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A facile synthesis of (–)- and (+)-Geissman–Waiss lactone via intramolecular Rh(II)-carbenoid mediated C–H insertion reaction: synthesis of (1*R*,7*R*,8*R*)-turneforcidine

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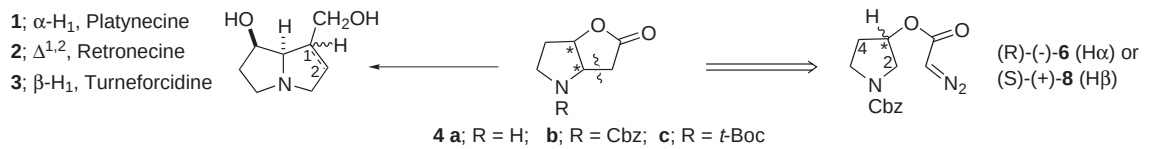
Abstract

The intramolecular C–H insertion reaction in chiral non-racemic diazoacetates (–)-**6** and (+)-**8** catalyzed by chiral $Rh_2(MPPIM)_4$ proceeded efficiently, with excellent regioselectivity and *cis*-diastereoselectivity, to give (–)- and (+)-Geissman–Waiss lactone, **4b**, respectively. Bicyclic lactone (–)-**4b** was used in the synthesis of the necine base (–)-turneforcidine **3**. © 2000 Elsevier Science Ltd. All rights reserved.

Pyrrolizidine alkaloids belonging to the necine group are found in many plant families.[1a] Their diverse structures and interesting biological activities[1b] have stimulated much interest in their synthesis with most of the attention directed at the synthesis of the pyrrolizidine base. Recent efforts have addressed the enantioselective construction of the pyrrolizidine moiety,[2] wherein the Geissman–Waiss lactone **4a**[3] and its *N*-protected derivatives, **4b**,**c**, have proven to be versatile building blocks (Scheme 1). Non-racemic **4a**–**c** have been prepared, using routes of varying lengths, from intermediates derived from: (1) the 'chiral pool';[1b,f] (2) kinetic resolution of racemates,[1b] and (3) chiral auxiliary-based diastereoselective reactions.[1b,g,h] More direct routes to non-racemic **4** would be invaluable in pyrrolizidine alkaloid synthesis and, to our knowledge, only one such approach[4] has been reported.



Scheme 1.

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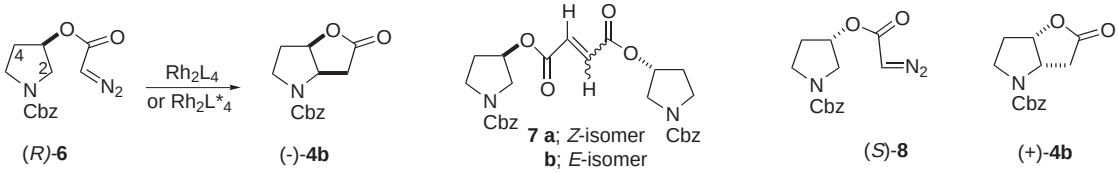
Herein we report the realization of the Rh(II)-carbenoid mediated transformation **6** (or **8**)→**4b**. Carbon–hydrogen insertion was found to proceed with excellent regioselectivity, occurring only at C-2, even though a second (C-4) potential site for insertion was present. In addition, the reaction proceeded with high diastereoselectivity to provide only the *cis*-bicyclic lactone product. This method was used in the facile construction of both (−)- and (+)-**4b**.[1b] (−)-**4b** was employed in the synthesis of (−)-turneforcidine **3**.

Our initial studies used diazoacetate (*R*)-(−)-**6**, which was readily prepared via acylation of the known[5a] (*R*)-(−)-*N*-benzyloxycarbonyl-3-hydroxypyrrolidine (**5**)[5b] with α-(*p*-toluenesulfonylhydrazone)acetyl chloride[6a] under Corey–Myers conditions.[6b] Compound **6** was then exposed to achiral and chiral Rh(II) catalysts and the results are summarized in the Table 1.

Table 1
Dirhodium(II)-catalyzed reaction of (*R*)-**6**[a]



Entry	Catalyst	Yield[b]	(−)-**4b**[c]	**7** (**a**:**b**)[c,d]
1	$Rh_2(OAc)_4$	14	78	22 (1:2)
2	Rh_2(4*R*-MEPY)$_4$	5	72	28 (1:3)
3	Rh_2(4*R*-MEOX)$_4$	15	72	28 (1:4)
4	Rh_2(4*S*-MEOX)$_4$	54	86	10[e] (1:4)
5	Rh_2(4*R*-MPPIM)$_4$	78	100	0
6	Rh_2(4*S*-MPPIM)$_4$	25	74	26 (1:1.3)

[a] Reactions ran in dry $Cl(CH_2)_2Cl$ (0.03 M), 2 mol% catalyst, 60°C, addition of (*R*)-**6** over 2 h (syringe pump), under Ar.

