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Total synthesis of (−)-eburnamonine and (+)-*epi*-eburnamonine from a chiral non-racemic 4,4-disubstituted γ-lactone

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Abstract

The total synthesis of (−)-eburnamonine and (+)-*epi*-eburnamonine was successfully achieved using a key chiral non-racemic 4,4-disubstituted γ-lactone **4** that was prepared via the Rh(II) carbenoid mediated tertiary C–H insertion reaction of a chiral non-racemic diazomalonate **5**.

Keywords: rhodium(II) carbenoid; asymmetric synthesis; tertiary C–H; insertion.

Many natural products, such as alkaloids and terpenes, possess quaternary carbon centers that are part of the skeletal framework of the molecules. The synthesis of these natural products must invariably address the challenging task of the enantioselective construction of the quaternary carbon centers. Many different strategies[1] have been developed, but some limitations[1c,d,g,h] have been noted. We recently described a strategy[2a] for the synthesis of (±)-quebrachamine wherein an unsymmetrical 4,4-disubstituted γ-lactone was employed as a key intermediate. The requisite γ-lactone was readily accessed via our Rh(II) carbenoid mediated intramolecular tertiary C–H insertion reaction.[2b] This success prompted us to investigate a similar strategy for the asymmetric synthesis of the pentacyclic indole alkaloids[3] (−)-eburnamonine **1a** and (+)-*epi*-eburnamonine **1b**, and we report our findings in this Letter.

The retrosynthetic analysis of **1a**,**b** is shown in Fig. 1. The hydroxy-lactam aldehyde **2** can be derived from the γ-lactone amide **3**, which in turn, is accessible from the chiral non-racemic γ-lactone carboxylic acid **4**. Compound **4** is prepared via Rh(II)-catalyzed tertiary C–H insertion reaction of chiral non-racemic diazo compound **5**.

The diazomalonate **5** was readily prepared starting from the known *N*-butanoyloxazolidinone[4] **6** as summarized in Scheme 1. Alkylation of **6** with allyl bromide followed by hydrolysis[5] and reduction gave the volatile primary alcohol (*S*)-**7a** {$[\alpha]_D^{24}$ +1.8 (*c* 1.4, $CHCl_3$)}. The absolute configuration of **7a** was confirmed by conversion to the *p*-methoxybenzyl ether **7b** {$[\alpha]_D^{24}$ −2.8 (*c* 1.8, $CHCl_3$)}, whose optical rotation is of the same magnitude but opposite in sign to the optical rotation of the known

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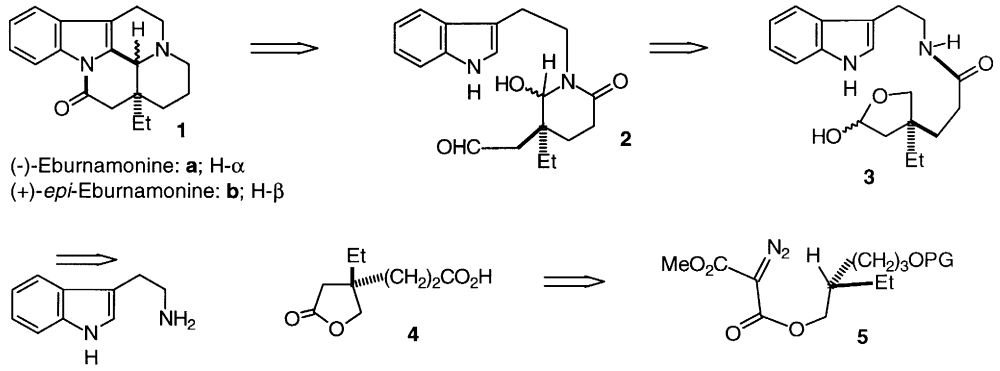
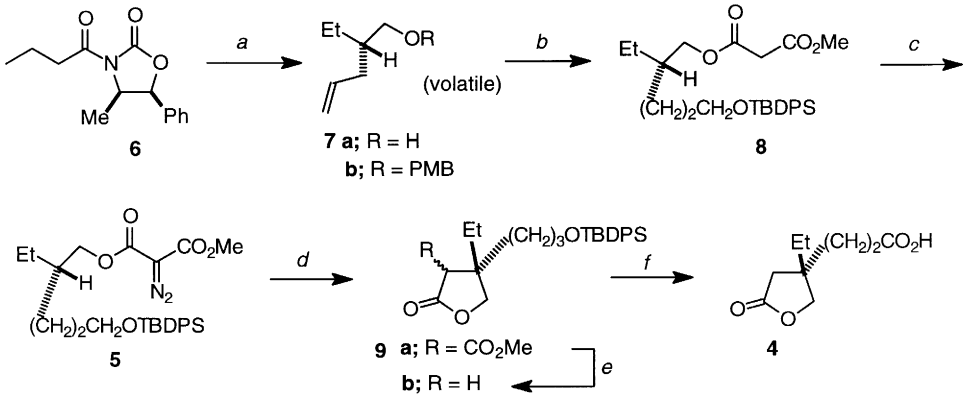


