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First asymmetric total synthesis of (−)-(*R*)- and (+)-(*S*)-geibalansine

Ademir F. Morel* and E. L. Larghi

Universidade Federal de Santa Maria, Lab. 2122b, Prédio 18, Campus Universitário, Camobi, 97119-900 Santa Maria, RS, Brazil

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Abstract—Treatment of prochiral chromenoquinoline **2** with (*R*,*R*)- and (*S*,*S*)-(1,4-di-*tert*-butyl-salicilydene)-diaminocyclohexane (manganese III) chloride, and buffered house bleach (pH ~ 11) gave the epoxide **3** with 90–95% yield and ee >93% (estimated by polarimetry). The epoxides were opened with H_2 Pd/C 10% affording geibalansine **1** in 75% yield and ee 94–98%, determined by HPLC analysis.

1. Introduction

In a program to study medicinal plants of southern Brazil, we isolated a sequence of metabolites from *Zanthoxylum hyemale* (Rutaceae).[1] After ^{1}H, ^{13}C NMR, and HRMS analysis, Horeau and chiroptical methods, the structure of (−)-(3*R*)-3,4-dihydro-3-hydroxy-5-methoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline **1** alkaloid[1] was proposed.

Surprisingly, **1** was a known compound called geibalansine that had already been isolated from *Geijera balansae* (Rutaceae) as a racemate.[2] Compound **1** had previously been synthesized in its racemic form[3] and via only one asymmetric synthesis,[4,5] based on the resolution of a diastereomeric pair of 2-methoxy-2-phenyl-2-trifluoromethylacetates (derived from a *trans*-bromohydrin and 2-methoxy-2-phenyl-2-trifluoromethyl-chloride) by preparative TLC. These compounds were subjected to elimination promoted by KO*t*-Bu to afford an epoxide, which after hydrogenolysis resulted in the enantiopure forms of **1**.[5]

2. Results and discussion

The fundamental part of our work was to achieve a total asymmetric synthesis of (−)-(3*R*)- and (+)-(3*S*)-geibalansine. To synthesize these optically active compounds with high ee, it was necessary to find an appropriate prochiral precursor. The 5-methoxy-2,2-dimethyl-(2*H*)-pyrano[2,3-*b*]quinoline **2** was selected as the substrate,[6] as it has been previously used by Boyd et al. as the starting material for the racemic *trans*-bromohydrin.[4,5] An asymmetric *cis*-dihydroxylation (Sharpless approach),[7] as well as an enantioselective epoxidation with SalenMn^{III}Cl/NaOCl (Jacobsen approach), was performed on **2**. The latter method, having been employed for the epoxidation of the structurally related 2,2-dimethychromenes.[8]

Sharpless asymmetric *cis*-dihydroxylation of the chromenoquinoline with AD-mix-α in *t*-BuOH/H_2O at 0 °C, gave the diol **4** in 28% yield, and with a 50% ee. In fact, this diol showed some epimerization at the benzylic position during chromatographic purification, but the problem was solved via the use of deactivated silica.[9]

The poor yield and modest ee prompted us to try the reaction of **2** using Jacobsen's method. Since we had two forms of the catalyst, (−)-(*R*,*R*)- and (+)-(*S*,*S*)-bis-(1,4-di-*tert*-butyl-salicilydene)-diaminocyclohexane-(manganese III)-chloride, it was not necessary to have a racemic form of the epoxides and geibalansine for the determination. After stirring a mixture of **2**, the (*R*,*R*)-Mn complex and NaOCl for 6–12 h, the known (+)-(3*R*,4*R*)-3,4-dihydro-3,4-epoxy-5-methoxy-2,2-dimethyl-(2*H*)-pyrano[2,3-*b*]quinoline **3** was isolated by chromatographic column in 90% yield. We then analyzed the samples by HPLC, to determinate a concise ratio of the enantiomers, but it was found not possible to achieve enantiomeric

* Corresponding author. Tel.: +55-55-220-8869; fax: +55-55-220-8031; e-mail: afmorel@base.ufsm.br

