

## STUDIES INTO THE DIRECT OXIDATION OF CODEINONE TO 14-HYDROXYCODEINONE

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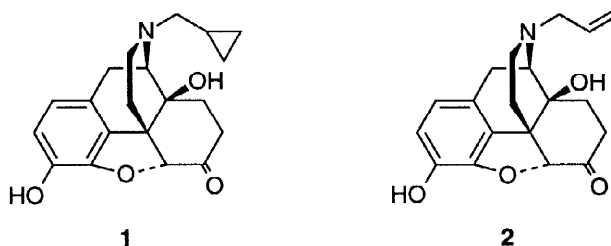
Received 1 June 1999; accepted 29 July 1999

**Abstract:** The direct oxidation of codeinone (**5**) to 14-hydroxycodone (**6**) was investigated with a wide range of oxidizing agents. The majority of reagents gave little or no desired product. Peracids were found to be moderately successful, with dimethyl peracetic acid giving the greatest yield (37%). Metallic oxidants generally gave rise to competing oxidations, however  $\text{Co}(\text{AcO})_3$  was found to conveniently oxidize **5** to **6** in 51% yield, representing a practical, non-chromatographic procedure for the preparation of 14-hydroxycodone.

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*Keywords:* Alkaloids; Oxidation; Cobalt and compounds.

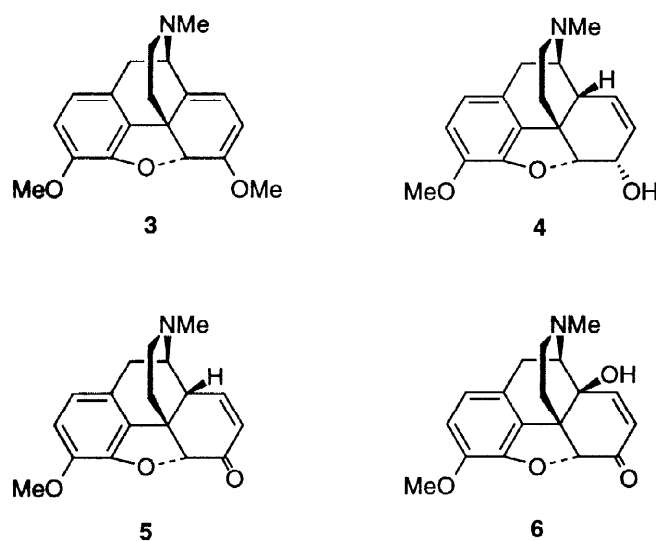
The 14-hydroxyl substituted opioid antagonists, such as naltrexone (**1**) and naloxone (**2**), are valuable medications for the treatment of opiate abuse,<sup>1</sup> opiate overdose,<sup>2</sup> and alcohol addiction.<sup>3</sup> However, the ever increasing demand for these medicinal opioids, coupled with the findings that delta subtype selective derivatives may be useful immunosuppressants<sup>4</sup> and also prevent the development of tolerance to morphine,<sup>5</sup> has placed a premium on thebaine (**3**), the common starting material<sup>6</sup> that has only a low natural abundance in opium.<sup>7</sup>



Obviously, the replacement of **3** as the starting material with a more available opiate, such as codeine (**4**) would alleviate the pressure on thebaine. As part of our program directed toward this goal, we recently reported a novel and practical synthesis of **3** from **4**.<sup>8</sup> Codeinone (**5**), which can be prepared through simple Oppenauer

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oxidation of **4**,<sup>9</sup> was shown to undergo enol ether formation to **3** by treatment with  $t\text{BuOK}$ , 18-crown-6, and  $\text{Me}_2\text{SO}$ , thus removing the need for the isolation of **3** from opium. Peracid oxidation of **3** gives the key intermediate 14-hydroxycodeinone (**6**),<sup>10,11,12</sup> from which the important antagonists can be prepared.<sup>6</sup> We now wish to present our studies into the oxidation of **5** at the allylic position to give 14-hydroxycodeinone (**6**) directly, and thus remove the requirement for the preparation of thebaine as an intermediate in the syntheses of the antagonists.



