture. A suspension of spirodienone **3** and NaN_3 in DMF was stirred under nitrogen at 70 °C for 40 min. The mass spectrum of the reaction mixture revealed the ion peak of TsN_3. The other was the reaction of *N*-H spirodienone **6** and TsN_3 under



Scheme 3. Plausible reaction mechanism using NaN_3.

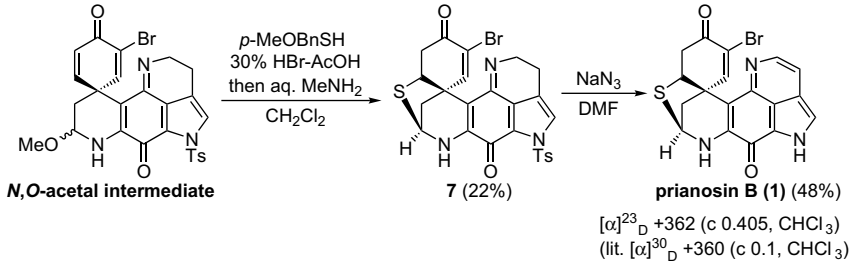


Scheme 4. The reaction of *N*-H spirodienone **6**, TsN_3, and NaH.

basic conditions. Thus, NaH and TsN_3 were added to a solution of **6** in DMF and the aromatic compound **5** was obtained in 41% yield (Scheme 4).

As presumed from these two experiments, a plausible reaction mechanism for the aromatization reaction of the pyrroloiminoquinone unit of spirodienone **3** is outlined in pathway 3 of Scheme 3.[8] Reproduction of the azide anion during the reaction would make use of the catalytic amount of NaN_3 possible. The reproduction of the azide anion was deduced from the presence of toluenesulfinic acid observed in the ^1H NMR spectrum. On the other hand, it might proceed via pathway 1 or 2 in the reaction with halogen anion (CsF, TMSBr). However, for determining the reaction mechanism in detail, more study would be needed.

Since it was revealed that the detosylation and dehydrogenation reaction of the pyrroloiminoquinone unit with a catalytic amount of NaN_3 proceeded in good yield, the total synthesis of prianosin B (**1**) was next studied (Scheme 5). In our own total synthesis of discorhabdin A (**2**), the *N*,*O*-acetal intermediate was prepared from the L-tyrosine methyl ester hydrochloride in 8 steps.[4t] The sulfur cross linkage reaction of the intermediate was carried out using *p*-MeOBnSH and 30% HBr–AcOH followed by aq $MeNH_2$ to give the sulfur-linked pyrroloiminoquinone compound **7**. The treatment of **7** with NaN_3 in DMF caused detosylation and dehydrogenation to produce prianosin B (**2**) in 48% yield. The spectral data were identical to that reported for the natural prianosin B (**1**) ($[\alpha]_D^{23}$ +362 (*c* 0.405, $CHCl_3$), lit.[1e] $[\alpha]_D^{30}$ +360 (*c* 0.1, $CHCl_3$)).



Scheme 5. Synthesis of prianosin B.

3. Conclusion

In summary, we succeeded in the development of an efficient synthetic method for the 16,17-dehydropyrroloiminoquinone unit, observed in discorhabdin alkaloids, using a catalytic amount of NaN_3. The first asymmetric total synthesis of prianosin B in 1.3% total yield over 10 steps from the known L-tyrosine methyl ester hydrochloride was then achieved.

4. Experimental section

4.1. General

The ^1H NMR spectra were measured by 300 MHz or 270 MHz spectrometer with tetramethylsilane as the internal standard at 20–25 °C. IR spectra were recorded by a diffuse reflectance measurement of samples dispersed in KBr powder. E. Merck silica gel 60 for column chromatography and E. Merck pre-coated TLC plates, silica gel F_{254}, for preparative thin-layer chromatography were used.

