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Total Synthesis of (+)-Bourgeanic Acid Utilizing Desymmetrization Strategy

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A highly stereoselective total synthesis of an aliphatic depside (+)-bourgeanic acid via (–)-hemibourgeanic acid and bourgeanic lactone is described. The key steps involved in this synthesis are desymmetrization of bicyclic olefin with Brown's asymmetric hydroboration, Gillman's reaction, TEMPO-BAIB mediated selective oxidation of 1,3-diol, Yamaguchi macro-lactonization and LiOH-mediated partial hydrolysis of unusually stable eight-membered cyclic dilactone.

Introduction

The first member of the lichen metabolites of a new class of naturally occurring aliphatic depsides, (+)-bourgeanic acid (**1**) was isolated by Bodo group in 1973 from the species of lichen Ramalina.[1] The structure of **1** was deduced by the same group as an esterification product of two molecules of (–)-hemibourgeanic acid **3** [(2*S*,3*S*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid], which was further confirmed by the saponification of **1**. The absolute configuration of (–)-hemibourgeanic acid **3** was proposed by the X-ray crystallographic analysis of its *p*-bromophenacyl ester.[2,3] An interesting property of the (+)-bourgeanic acid (**1**), discovered by Bodo et al. During the degradative studies was the formation of an eight-membered dilactone (bourgeanic lactone) **2** under mild dehydrating conditions.[2] The conformational analysis of this dilactone showed that, it contains an eight-membered ring, which adopts a crown-shaped conformation with C_2-axis of symmetry with all the substituent's in equatorial orientation. This special feature undoubtedly contributes to the ready formation of the eight-membered structure (Figure 1).[3]

The first total synthesis of (+)-bourgeanic acid (**1**) was reported by White et al. using (*S*)-*N*-propionylprolinol-mediated asymmetric alkylation followed by condensation with (*E*)-crotylboronate (Roush's modified procedure).[4] Recently, Breit et al. reported the second total synthesis using the *o*-DPPB-directed [*o*-DPPB = *o*-(diphenylphosphanyl)benzoyl] organocopper-mediated allylic substitution and the Sharpless asymmetric epoxidation as the key steps.[5] For the last few years, our laboratory has explored the potentials of desymmetrization strategy in natural product synthesis. Our approach typically involves in the desymmetrization of bicyclic olefin and substrate-controlled stereoselective transformations to create contiguous stereocenters. This strategy was successfully employed in our laboratory for the total synthesis of several biologically potent and structurally novel natural products.[6] Herein we report a highly stereoselective total synthesis of an aliphatic depside, (+)-bourgeanic acid (**1**) via the unusual and remarkably stable bourgeanic lactone (**2**) and (–)-hemibourgeanic acid (**3**), radically different from the procedures reported so far.

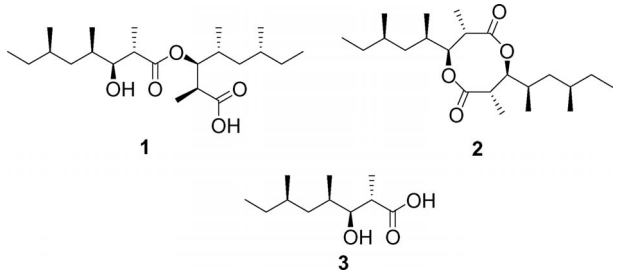

Figure 1. Chemical structures of (+)-bourgeanic acid (**1**), bourgeanic lactone (**2**) and (–)-hemibourgeanic acid (**3**).

Results and Discussion

Retrosynthetic analysis of (+)-bourgeanic acid (**1**) via the formation of bourgeanic lactone (**2**) and (–)-hemibourgeanic acid (**3**) is depicted in Scheme 1, which illustrates that (+)-bourgeanic acid could be achieved by the partial hydrolysis of bourgeanic lactone (**2**), which in turn could easily be obtained from (–)-hemibourgeanic acid using Yamaguchi macrolactonization. Compound **3** could be prepared from triol **4**, which would be easily achieved by the $LiAlH_4$ mediated reductive opening of *exo*-alkylated bicyclic lactone **5**. Lactone **5** can be easily prepared from bicyclic olefin **6** through desymmetrization using Brown's asymmetric hydroboration and subsequent substrate-controlled transformations.