The oxidation of **5** to **6** can be accomplished by a variety of 2 step procedures via formation of a diene system followed by oxidation.<sup>13,14</sup> Obviously, a direct procedure would offer the advantages of less synthetic steps and remove the necessity for the isolation of a diene intermediate. Previous attempts at such a direct oxidation have met with limited success due to competing oxidation at other positions on the opioid skeleton.<sup>14,15</sup> The only direct method resulting in a reasonable yield involves the use of  $\text{MnO}_2$ ;<sup>16</sup> treatment of codeine with  $\text{MnO}_2$  leads to codeinone, however prolonged treatment gives **6** in 30% yield. Although this procedure was subsequently improved using a 3-silyl ether derivative (59%)<sup>17</sup>, the large quantities of  $\text{MnO}_2$  employed limits its practicality for industrial scales. In an attempt to develop a practical method for this transformation, we investigated the treatment of **5** with a variety of readily available and easily handled oxidizing agents, with the ultimate aim of discovering a procedure that could be conveniently performed on commercial scales.

#### PERACID MEDIATED OXIDATIONS

Initial studies concentrated on the fact that in acidic media, codeinone (**5**) exists in equilibrium with neopinone (**7**).<sup>18</sup> It was envisaged that the different electronic character of the C-ring double bonds in **5** and **7** may allow selective oxidation of **7** with peracids, whereas the electron deficient double bond in **5** would not undergo oxidation. It was found that treatment of an equilibrium mixture of **5** and **7** under the performic acid conditions described by Iijima *et al.* for thebaine,<sup>10</sup> led to low yields of **6** (Table 1, entry 1). Although somewhat encouraging, the fact that the balance of the material could not be recovered suggested competing oxidations to give water soluble products. A range of peracids, with differing steric and electronic properties were therefore

investigated in order to determine if the nature of the peracid affected product distribution and the results are summarized in Table 1.

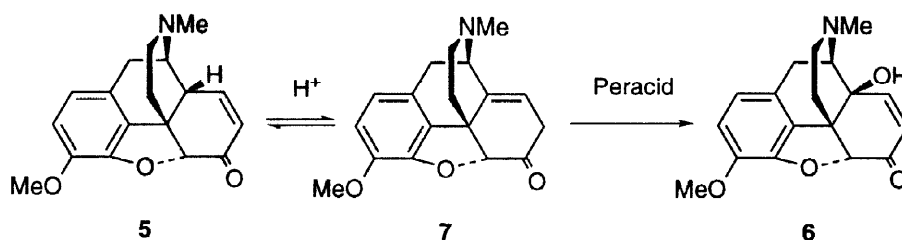


Table 1; Oxidation of **5** with peracids

Reagents <sup>a</sup>	Yield of <b>6</b>
1. HCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , 40°C, H <sub>2</sub> SO <sub>4</sub>	10% <sup>b</sup>
2. HCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	13%
3. HCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , HClO <sub>4</sub>	9%
4. F <sub>3</sub> CCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	c
5. H <sub>3</sub> CCO <sub>2</sub> H, H <sub>3</sub> CCO <sub>3</sub> H, H <sub>2</sub> SO <sub>4</sub>	5%
6. <i>m</i> -CPBA, H <sub>2</sub> SO <sub>4</sub>	4% <sup>d</sup>
7. <i>m</i> -CPBA, F <sub>3</sub> CCO <sub>2</sub> H	c, e
8. Cl <sub>2</sub> HCCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	5%
9. Cl <sub>3</sub> CCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	c
10. (CH <sub>3</sub> ) <sub>2</sub> HCCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	37%
11. (CH <sub>3</sub> ) <sub>3</sub> CCO <sub>3</sub> H, H <sub>2</sub> SO <sub>4</sub>	c, f, g

<sup>a</sup>All reactions stirred for 24h at rt, unless otherwise stated; <sup>b</sup>Conditions as described by Iijima *et al.* for thebaine<sup>10</sup>; <sup>c</sup>No desired product detected by TLC; <sup>d</sup>Reaction performed in water as described by Coop *et al.* for oripavine<sup>12</sup>; <sup>e</sup>As entry 6, but with CF<sub>3</sub>CO<sub>2</sub>H solvent. <sup>f</sup>Peracid prepared as previously described.<sup>19</sup> <sup>g</sup>Reaction performed in *t*-BuOH.