[b] Total combined yield of **4b** and **7a**,**b**.

[c] Relative yields determined for the mixture of closely moving products, obtained after filtration (SiO_2, 1:1 hexanes:EtOAc), by ^{1}H NMR analysis: relative yields were based on the integration of the α-CH_2 signals (δ 2.64–2.93) in the γ-lactone moiety of **4b**, the singlet at δ 6.25 of **7a**, and the singlet at δ 6.85 of **7b**.

[d] Ratio of **7a**:**7b** is based on the integration of olefinic protons.

[e] The remaining 4% is due to the ether product (δ 4.25, s, CH_2O) formed from insertion reaction of water and two molecules of metallocarbenoid intermediate.

The widely used $Rh_2(OAc)_4$ gave the desired (−)-**4b** albeit in poor yield (entry 1, Table 1). However, it was found that C–H insertion had occurred with excellent regioselectivity (at C-2) and *cis*-diastereoselectivity. Surprisingly, the use of $Rh_2(Cap)_4$, a catalyst shown to be effective for C–H insertion,[7] did not afford (−)-**4b** and only dimers **7a**,**b** (*Z*:*E* = 3:1, 36%) were produced. From these initial results, it is apparent that olefin formation via dimerization is a significant competitive pathway in this system. To improve on the yield of (−)-**4b**, as well as to suppress dimer formation, diazoacetate **6** was evaluated against three enantiomeric sets of chiral catalysts, $Rh_2(MEPY)_4$,[7] $Rh_2(MEOX)_4$,[8] and $Rh_2(MPPIM)_4$.[9]

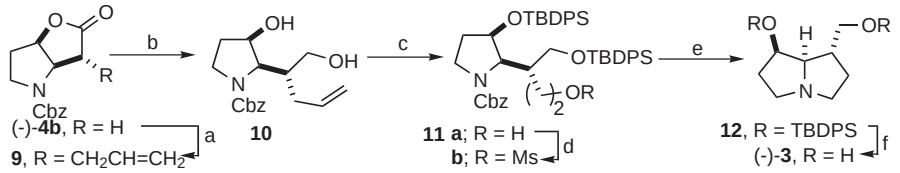
With the chiral catalysts, it was found that the C–H insertion reaction again proceeded with high regio- and diastereoselectivity to give (−)-**4b**. The preference for metallocarbenoid insertion into the C_2–H bond is likely due to activation of this sigma bond by the adjacent carbamoyl

nitrogen atom.[10] The yield of (–)-**4b** was found to vary with the type and configuration of the catalyst employed. Dimer formation was still observed. $Rh_2(4S\text{-MEPY})_4$ was found to be inefficient as a catalyst and gave the lowest yield (3.6%) of (–)-**4b** (entry 2).[11] Among the chiral catalysts examined, $Rh_2(4R\text{-MPPIM})_4$ emerged as the best catalyst for the C–H insertion reaction (entry 5), which afforded (–)-**4b** {$[\alpha]_D^{25.2}$ –115.5° (*c* 1.12, $CHCl_3$), lit.[4] $[\alpha]_D^{26}$ –122.3 (*c* 4.7, $CHCl_3$)}as the exclusive product and in excellent yield (78%). Dimer formation was completely suppressed in this case. This result can be contrasted to the lower yield (19%) obtained with the *S*-enantiomer (entry 6). Interestingly, $Rh_2(4S\text{-MEOX})_4$ gave a good yield (46%) of (–)-**4b**, whereas the *R*-enantiomer gave a lower yield (11%) of (–)-**4b** (entries 5 and 6).

Doyle and co-workers[9,12] have shown that C–H insertion reactions of select chiral non-racemic diazoacetates that are configurationally matched with chiral Rh(II) carboximidates exhibit high regio- and diastereoselectivity. That is, for a given non-racemic diazoacetate, a *R*-configurated catalyst promotes the preferential formation of one regio- and diastereomer and the *S*-configurated catalyst favours another regio- and diastereomer. In contrast, our results do not indicate that a matched/mismatched relationship is occurring in the reaction between (*R*)-**6** and the chiral Rh(II) catalysts used in this study since only *cis*-**4b** was formed in all cases examined. Furthermore, $Rh_2(4R\text{-MPPIM})_4$ and $Rh_2(4S\text{-MEOX})_4$ efficiently catalyzed the formation of (–)-**4b** from (*R*)-**6**.

