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Rapid access to morphinones: removal of 4,5-ether bridge with Pd-catalyzed triflate reduction

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ABSTRACT

A new synthetic method for the removal of the 4,5-bridged ether moiety of several opioids has been developed. This process offers a faster, simpler synthetic route to obtain the morphinone scaffold in high yields without the need for protection of the ketone moiety.

Opioids such as morphine (**1**) and codeine (**2**) (Fig. 1) and analogs offer a wealth of therapeutic benefit as analgesics and as building blocks for valuable therapeutics.[1–3] Opioid analgesics such as hydrocodone (**3**) and oxycodone (**4**) (Fig. 1) are used to treat intense pain[1] while the opioid, naltrexone (**5**, Fig. 1), is used to aid in reducing opioid dependence.[4–6] More facile synthetic methods to gain access to new opioid analogs can offer the opportunity to discover potentially useful opioid therapeutics.

Opioids without the 4,5-ether bridge (referred to as morphinones, Fig. 1) are of particular interest due to their novel biological and pharmacological properties.[7–11] The only reported method used today to remove the 4,5-ether bridge[7–13] was originally described by Sawa and co-workers in the 1960s and uses ammonia gas and solid sodium metal.[14,15] This synthetic route involves multiple steps, including protection and deprotection of the ketone moiety, resulting in a low overall yield of the final morphinone product.[7–15] A shorter, higher yielding alternative route to these intriguing compounds would be quite valuable and necessary to access the morphinone scaffold efficiently making them readily available for pharmacological and biological evaluations.

In a continuing effort in our laboratory to synthesize novel kappa opioid agonists and mixed kappa/mu agonists for the treatment of drug abuse,[11,16–22] we have developed an efficient synthetic route that allows easier access to this pharmacologically important class of compounds. Our method for the synthesis of the morphinone scaffold includes a palladium-catalyzed aryl triflate reduction. In general, aryl triflate reductions are highly precendented[23–28] and were believed to be applicable to our substrates. Furthermore, this transformation could circumvent the ketone protection/deprotection sequence needed in Sawa's synthesis.[14,15]

The opioid-4-triflates used in the palladium-catalyzed reduction were synthesized according to Scheme 1, shown below. The phenol moiety of naltrexone (**5**) and naloxone (**6**) was methylated using iodomethane and potassium carbonate to yield derivatives **7**[29] and **8**, respectively. Hydrocodone (**3**), oxycodone (**4**), **7**, and **8** were then reduced to their phenol derivatives (**9–12**) using zinc under acidic conditions.[7,11,30] Finally, the triflates (**13–16**) were obtained after treating phenols (**9–12)** with *N*-phenylbis(trifluoromethanesulfonate)amide and cesium carbonate or sodium hydride (see Supplementary data for details).

The reduction of the opioid-4-triflates (**13–16**) was initially attempted using 10% Pd/C, Mg, and NH_4OAc.[28] However, in our hands, this reduction protocol failed to afford any product. Success was achieved when 10% palladium acetate, 10% diphenylphosphinopropane (dppp), and 2.5 equiv of triethylsilane[25] at 60 °C for 4 h was used to produce the desired morphinones (**17–19**, Table 1).

As shown in Table 1, the reduction worked very well for opioid-4-triflates (**13**, **15** and **16**) affording yields of 90–95% of morphinone products (**17–19**, respectively). The naloxone triflate (**14**), which contained an *N*-allyl moiety, produced multiple byproducts under these reaction conditions and no product was isolated.

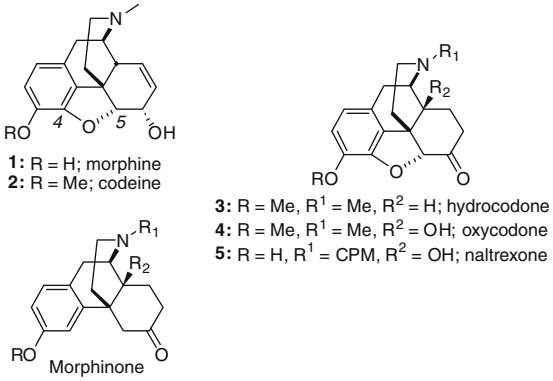

Figure 1. Structures of opioids (CPM = cyclopropylmethyl).