As can be seen from the table, all reactions gave rise to only minor yields of **6**, the greatest yield (37%) was obtained by the use of dimethylperacetic acid (entry 10). The low yields make it difficult to draw any definitive conclusions, however the fact that dimethylperacetic acid gave a higher yield than peracetic acid (entry 5) tends to suggest that steric bulk may be one factor in minimizing unwanted side reactions. This however, is not consistent with the poor results obtained with the even more bulky tri-substituted peracetic acids (entries 9 and 11). In all reactions the side products were water soluble and could not be isolated.<sup>20</sup> Although strong acid was included in all cases, the possibility of *N*-oxidation as one side reaction cannot be dismissed,<sup>21</sup> and therefore the action of peracids on the corresponding carbamate protected derivative (**8**)<sup>8</sup> was investigated (Table 2).

Surprisingly, treatment of **8** with peracids led to none of the desired 14-hydroxyl substituted product (**10**). This is however consistent with previous findings that basic and non-basic opioid derivatives can react very

differently when treated under the same conditions.<sup>22</sup> Little starting material could be recovered in any of the reactions and it was concluded that alternative oxidations (possibly Baeyer-Villiger<sup>20</sup>) competed successfully.

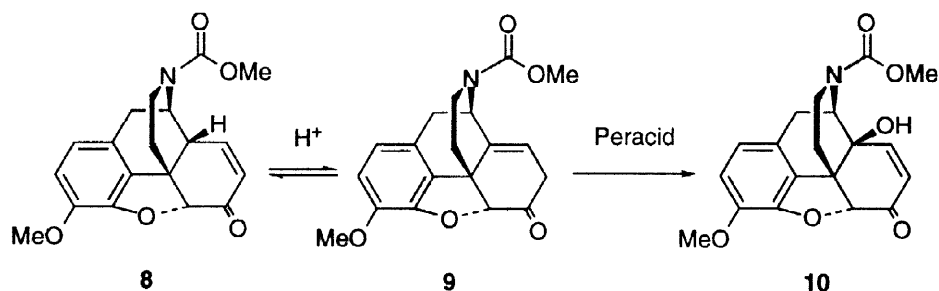


Table 2; Oxidation of **8** with peracids

Reagents <sup>a</sup>	Result
1. HCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	b
2. F <sub>3</sub> CCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	b
3. H <sub>3</sub> CCO <sub>2</sub> H, H <sub>3</sub> CCO <sub>3</sub> H, H <sub>2</sub> SO <sub>4</sub>	b
4. (CH <sub>3</sub> ) <sub>2</sub> HCCO <sub>2</sub> H/H <sub>2</sub> O <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>	b

<sup>a</sup>All reactions stirred for 24h at rt, unless otherwise stated; <sup>b</sup>Complex mixture of oxidation products, no desired product detected by TLC.

### METALLIC OXIDANTS

The possibility that Baeyer-Villiger reactions of **7** and **9** were successfully competing with the desired oxidations above, suggested that the optimal reagent for this transformation will be one that is not capable of performing a Baeyer-Villiger reaction. In addition, it was concluded that some method of regiocontrol may be necessary to favor the desired oxidation over benzylic oxidation at C-10.<sup>23</sup> As it has been shown that the *N*-lone pair of opioids occupies a position above the C-ring,<sup>24</sup> it was considered that an oxidizing metallic species coordinated to the *N*-lone pair of **5** may be suitably positioned close to the desired site of oxidation thus favoring oxidation at this position. (Figure 1).

