Concise Synthesis of Dimemorfan (DF) Starting from 3-Hydroxymorphinan (3-HM)

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Dimemorfan (DF) has been known to possess neuroprotective properties. While this promising compound deserves further biological evaluation, synthetic methods have not improved since Murakami group unveiled the synthetic efforts in 1972. Herein a succinct synthesis toward DF from commercially available 3-hydroxymorphinan (3-HM) is disclosed. Other morphinan analogs have been effectively prepared by adopting the similar methodology.

Key words amine; biaryl; protecting group; cross-coupling; reduction

As an expansion of the human's life span and a progression of an aging society, brain diseases such as Alzheimer and Parkinson's disease are raised. The brain diseases feature that death or degeneration of certain brain cells is progressed temporarily or for a long time. Since the dead brain cells are not restored, the death of brain cells leads to mortal damage of brain function. In particular, the incompletion of brain function accompanying the progressive weakness of cognitive function, sensory function, movement function and whole body function causes change of characteristics and behavior.[1)]

Dextromethorphan (**1**, DM) is widely used as a nonnarcotic antitussive for 40 years and has anticonvulsant and neuroprotective properties (Fig. 1).[2—14)] However, DM is reported toxic in children and abuse potential in adolescent youths. Therefore, a dextromethorphan analog that retains its anticonvulsant and neuroprotective activities without being converted into dextrorphan *in vivo* would be ideal.[15—19)]

A dextromethorphan analog, dimemorfan (**2**, DF) has been recognized as an antitussive since 1975.[16)] The antitussive efficacy of dimemorfan is approximately equal to that of dextromethorfan (Fig. 1).[16)] As with dextromethorphan, dimemorphan has potent anticonvulsant activity, although its precise mechanism remains unknown. As DF has an established safety record in humans at antitussive doses and it is not metabolized to dextrorphan, which causes phencyclidine (PCP)-like behavioral effects, it is a promising compound deserving further study of its anticonvulsant and neuroprotective properties.[16)]

Results and Discussion

Because of our interest in discovering and developing a neuroprotective agent for the treatment of Alzheimer or Parkinson's disease, we were attracted to morphinan analogs such as DF as a potential target. There is only one synthesis of DF reported in 1972.[20,21)] The overall yield for preparation of DF was only 15% and it took 70 h to cyclize the requisite ring system by phosphoric acid.[20,21)]

Thus, it is a primary goal to provide a novel method toward DF. We envisioned that this compound might be more readily prepared by using commercially available 3-hydroxymorphinan (**3**, 3-HM) as a starting material (Fig. 1). The 3-methyl group of DF would be introduced by palladium-catalyzed Suzuki–Miyaura cross-coupling reaction if 3-hydroxy group of 3-hydroxymorphinan (**3**, 3-HM) is appropriately converted into the corresponding triflate or phosphate. Subsequently, nitrogen would be prone to undergo facile reductive alkylation, thereby resulting in DF in a straightforward manner.

The synthesis of DF commenced with the conversion of commercially available 3-hydroxymorphinan (**3**, 3-HM)[22)] into the *N*-17-Cbz-3-hydroxymorphinan **4** in 99% yield. Treatment of this compound with trifluoromethanesulfonyl chloride in the presence of triethylamine generated an intermediate triflate **5**, which was purified by silica gel column chromatography as colorless gum in 87% yield (Chart 1).

The stage was now set for the key palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[23)] In the event, a mixture of triflate **5**, trimethylboroxine (2.0 eq), tetrakis-(triphenylphosphine)palladium (0) (0.10 eq) and potassium

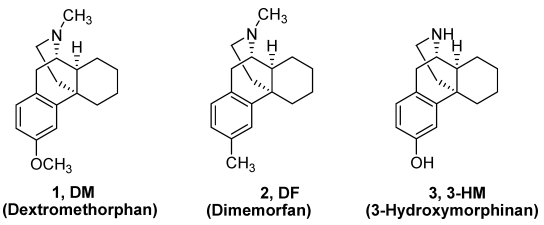

Fig. 1

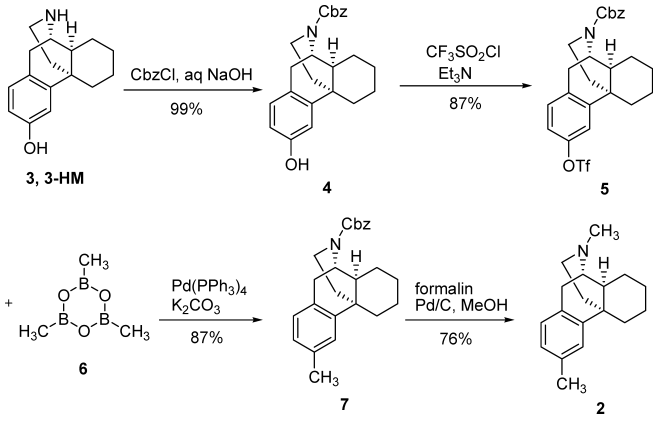

Chart 1

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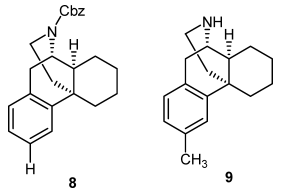
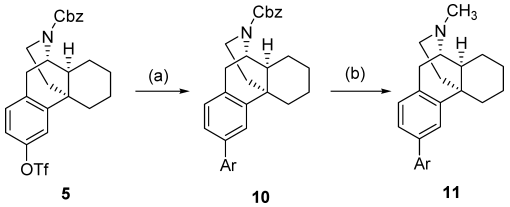


