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Diastereoselective total synthesis of 8-epigrosheimin

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ABSTRACT

The first diastereoselective total synthesis of 8-epigrosheimin was accomplished relying entirely on substrate-controlled methods. 8-Epigrosheimin, isolated as an amoebicidal and antibiotic compound from *Crepis virens*, is a multi-chiral-centered guaianolide with a *cis*-hydroazulene and a trans-annulated γ-butyrolactone ring. Our approach featured that the γ-butyrolactone unit was formed firstly before the construction of the cycloheptane ring system. The key steps of the synthesis involved (1) a stereoselective Mukaiyama aldol addition; (2) an oxidative γ-lactonization; and (3) an intramolecular aldehyde-ene cyclization.

Guaianolides constitute one of the largest groups of naturally occurring sesquiterpene lactones with structural complexity and a wide range of biological activities.[1] The structure–activity relationship (SAR) of this class of natural products is currently under intensive investigation. In addition to the functional groups in the cyclopentane ring system, the oxygen substituent at C-8 and the double bond at C-10, as well as the *exo*-methylene group in the trans-annulated γ-butyrolactone moiety, play an important role in their biological activities (Fig. 1).[2] Although there are some reports in the literature on the synthesis of guaianolide-related compounds, to the best of our knowledge, the only example of total synthesis that could efficiently assemble the above-mentioned functional groups was reported by Rigby et al. in 1987 on the synthesis of (±)-grosheimin **1a** from tropone.[3] Herein, we wish to report a short and stereoselective approach to the first diastereoselective total synthesis of 8-epigrosheimin **1b**, which was isolated firstly as an amoebicidal and antibiotic compound from *Crepis virens* 20 years ago.[4]

As shown in Scheme 1, our strategy featured the C-ring formation before addressing the construction of the B-ring from cyclopentyl carbaldehyde **2a**.[5] We envisaged that the γ-butyrolactone of C-ring could impose considerable rigidity, and the intramolecular aldehyde-ene reaction would react diastereoselectively to give the hydroxyl group, as well as the *exo*-methylene group.[6] The installation of the two stereocenters at C6 and C7 could be realized by aldol reaction of cyclopentyl carbaldehyde **2a** with γ-butyrolactone or by Mukaiyama reaction with the trimethylsilyl enol ether of γ-butyrolactone.[7]

However, instead of the desired *syn* diastereomer **4**, the undesired *anti* diastereomer **3a** (Scheme 2) was obtained almost exclusively through the aldol addition of cyclopentyl aldehyde **2a** with the lithium enolate of γ-butyrolactone either in the presence or absence of $ZnCl_2$ at −78 °C, which could be explained by the Felkin–

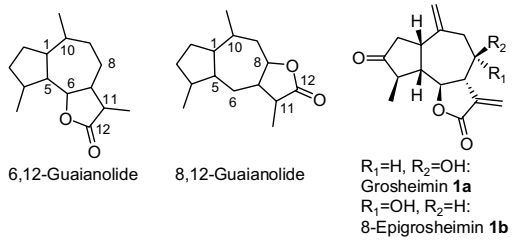
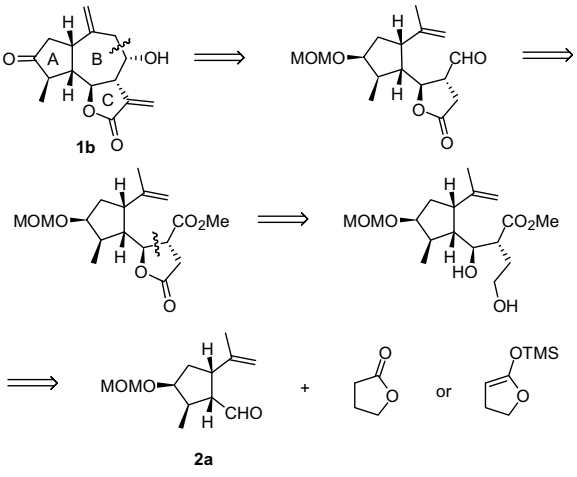


Figure 1. Structure of guaianolide and grosheimin **1a** and 8-epigroshimin **1b**.



Scheme 1. Retrosynthetic analysis of 8-epigrosheimin.