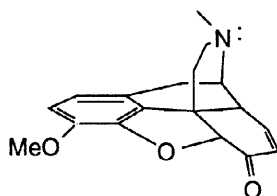
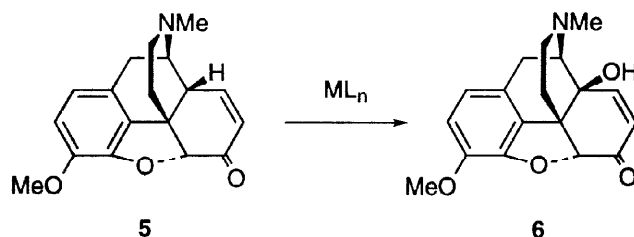


Figure 1

Encouraged by the recent report that a metallic species coordinated to a polyaniline ligand together with a cooxidant gave rise to allylic oxidation,<sup>25</sup> we decided to investigate the application of such a procedure to **5**, where the opioid tertiary amine could act as the amino ligand. Thus **5** was treated with a range of readily available metallic oxidants, and the results are summarized in Table 3.

Table 3; Oxidation of **5** with metallic oxidants.

Reagents <sup>a</sup>	Yield of <b>6</b>
1. FeCl <sub>3</sub>	b
2. Co(OAc) <sub>2</sub> cat., NaIO <sub>4</sub>	12% <sup>c</sup>
3. Co(OAc) <sub>2</sub> cat., Oxone <sup>®</sup>	b
4. Co(OAc) <sub>2</sub> , 2-methylpropanal, O <sub>2</sub>	d, e
5. RuO <sub>4</sub>	b, f
6. Mn(OAc) <sub>3</sub> , 2 equiv.	3%
7. (NH <sub>4</sub> ) <sub>2</sub> Ce(NO <sub>3</sub> ) <sub>6</sub>	b
8. Cu(OAc) <sub>2</sub>	e
9. <i>t</i> -BuOK, KMnO <sub>4</sub>	b, g
10. Na <sub>2</sub> Cr <sub>2</sub> O <sub>7</sub>	b
11. Pd(OAc) <sub>2</sub> , benzoquinone, LiOAc	b, h

<sup>a</sup>Reactions performed for 24h at rt in AcOH, unless otherwise stated; <sup>b</sup>Complex mixture of oxidation products, no desired product detected by TLC; <sup>c</sup>Numerous side products including products of iodination; <sup>d</sup>Conditions described by Das *et al.* for polymer supported cobalt<sup>25</sup>; <sup>e</sup>Recovered the majority of starting material; <sup>f</sup>Reaction performed under the standard conditions described by Sharpless<sup>26</sup>; <sup>g</sup>The anion was formed by the method described previously<sup>8</sup>, followed by the addition of KMnO<sub>4</sub> and subsequent stirring at rt for 24h; <sup>h</sup>Reaction performed under the standard conditions described by Bäckvall.<sup>27</sup>

A complex mixture of materials resulted from all reactions which made isolation and identification of the products difficult. MS analysis of the mixtures showed signals corresponding to various oxidized products, however it was decided that further analysis was not useful in most of the cases. Of all the reactions, only the cobalt mediated oxidation (entry 2) appeared promising. Although giving just a minor yield of **6**, it was noted by MS that the major side reaction appeared to be iodination when periodate was employed, and the loss of material with the use of Oxone<sup>®</sup> was shown to be due to direct reaction of Oxone<sup>®</sup> with **5**.<sup>28</sup> In order to remove the complications obviously caused by the cooxidant, it was decided to investigate the reaction using stoichiometric quantities of Co(OAc)<sub>3</sub>, a reagent that can be easily formed by the ozonolysis of an acetic acid solution of Co(AcO)<sub>2</sub>·4H<sub>2</sub>O.<sup>29</sup> The results of these Co(III) mediated oxidations are summarized in Table 4.