Encouraged by the outcome from the reaction of $Rh_2(4R\text{-MPPIM})_4$, we prepared[7] the (*S*)-diazoacetate **8** (vide supra, Table 1) from the known[13] (*S*)-(+)-*N*-benzyloxycarbonyl-3-hydroxypyrrolidine. Treatment of (*S*)-**8** with $Rh_2(4S\text{-MPPIM})_4$ led to a high yield (76%) of the enantiomeric Geissman–Waiss lactone, (+)-**4b**; $[\alpha]_D^{26.8}$ +123° (*c* 1.14, $CHCl_3$), lit.[4] $[\alpha]_D^{24}$ 122.9° (*c* 1.14, $CHCl_3$)] and no dimer products were detected.

Equipped with a facile method for the synthesis of either (–)- or (+)-**4b**, and to demonstrate the synthetic utility of this method, we turned our attention to the synthesis of (–)-turneforcidine, (–)-**3**, from (–)-**4b** (Scheme 2).



Scheme 2. (a) LiHMDS, THF, HMPA (1 equiv.), –78°C; then allyl bromide, HMPA (1 equiv.), –78°C (1 h) to –45°C (30 min), 57%; (b) $NaBH_4$, 95% EtOH, rt, 24 h, 86%; (c) (i) TBDPSCl, imidazole, DMF, rt, (ii) 20 mol% OsO_4, 3 equiv. $NaIO_4$, Et_2O–H_2O, then $NaBH_4$, 95% EtOH, 73% (two steps); (d) MsCl, Et_3N, cat. DIPEA, CH_2Cl_2, 0°C, 88%; (e) 10% Pd/C, cyclohexene, MeOH, reflux, then K_2CO_3, reflux, 92%; (f) Bu_4NF, THF, rt; 68%

(–)-Turneforcidine is a naturally occurring necine base found in pyrrolizidine alkaloids typified by cropodine, retusine[1a] and the recently isolated racemozine.[14] Two routes[15a,b] leading to (±)-turneforcidine have been reported and, surprisingly, only two reports[15c,d] have described the enantioselective synthesis of (–)-turneforcidine. In the latter two enantioselective routes both of the starting compounds were derived from pyrrolizidine alkaloids.

The synthesis began with the allylation (57%) of the lactone moiety in (–)-**4b**, which would provide the requisite side-chain to be used for the construction of the second ring. Reduction[15a] of the γ-lactone moiety in **9** was accomplished using four equivalents of $NaBH_4$ which led to a high yield of the diol **10**. Subsequent silylation of the diol **10** with *t*-butylchlorodiphenylsilane,

followed by oxidative cleavage[16] of the double-bond yielded the corresponding aldehyde, which was immediately reduced with $NaBH_4$ to give the primary alcohol **11a**. Mesylation of **11a**, followed by catalytic transfer hydrogenolysis[17] of the *N*-Cbz protecting group in **11b** and base-mediated intramolecular alkylation provided an excellent yield of the pyrrolizidine bis-silyl ether, **12** {$[\alpha]_D^{27.7}$ −7.6° (*c* 1.05, $CHCl_3$)}. Interestingly, attempted hydrogenolysis of the *N*-Cbz group over 10% Pd/C using either 1 atm. (balloon) or 35 psi of hydrogen pressure only returned unreacted **11b**. Desilylation of **12** with TBAF gave the very polar (−)-**3** {$[\alpha]_D^{26}$ −13.9° (*c* 0.36, MeOH). Lit.[15c] $[\alpha]_D^{23}$ −12° (*c* 0.82, MeOH), lit.[15d] $[\alpha]_D^{23}$ −12.5° (*c* 1.3, MeOH)} in 68% yield. Synthetic (−)-**3** showed ^1H and ^{13}C NMR data that are in accord with those reported.[15]

In conclusion, the enantiomeric pair of *N*-Cbz protected Geissman–Waiss lactone, (−)- and (+)-**4b**, is readily prepared via the Rh_2[4(*R* or *S*)-MPPIM]$_4$ catalyzed reaction of the enantiomeric diazoacetates (*R*)-**6** or (*S*)-**8**. (−)-Turneforcidine was prepared in an overall yield of 20% starting from (−)-**4b**. Further work using this Rh(II)-carbenoid approach in the synthesis of naturally occurring saturated *N*-heterocycles is in progress and will be reported in the future.

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