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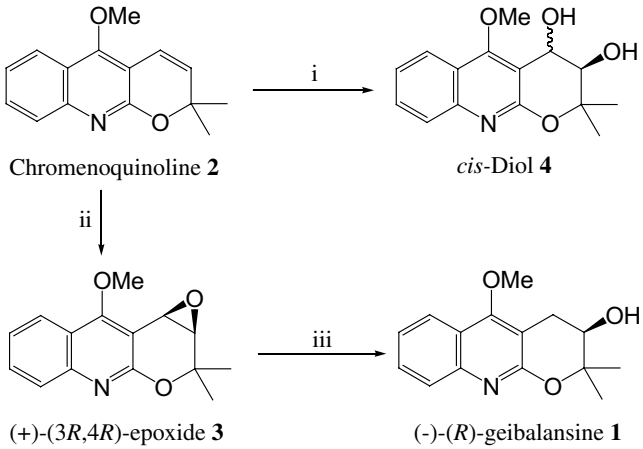

Scheme 1. Reagents and conditions: (i) AD-mix-α; *t*-BuOH/H_2O 1:1, 0 °C; (ii) (*R*,*R*) catalyst form, NaOCl (pH ~ 11), CH_2Cl_2, 6–12 h, 0 °C; (iii) H_2 (1 atm), Pd/C 10%, MeOH, rt.

separation with our system.[10] By polarimetric analysis, the ee was estimated to be up to 93%. The epoxide ring opening being performed with H_2 (1 atm) and Pd/C 10% in MeOH, to afford (−)-(*R*)-geibalansine in 75% yield. When the sample was analyzed by HPLC, separation was observed, and the ee determined to be 94%.[10]

Repeating the process in the presence of the (*S*,*S*)-catalyst, gave better results (95% yield and 98% ee). The absolute configuration of the epoxide was in agreement with the model proposed by Jacobsen et al.[8] The (−)-(*R*,*R*)-salicilydene catalyst afforded the (+)-(3*R*,4*R*)-epoxide (and after hydrogenolysis, (−)-(*R*)-geibalansine) (Scheme 1). Naturally, the opposite was true when the (*S*,*S*)-salicilydene was used.

In conclusion, we have efficiently applied for the first time, Jacobsen's method to chromenoquinolines, with excellent yields and high ee. We have developed a straightforward asymmetric total synthesis of (+)- and (−)-geibalansine from the related epoxides, versatile precursors to a range of related quinoline alkaloids.[4,5] Finally, this procedure should allow the functionalization of the pyranoquinoline ring in a concise and predictable way.

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9. The silica for this chromatography column was deactivated by flushing with a solution 10% Et_3N in hexanes and then, was washed with hexanes prior to use.
10. (+)-(3*R*,4*R*)-3,4-Dihydro-3,4-epoxy-5-methoxy-2,2-dimethyl-(2*H*)-pyrano[2,3-*b*]quinoline **3**: To a stirred solution of **2** (21.5 mg, 0.09 mmol) in CH_2Cl_2 (0.2 mL) was added the (*R*,*R*)-catalyst (1.7 mg, 2.7×10^{-3} mmol), and the system then cooled to 0 °C. Afterwards, commercial cooled buffered bleach (2.0 mmol, 0.6 mL), was slowly added. The biphasic mixture was stirred and kept at the same temperature, until complete consumption of the starting chromenoquinoline (by TLC). The mixture was diluted with H_2O (4 mL), extracted several times (4 × 2 mL CH_2Cl_2), and dried over Na_2SO_4. The volatiles were removed in vacuo, and flash chromatographed in silica 200–400 mesh, eluting with mixtures of hexanes/AcOEt. The epoxides were obtained in pure forms (90–95% isolated yield), and ee >93%, estimated by polarimetry. Synthesis of (−)-(*R*)-geibalansine **1**: A solution of (+)-(*R*,*R*)-epoxide **3** (11 mg, 0.043 mmol) in MeOH (2.5 mL) was hydrogenated using Pd/C 10%, at 1 atm of H_2 at room temperature. When all the oxirane was consumed, the reaction mixture was filtered through Celite®, the volatiles distilled off, and column chromatographed to afford (−)-geibalansine in 75% yield. The product was analyzed in an HPLC, equipped with a Chiracel® column, using a mixture of *n*-hexane/*i*-PrOH 95:5 as mobile phase, at 0.85 mL min^{-1}. The (*S*)-eluted before the (*R*)-form, with (−)-(*R*)-**1** being obtained with ee of 94%.