Fig. 2



Reaction conditions: (a) arylboronic acid, $(PPh_3)_4Pd$, K_2CO_3, dioxane, microwave, 180 °C, 60 min; (b) (i) H_2 (g), 37% formalin, 10% Pd/C, MeOH; (ii) prep HPLC (CH_3CN/H_2O).

Chart 2

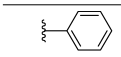
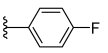
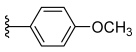
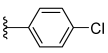
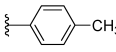
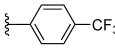
carbonate (2.0 eq) in dioxane (0.1 M) was stirred at 110 °C for 18 h to furnish **7** in 87% yield after purification by column chromatography. Only a trace amount of reduced product **8** was isolated under these conditions. Likewise, microwave irradiation[24] can be adopted to conduct the Suzuki–Miyaura cross-coupling reaction to produce **7** in 73% yield.[25]

At this stage, we briefly considered the possibility of converting **7** into **9** in order to make DF (**2**) in a stepwise fashion. However, we were also intrigued by the more attractive possibility of transforming **7** directly into DF (**2**). Indeed, subjecting a MeOH solution of **7** under hydrogen gas in the presence of palladium on charcoal and formalin produced DF (**2**) in 76% yield.[26,27] The compound was isolated by preparative reverse-phase HPLC (CH_3CN/H_2O) to provide DF **2** (Fig. 2).[28]

With a satisfactory route to DF in hand, we next parlayed the key Suzuki–Miyaura cross-coupling reaction into preparation of the needed biaryl-type morphinan derivatives (Table 1).

As illustrated in Chart 2, the triflate **5** reacted with some of the commercially available arylboronic acids to give biaryl-type morphinan analogs as in structure **10**. All of these cross-coupling reactions went smoothly giving rise to the corresponding biaryl compounds in moderate to good yields. Especially, we observed that the cross-coupling of pyridin-4-ylboronic acid or pyridin-3-ylboronic acid with the triflate **5** furnished the corresponding biaryl morphinan analogs in higher yields (entry **10g** in Table 1). Further elaboration of the coupled products demonstrates the utility of amino functionality. Thus, subjecting a MeOH solution of compounds of **10a**—**g** under hydrogen gas in the presence of palladium on charcoal and formalin produced methylated compounds of structure **11a**—**g** in 57—84% yields. The compounds were isolated by preparative reverse-phase HPLC (CH_3CN/H_2O) to afford structure **11** (Chart 2, Table 1). Regarding thiophene-containing compounds (entry **11h**, **i**), we found out that *N*-17-Boc-3-hydroxymorphinan in lieu of *N*-17-Cbz-3-hydroxymorphinan **4** can be employed to produce **11h** or **11i**, adopting the analogous reaction sequence in Chart 2.

Table 1. Synthesis of Morphinan Derivatives

Ar	Entry	Isolated yield (%)	Entry	Isolated yield (%)
	**10a**	60	**11a**	65
	**10b**	63	**11b**	76
	**11c**	43	**11c**	57
	**10d**	45	**11d**[a]	66
	**10e**	57	**11e**	75
	**10f**	65	**11f**	84
	**10g**	81	**11g**	83
	**10h**[b]	45	**11h**[c]	59
	**10i**[b]	46	**11i**[c]	60

a) A small amount of dechlorinated compound was also observed on LC-MS. *b*) Thiophene derivatives did not undergo smooth hydrogenation as usual. *c*) *N*-17-Boc-3-hydroxymorphinan was employed to produce these compounds.

Conclusion

In summary, we have achieved a convenient synthesis of dimemorfan (DF), a potential neuroprotective agent for the treatment of the brain diseases such as Alzheimer or Parkinson's disease by adopting Suzuki–Miyaura cross-coupling reaction. This concise synthesis of dimemorfan clearly exemplifies the utility of the Suzuki–Miyaura cross-coupling reaction, thereby providing dimemorfan in 57% overall yield in a sequence of only four steps starting from the commercially available 3-hydroxymorphinan. Since the synthetic route towards dimemorfan unveiled here readily provides morphinan derivatives, the synthetic method will be further utilized to provide morphinan libraries for the in-depth studies of structure–activity relationships (SAR).

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References and Notes

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22) 3-Hydroxymorphinan hydrobromide was purchased in bulk from Estechpharma Co., Korea (http://estechpharma.com).
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24) Microwave reaction was conducted with a Biotage microwave reactor (model: Initiator sixty).
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28) For Gilson preparative HPLC, *ca.* 100 mg of a product was injected in 1 ml of CH_3CN onto a SunFire^{TM} Prep C_{18} OBD 5 μm 19$\times$100 mm column with a 8 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O.