4.2. Dehydrogenation reaction using a catalytic amount of NaN_3 (Table 2, entry 20)

NaN_3 (0.013 mmol) was added to a solution of spirodienone **3** (0.131 mmol) in DMF (2.6 mL) at rt under N_2 atmosphere. The mixture was allowed to warm to 70 °C and stirred for 1 h. The reaction mixture was quenched by H_2O and extracted with AcOEt. Organic phase was washed by H_2O (×3) and brine (×1). Organic phase was dried over Na_2SO_4 and evaporated in vacuo. Residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH=20:1) to give compound **5** (26.5 mg, 66%) as red solid.

Compound **5**: red solid; mp >300 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.00 (d, 1H, J=6.0 Hz), 7.89 (s, 1H), 7.28 (d, 1H, J=6.0 Hz), 7.24 (d, 2H, J=9.6 Hz), 6.23 (d, 2H, J=9.6 Hz), 3.54 (m, 2H), 1.90 ppm (dd, 2H, J=6.0, 3.9 Hz); ^{13}C NMR (125.65 MHz, DMSO-d_6): δ=185.4, 165.3, 156.8 (2C), 145.6, 141.2, 126.1 (2C), 111.2, 106.1, 106.0 (2C), 105.9, 105.8 (2C), 40.9, 37.2, 34.6 ppm; IR (KBr): 3313, 3115, 1651, 1601, 1539, 1487 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{14}N_3O_2$ $[M+H]^+$: 304.1086, found: 304.1085.

4.3. Total synthesis of prianosin B

NaN_3 (1.1 mg, 0.0175 mmol) was added to a solution of compound **7** (99.7 mg, 0.175 mmol) in DMF (0.3 mL) at rt under N_2 atmosphere. The mixture was allowed to warm to 70 °C and stirred for 1 h. The reaction mixture was quenched by H_2O and extracted with AcOEt. Organic phase was washed by H_2O (×3) and brine (×1). Organic phase was dried over Na_2SO_4 and evaporated in vacuo. Residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH=20:1) to give prianosin B (35.1 mg, 48%) as red solid. Mp 253 °C; $[\alpha]_D^{23}$ +362 (c 0.405, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ=8.49 (d, 1H, J=5.5 Hz), 8.03 (s, 1H), 7.78 (s, 1H), 7.54 (d, 1H, J=5.5 Hz), 6.30 (br s, 1H), 5.49 (m, 1H), 4.80 (dd, 1H, J=12.0, 6.5 Hz), 2.98 (dd, 1H, J=16.5, 4.0 Hz), 2.87–2.94 ppm (m, 3H); ^{13}C NMR (75.45 MHz, $CDCl_3$): δ=188.3, 167.6, 155.7, 146.1, 143.6, 143.0, 129.0 (2C), 125.3, 120.2, 119.6, 118.2, 113.7, 61.7, 56.5, 50.8, 45.6, 40.0 ppm; IR (KBr): 3057, 2924, 2853, 1682, 1645, 1595, 1472, 1303 cm^{-1}; HRMS (FAB): calcd for $C_{18}H_{13}BrN_3O_2S$ $[M+H]^+$: 413.9912, found: 413.9920.

Acknowledgements

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6. The condensation of tyramine with iminoquinone was carried out according to Ref. 4r. Spiro-cyclization was carried out by using PIFA according to Ref. 4t.
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8. After finishing to prepare our manuscript, the reaction of *N*-tosyl-7-methoxyiminoquinone (compound **A** in Scheme 2) with 1.2 equiv of NaN_3 in DMF at rt was reported to cause detosylation. However, no aromatized product was obtained under their reaction conditions (Patel, S. P.; Nadkarni, D. H.; Murugesan, S.; King, J. R.; Velu, S. E. *Synlett* **2008**, 2864--2868). The fact that only detosylation occurred from **A** under their conditions also fortifies our deduction about the reaction mechanism, pathway 3 in Scheme 3. From the results of White's, Velu's, and ours, we conclude that the reaction of pyrroloiminoquinone and NaN_3 in DMF depend on the reaction temperature and the quantity of NaN_3. In the reaction at rt, the use of a large amount of NaN_3 causes detosylation and dehydrogenation (Whites's result). On the other hand, the use of a equivalent amount of NaN_3 at rt causes only detosylation (Velu's result). In the reaction at 70 °C, the use of a catalytic amount of NaN_3 causes detosylation and dehydrogenation (our result).