It was found that treatment of **5** with 2 equivalents of Co(AcO)<sub>3</sub> in acetic acid at room temperature led to a 38% yield of the desired **6** in a very convenient reaction (entry 1). Further study of the reaction showed that the initial addition of 1 equivalent of Co(OAc)<sub>3</sub> and stirring for 24h, followed by the addition of a second equivalent

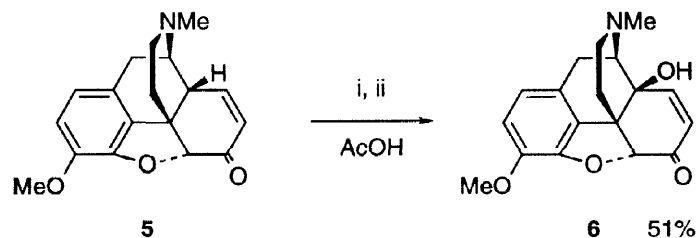
Table 4; Investigation of cobalt mediated oxidation

Reagents <sup>a</sup>	Ketone	Yield
1. Co(OAc) <sub>3</sub>	<b>5</b>	38% <sup>b</sup>
2. Co(OAc) <sub>3</sub>	<b>5</b>	51% <sup>b, c</sup>
3. 4 equiv. Co(OAc) <sub>3</sub>	<b>5</b>	d
4. Co(OAc) <sub>3</sub> , H <sub>2</sub> SO <sub>4</sub>	<b>5</b>	e, f
5. Co(OAc) <sub>3</sub> , F <sub>3</sub> CCO <sub>2</sub> H	<b>5</b>	d, f
6. Co(F <sub>3</sub> CCO <sub>2</sub> ) <sub>3</sub>	<b>5</b>	d
7. Co(OAc) <sub>3</sub>	<b>8</b>	e

<sup>a</sup>Reactions performed for 24h at rt in AcOH with two equivalents of the cobalt species unless otherwise stated;

<sup>b</sup>Numerous side products including products of N-oxidation; <sup>c</sup>One equivalent of Co(OAc)<sub>3</sub> was added and the reaction stirred for 24h, followed by the addition of a further equivalent of Co(OAc)<sub>3</sub> and stirring for a further 4h; <sup>d</sup>Complex mixture of oxidation products, no desired product detected by TLC; <sup>e</sup>Majority of starting material recovered, no desired product detected by TLC; <sup>f</sup>1 equivalent of additional acid.

and stirring for a further 4h led to an improved 51% yield of **6** (entry 2). Yields could not be improved further due to competing N-oxidation to N-formyl and N-nor derivatives (detected by MS), however the presence of the nitrogen lone pair was shown to be essential as the addition of 1 equivalent of H<sub>2</sub>SO<sub>4</sub> inhibited the reaction (entry 4), and carbamate **8**<sup>30,8</sup> was inert to the reaction conditions (entry 7). These results suggested that the basic tertiary amine was indeed acting as a ligand for the cobalt and directing oxidation to the correct position, however when coordinated, oxidation of this amino ligand was a competing reaction.<sup>31</sup> Although allylic oxidation has been observed with Co(III) salts,<sup>32,33</sup> the reaction is less favorable than either benzylic<sup>34</sup> or aromatic oxidation<sup>35</sup> underscoring the importance of coordination of the metal to the tertiary amine.<sup>36</sup> Interestingly, the treatment of **5** with Co(F<sub>3</sub>CCO<sub>2</sub>)<sub>3</sub><sup>35</sup> led only to a complex mixture from which no product could be readily identified, clearly showing the dramatic influence of the carboxylate ligands employed. The current work confirms that the direct oxidation of **5** to **6** cannot be performed with the vast majority of common oxidizing agents, however we have shown that this transformation can be conveniently performed by the use of Co(OAc)<sub>3</sub> in acetic acid at room temperature. This simple procedure gives comparable yields to the improved MnO<sub>2</sub> oxidation<sup>17</sup> but, importantly, offers a truly practical method for the direct oxidation of **5** to **6**.



(i) 1 equiv. Co(OAc)<sub>3</sub>, 24h, (ii) 1 equiv. Co(OAc)<sub>3</sub>, 4h

In summary, we have developed a practical 1 step synthesis of 14-hydroxycodeinone from codeinone by the use of  $\text{Co}(\text{OAc})_3$  in 51% yield without the need for chromatography.