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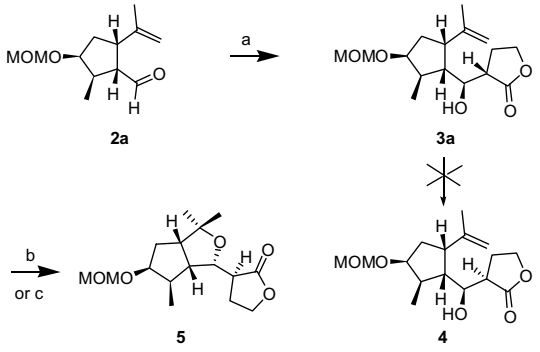
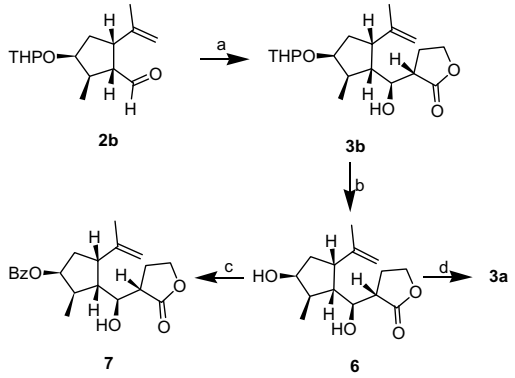
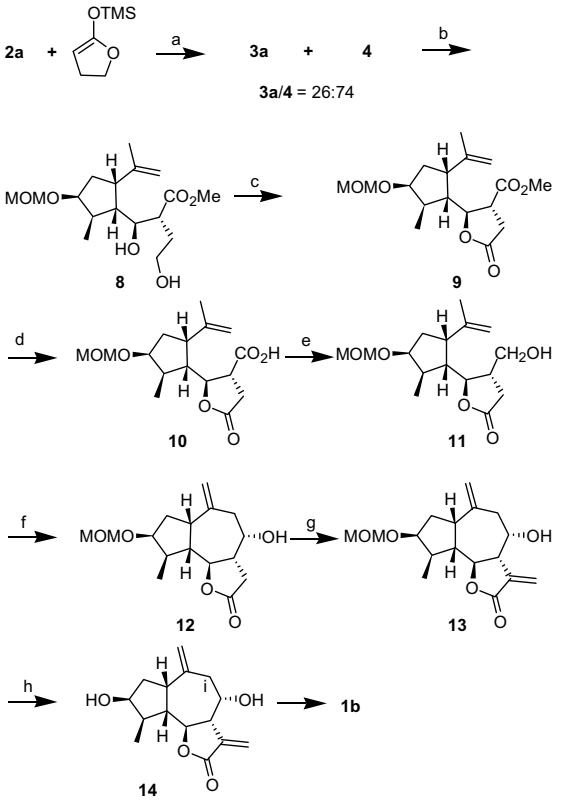


Scheme 2. Reagents and conditions: (a) γ-butyrolactone, THF, LDA, $ZnCl_2$, −78 °C, 2.5 h, 87%; (b) TMSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C, 1 h; then HF, rt, 1.5 h, 61%; (c) concd HCl, *i*-PrOH, 50 °C, 2.5 h, 67%.



Scheme 3. Reagents and conditions: (a) γ-butyrolactone, THF, LDA, $ZnCl_2$, −78 °C, 2.5 h, 72%; (b) MeOH, TsOH, rt, 6 h, 67%; (c) Py, CH_2Cl_2, BzCl, 0 °C, 3 h, 73%; (d) MOMCl, CH_2Cl_2, DIPEA, rt, 3.5 h, 71%.



Scheme 4. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 1.5 h, 92%; (b) KOH, H_2O, THF, rt, 4 h; HCl, pH 1, rt; CH_2N_2, 94%; (c) TEMPO, CH_2Cl_2, H_2O, TBAC, NCS, rt, 7 h, 89%;(d) NaOH, H_2O, THF, rt, 80 min; then HCl, 95%; (e) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C, 1 h; then $NaBH_4$, DMF, THF, −78 to −18 °C, 7 h, 68%; (f) (1) Swern oxidation; (2) $(i\text{-PrO})_2TiCl_2$, CH_2Cl_2, −15 °C, 5 h, 85%, two steps; (g) LDA, THF, −78 °C, Eshenmoser's salt, 4.5 h; *m*-CBPA, 0 °C, 20 min, 72%; (h) *i*-PrOH, TsOH, 24 h, reflux, 95%; (i) IBX, DMSO, 1.5 h, rt, 96%.