Fig. 1.

enantiomer,[6] (*R*)-**7b** {$[\alpha]_D^{24}$ +1.9 (*c* 2.01, $CHCl_3$)}. Esterification[7] of the primary hydroxyl group with α-(carbomethoxy)acetic acid (DCC, DMAP) followed by diazotization afforded **5**.

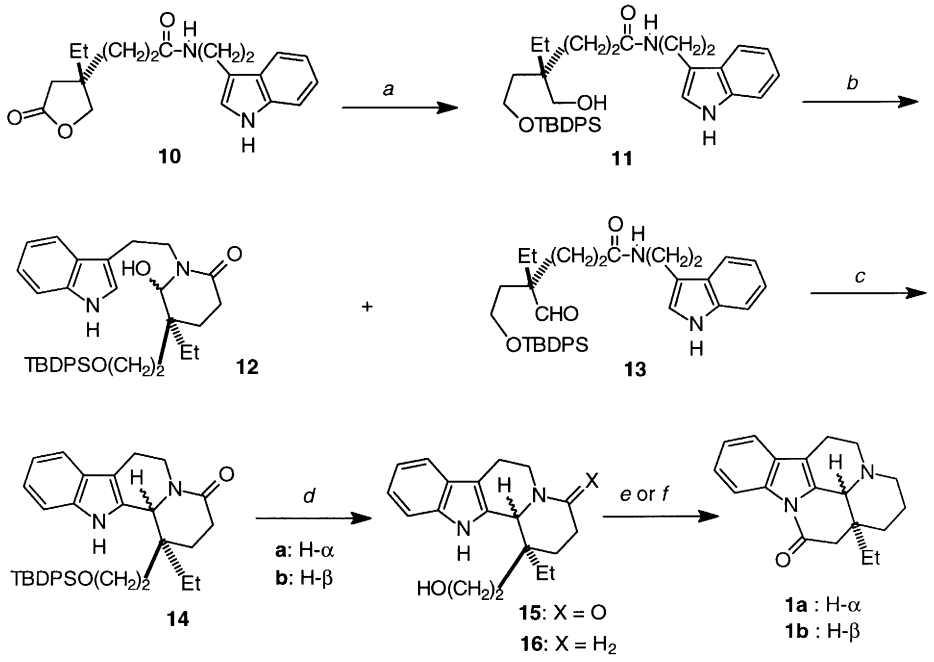


Scheme 1. Reagents and conditions: PMP=*p*-methoxybenzyl, TBDPS=*t*-butyldiphenylsilyl: (a) (i) $NaN(SiMe_3)_2$, THF, −78°C, then allyl bromide, −40°C, 89%; (ii) LiOH, H_2O_2, THF, 99%; (iii) $LiAlH_4$, THF, 0°C, 50%; (b) (i) $MeO_2CCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 91%; (ii) Sia_2BH, THF, 0°C, then H_2O_2, NaOH, 70%; (iii) TBDPS–Cl, pyridine, 89%; (c) MsN_3, Et_3N, MeCN, 88%; (d) 2 mol% Rh_2OAc_4, CH_2Cl_2, reflux, 90%; (e) 10:1 v/v DMSO:H_2O, NaCl, 110°C, 84%; (f) (i) Bu_4N F, THF, 93%; (ii) CrO_3, H_2SO_4, H_2O, 95%

With compound **5** in hand, we examined the preparation of the γ-lactone carboxylic acid **4**. Rhodium(II) carbenoid insertion into the C–H bond of a configurationally defined tertiary carbon stereocenter has been shown to proceed stereospecifically and with retention of configuration.[8] With this fact in mind, **5** was treated with 2 mol% of $Rh_2(OAc)_4$ under our previously described[2] reaction conditions to furnish a high yield (90%) of a 1:1 diastereomeric mixture of **9a**, which was efficiently decarboxylated[9] to yield (*S*)-**9b** {$([\alpha]_D^{23}$ −3.3 (*c* 1.5, $CHCl_3$)}. The configuration at the new C-4 stereocenter was confirmed by the successful transformation of (*S*)-**9b** to eburnamonine **1a** (and its epimer **1b**).