## EXPERIMENTAL

### GENERAL PROCEDURES

The spectral (NMR, MS, IR) and other physical data (mp) for **6** agreed with literature values and it was shown to be identical to an authentic sample.<sup>10</sup> Peracid oxidations were performed as described in the example below for dimethylacetic acid with the differences noted in Tables 1 and 2. Reactions employing stoichiometric metal oxidants were performed as described below for  $\text{Mn}(\text{OAc})_3$ , and reactions employing catalytic metal oxidants as described for  $\text{Co}(\text{OAc})_2/\text{NaIO}_4$  below, with the differences noted in Table 3. Stoichiometric Co(III) mediated oxidations were performed as described for  $\text{Co}(\text{OAc})_3$  (procedure D) below, with the differences noted in Table 5. The best result obtained is presented in Procedure D, Method 2. For reactions that greatly differ from the examples below, reference to the literature oxidation procedure followed is given in the relevant Table. All reactions were performed under an atmosphere of argon, and all solutions were dried with  $\text{Na}_2\text{SO}_4$  and evaporated to dryness on a rotary evaporator unless otherwise noted.  $\text{H}_2\text{O}_2$  was a 30 wt. % solution in water,  $\text{H}_2\text{SO}_4$  was a 10% solution in water by volume.

#### A. OXIDATION OF **5** WITH DIMETHYLPERACETIC ACID

Hydrogen peroxide (0.2 mL, 1.95 mmol) was added slowly to a solution of **5** (500 mg, 1.7 mmol) and  $\text{H}_2\text{SO}_4$  (1 mL, 1.9 mmol) in dimethylacetic acid (5 mL). After stirring for 24h, the mixture was diluted with water (30 mL), excess oxidant was destroyed with  $\text{NaHSO}_3$ , and the solution basified with  $\text{NaHCO}_3$ . The products were extracted into  $\text{CHCl}_3$  (3 x 50 mL), washed with brine (100 mL), and dried. After removal of the solvent, **6** was purified by recrystallization from EtOH with a trace of  $\text{CHCl}_3$ . (195 mg, 37%). The **6** obtained gave spectral data identical with an authentic sample.

#### B. OXIDATION OF **5** WITH STOICHIOMETRIC MANGANESE (III) ACETATE

$\text{Mn}(\text{OAc})_3$  (450 mg, 1.7 mmol) was added to a solution of **5** (250 mg, 0.84 mmol) in acetic acid (2 mL) and the mixture stirred for 24h. The reaction was worked up as in procedure A to give the crude products. Column chromatography (Silica, EtOAc,  $\text{NH}_4\text{OH}$  (0.5%)) gave **6** (8 mg, 3%).

#### C. OXIDATION OF **5** WITH CATALYTIC COBALT (II) ACETATE AND SODIUM PERIODATE

$\text{NaIO}_4$  (95 mg, 0.44 mmol) was added to a solution of  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  (5 mg, 0.02 mmol) and **5** (130 mg, 0.44 mmol) in acetic acid (2 mL), and the mixture stirred for 24h. The reaction was worked up as in procedure A to give a mixture of products. Column chromatography (Silica, EtOAc,  $\text{NH}_4\text{OH}$  (0.5%)) gave **6** (16 mg, 12%). MS analysis of the balance of material showed iodinated products (m/z 423; **5**+126).

#### D. OXIDATION OF **5** WITH COBALT (III) ACETATE

##### METHOD 1.

$\text{Co}(\text{OAc})_3$  (2.7 mmol), prepared as previously reported,<sup>29</sup> was added to a solution of **5** (400 mg, 1.35 mmol) in acetic acid (4 mL), and the mixture stirred for 24h. The reaction was worked up as in procedure A and **6** purified by recrystallization from EtOH with a trace of  $\text{CHCl}_3$  (160 mg, 38%).

## METHOD 2.

Co(OAc)<sub>3</sub> (1.35 mmol), prepared as previously reported,<sup>29</sup> was added to a solution of **5** (400 mg, 1.35 mmol) in acetic acid (4 mL). After stirring for 24h, additional Co(OAc)<sub>3</sub> (1.35 mmol) was added and the solution stirred for a further 4h. The reaction was worked up as in procedure A and **6** purified by recrystallization from EtOH with a trace of CHCl<sub>3</sub> (215 mg, 51%).

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