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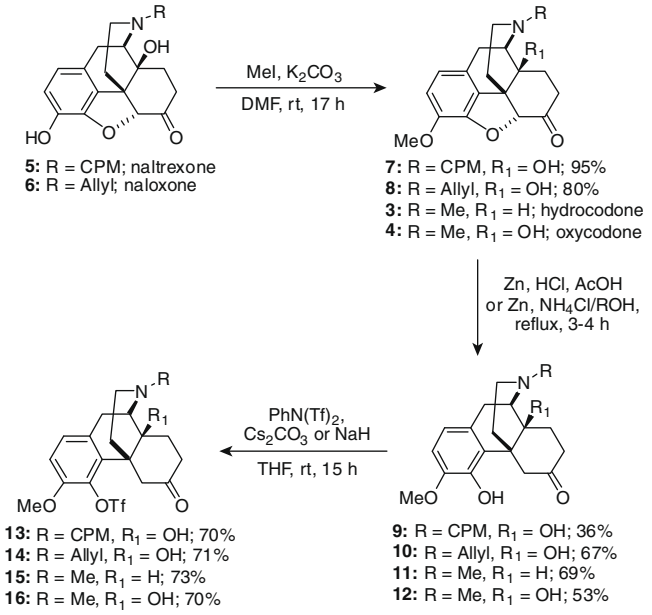
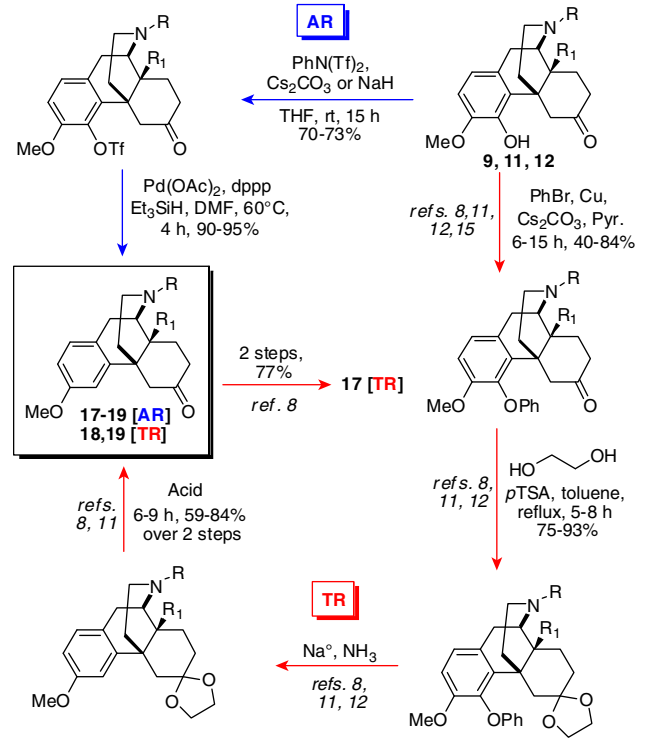


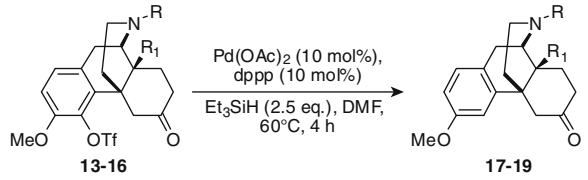
Scheme 1. Synthesis of opioid-4-triflates.



Scheme 2. Comparison of traditional route [TR] with new alternate route [AR] for the synthesis of the morphinone scaffold.

An overall comparison of the new alternate synthetic route [AR] versus the traditional route [TR] to the morphinone scaffold is shown in Scheme 2. As shown, the alternate route for the synthesis of morphinones **17–19** is accomplished in two steps (from intermediates **9, 11** and **12**) compared to the four steps needed for the synthesis of **18** and **19** and six steps for **17** via the traditional route.[7,8,11,12,15] The new method offers a faster, more efficient alternative and utilizes less harsh reaction conditions/reagents than that required for the traditional process.

Table 1
Reduction of opioid-4-triflates to morphinone products



Triflate	R	R_1	Yield (%)	Morphinone
13	CPM	OH	94	17
14	Allyl	OH	0	NA
15	Me	H	95	18
16	Me	OH	90	19

In conclusion, we have developed a new alternate synthetic route to remove the 4,5-ether bridge of opioids (**3–5**). Through the utilization of an opioid-4-triflate intermediate and subsequent palladium-catalyzed reduction, we were able to present a viable pathway to a class of pharmacologically important molecules. Further studies on this intriguing class of compounds are currently underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and characterization for compounds **7–19**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.146.

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