Desilylation of **9b** released the primary alcohol unit, which was oxidized using Jones' reagent to give a high yield of the γ-lactone carboxylic acid (*S*)-**4** {$[\alpha]_D^{24}$ −7.1 (*c* 1.4, $CHCl_3$)}. Condensation of **4** with tryptamine under standard conditions,[7] provided a 67% yield of amide **10** {$[\alpha]_D^{24}$ −2.9 (*c* 0.9, $CHCl_3$)}. Selective reduction of the lactone moiety in **10** (Scheme 2) with $LiBH_4$ produced the corresponding diol which was selectively protected, at the less hindered, non-neopentylic primary alcohol unit, as the *t*-butyldiphenylsilyl ether **11** {$[\alpha]_D^{24}$ −1.3 (*c* 2.0, $CHCl_3$)}. Oxidation of the neopentylic alcohol moiety was best achieved under Parikh–Doering conditions[10] to give an excellent yield of a 1.7:1 mixture of the

lactam alcohol **12** and the aldehyde **13**. Separation of the two products was not essential as treatment of the mixture of **12** and **13** in toluene (rt) with 50 mol% Nafion-H afforded a 95% yield of the readily separable lactams **14a** {$[\alpha]_D^{24}$ −50 (*c* 0.2, $CHCl_3$)} and **14b** {$[\alpha]_D^{24}$ +85 (*c* 0.5, $CHCl_3$)}, and in a ratio of 1:2.[11] Treatment of **14a** and **14b** with Me_3SiCl in dry methanol proceeded efficiently to furnish the known crystalline alcohols **15a**[12a] {$[\alpha]_D^{24}$ −192.3 (*c* 0.13, MeOH), lit.[3b] $[\alpha]_D$ −195.5 (*c* 0.16, MeOH)} and **15b**[12b] {$[\alpha]_D^{24}$ +111 (*c* 0.54, MeOH, lit.[3b] $[\alpha]_D^{24}$ +88.3 (*c* 0.13, MeOH)}, respectively. The conversion of **15a** to (−)-eburnamonine **1a** proved to be non-trivial. Brief treatment of **15a** with $LiAlH_4$ gave a moderate yield of the corresponding amino alcohol **16a**; it was found that prolonged reaction times resulted only in decomposition products. Attempted direct oxidation of **16a** to **1a** using TPAP[13] in the presence of *N*-methylmorpholine oxide (NMMO) only gave an intractable mixture of products. However, oxidation of **16a** under Parikh–Doering conditions[10] to obtain the corresponding aldehyde followed immediately by TPAP/NMMO oxidation furnished (−)-eburnamonine **1a**[14a] {$[\alpha]_D^{24}$ −77 (*c* 0.13, $CHCl_3$), lit.[3b] $[\alpha]_D^{24}$ −88 (*c* 0.09, $CHCl_3$)}. Unlike **15a**, $LiAlH_4$ reduction of **15b** proceeded to give a high yield of **16b**, which upon oxidation with TPAP/NMMO afforded (+)-*epi*-eburnamonine **1b**[14b] {$[\alpha]_D^{24}$ +158 (*c* 0.19, $CHCl_3$), lit.[3f] $[\alpha]_D$ +168 (*c* 1, $CHCl_3$)} in good yield.



Scheme 2. Reagents and conditions: (a) (i) $LiBH_4$, THF, 0°C to rt, 92%; (ii) TBDPS–Cl, imidazole, DMF, rt, 98%; (b) pyridine–SO_3, DMSO, Et_3N, rt, 95%; (c) 50 mol% Nafion-H, PhMe, rt, 18 h, 95%; (d) 4 equiv. Me_3SiCl, MeOH: **15a**, 97%; **15b**: 95%; (e) For **1a**: (i) $LiAlH_4$, THF, reflux, 30 min, 30%; (ii) pyridine–SO_3, DMSO, Et_3N, rt; then TPAP, NMMO, 4A MS, CH_2Cl_2, 37% (two steps); (f) for **1b**: (i) $LiAlH_4$, THF, reflux, 84%; (ii) TPAP, NMMO, 4A MS, CH_2Cl_2, 55%

In summary, we have demonstrated a strategy based on the use of the readily accessible chiral non-racemic 4,4-disubstituted γ-lactone **4**, for the synthesis of (−)-eburnamonine and (+)-*epi*-eburnamonine. The use of 4,4-disubstituted γ-lactones as intermediates in synthesis has received only limited attention and our investigations in this area are continuing.

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11. Equilibration of pure **14b** under Fuji conditions[3b] (BF_3OEt_2, 35–40°C, 10 h) led to a 1:4 ratio of **15a**:**15b**.
12. (a) Mp 285–286°C; lit.[3b] 263–265°C; (b) mp 110–113°C; lit.[3b] 107–108.5°C.
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