Anh transition state.[8] Conversion of C7-(*S*) isomer **3a** to C7-(*R*) isomer **4** by treatment with trimethylsilyl triflate (TMSOTf) in the presence of 2,6-lutidine at 0 °C for about 1.5 h followed by desilylation with HF in a similar method of Hanessian failed,[7d] and an intramolecular cyclization product **5** was obtained in 61% yield along with some unidentified by-products. In fact, the same product **5** was yielded when lactone **3a** was subjected to the acid-catalyzed deprotection of MOM group conditions (HCl/*i*-PrOH, TMSCl/TBAB, etc.).

In order to identify the configuration of **3a** (Scheme 3), the diol **6** was prepared smoothly via the aldol addition of aldehyde **2b** with lithium enolate of γ-butyrolactone in the presence of $ZnCl_2$ at –78 °C, followed by deprotection of THP group of **3b** with TsOH in methanol at room temperature. The benzoate **7** was obtained by selective acylation with benzoxyl chloride from diol **6**, whose hydroxyl group at C3 was protected selectively by treatment with methoxylmethyl chloride to yield the lactone **3a**. The structure of **3a** was determined as an *anti* diastereomer based on the X-ray crystallographic analysis of **7**.[9]

A survey of Lewis acid (ZnI_2, $ZnBr_2$, $MgBr_2$, $(i\text{-PrO})TiCl_3$, $(i\text{-PrO})_2TiCl_2$, $BF_3{\cdot}Et_2O$) catalysts for the Mukaiyama reaction of the aldehyde **2a** with trimethylsilyl enol ether of γ-butyrolactone at different temperature (−78 °C to 0 °C to rt) revealed that either decomposition or no reaction was observed except in the case of $BF_3{\cdot}Et_2O$. Treatment of **2a** with trimethysilyl enol ether of γ-butyrolactone in the presence of $BF_3{\cdot}Et_2O$ at −78 °C in methylene chloride afforded the desired **4** as the major product, and **3a** in 92% total yield (74:26, **4**/**3a**). The structure of **4** was established unambiguously by X-ray crystallography.[10] The two isomers **3a** and **4** were isolated readily by silica gel chromatography method. Hydrolysis of **4** with potassium hydroxide in THF and H_2O followed by careful acidification to pH 1 with HCl and final esterification with CH_2N_2 furnished the diol methyl ester **8** in 94% yield. Diol **8** was oxidized to lactone **9** in 89% yield using Einhorn's method.[11] The direct transformation of lactone methyl ester **9** to lactone alcohol **11** or aldehyde failed because the lactone carbonyl is more reactive than the methyl ester carbonyl under the reduction conditions. Fortunately, the lactone alcohol **11** was achieved in moderate yield by activation of the carboxyl group of the lactone carboxylic acid **10** with Vilsmeier reagent, followed by reduction with sodium borohydride in DMF.[12] The unstable aldehyde was provided by Swern oxidation of alcohol **11**, which gave the intramolecular ene cyclization product **12** in 85% yield exclusively under the catalysis of $(i\text{-PrO})_2TiCl_2$ over two steps. The structure of guaianolide **12** was determined unambiguously by X-ray crystallography.[13] Methylenation of **12** with Eshenmoser's salt furnished **13** in moderate yield (72%),[14] and subsequent deprotection of the MOM group of **13** afforded diol **14** in 95% yield. The final selective oxidation of diol **14** with 2-iodoxybenzoic acid (IBX) in DMSO[15] afforded (−)-8-epigrosheimin **1b**, $[\alpha]_D^{20}$ −34.4 (*c*, 1.18, $CHCl_3$) [lit.[4a] (+)-**1b**: $[\alpha]_D^{20}$ +31.5±1 (*c*, 0.1, $CHCl_3$)] (Scheme 4).

In conclusion, a new approach has been developed to synthesize C8-oxygenated guaianolide, and this led to the success of the first total synthesis of (−)-8-epigrosheimin **1b**. Studies on the biological activities of **1b** and its enantiomer and their analogs are currently underway. This novel synthetic route could be applied to the synthesis of similar guaianolides efficiently for biological studies.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.025.

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10. Crystallographic data for **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 704509. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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