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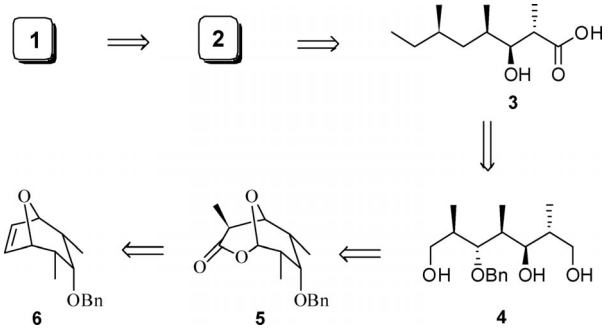
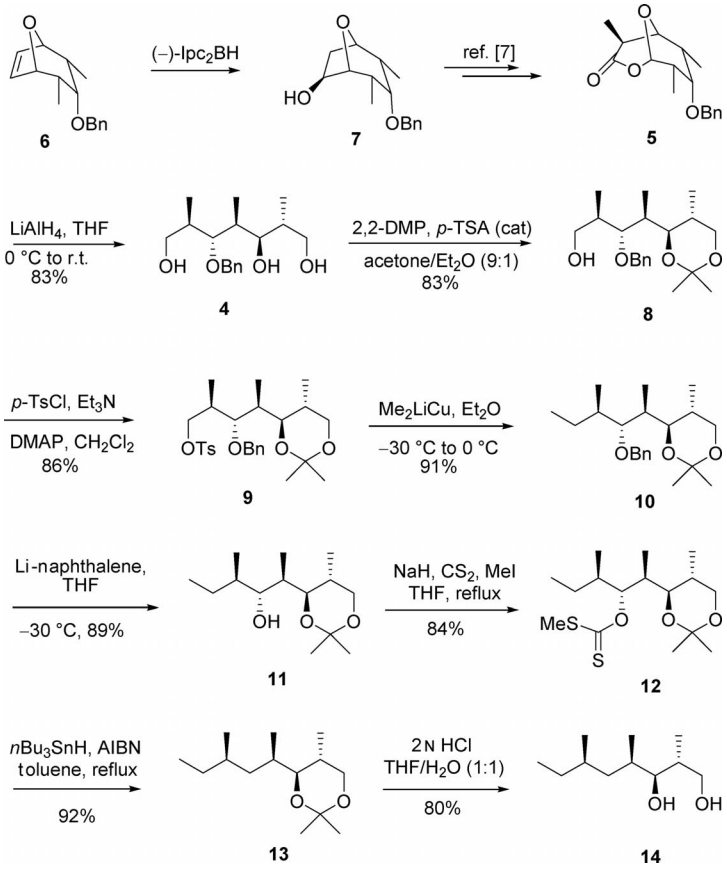
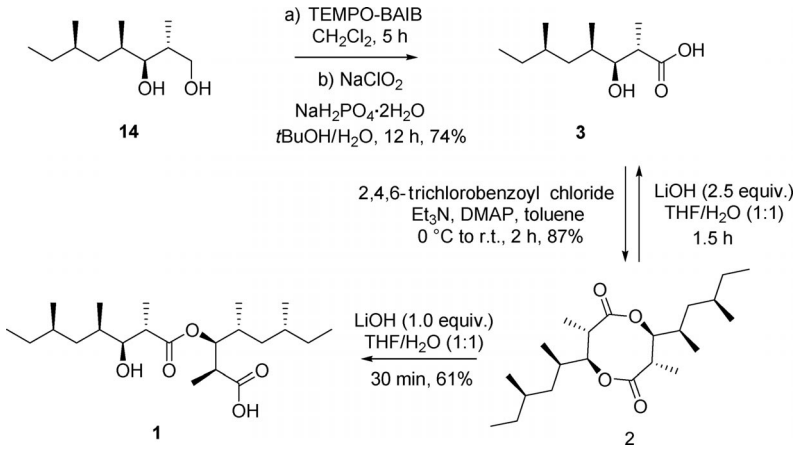


Scheme 1. Retrosynthetic analysis of (+)-bourgeanic acid (**1**).

As outlined in Scheme 2, the key fragment **14**, which contains all the required stereocenters of target molecule **1** was prepared mainly on the basis of desymmetrization of bicyclic olefin **6** using Brown's chiral hydroboration with diisopinocamphenylborane [(–)-Ipc$_2$BH]. High enantiomeric purity (97% *ee*) was achieved in hydroboration using (–)-Ipc$_2$BH prepared from borane–dimethyl sulfide complex and excess of (+)-α-pinene. The chiral bicyclic alcohol **7** was converted into the *exo*-alkylated bicyclic lactone **5** by following standard procedures.[7a] $LiAlH_4$ mediated reductive opening of *exo*-alkylated bicyclic lactone **5** gave the triol **4** in 83% yield,[7] the structure of which was confirmed by the ^{1}H NMR spectrum in which three methyl doublets appeared at δ = 0.73 (J = 6.7 Hz), 0.96 (J = 6.7 Hz) ppm and δ = 1.13 (J = 6.7 Hz) ppm, respectively and the two benzylic proton signals appeared as ABq at δ = 4.67 ppm, and the IR spectrum revealed the hydroxy absorption at 3430 cm^{-1}. Thus, the prepared triol **4** was extensively utilized by our group as a key building block in the synthesis of various natural products.[6] The chemoselective protection of 1,3-diol **4** using 2,2-DMP, *p*TsA (catalytic) in acetone:ether (9:1) afforded the corresponding acetonide **8** in 83% yield,[8] which was confirmed by the ^{13}C NMR spectrum analysis (δ = 98.0 ppm for the acetonide carbon flanked by two oxygen atoms). Tosylation of primary alcohol **8** using TsCl, Et_3N, DMAP in CH_2Cl_2 afforded the tosylate **9** in 86% yield,[9] ^{1}H NMR spectrum of the compound **9** revealed the presence of two *ortho* aromatic protons resonating as doublet at δ = 7.76 ppm, and the methyl protons of the tosyl group at δ = 2.45 ppm as a singlet. Then compound **9** was subjected to Gillman's reaction with 6.0 equiv. of dimethyllithium cuprate (Me_2CuLi) (prepared from 6 equiv. of CuI and 12 equiv. of MeLi, 1 M solution in Et_2O) in Et_2O at –30 °C to afford methylated product **10** in 91% yield.[10] The ^{1}H NMR spectrum of the compound **10** revealed the disappearance of tosyl signals at their positions. Debenzylation of compound **10** under radical conditions using Li-naphthalenide in anhydrous THF at 30 °C gave the alcohol **11** in 89% yield.[11] The C-5 oxygen of the compound **11** needs to be deoxygenated to get the complete stereochemistry of the target molecule. Accordingly, compound **11** was con-



Scheme 2. Synthesis of diol **14**.



Scheme 3. Synthesis of (+)-bourgeanic acid (**1**).

verted into xanthate ester **12** using NaH, carbon disulfide and methyl iodide. The ^{1}H NMR spectrum of xanthate ester **12** showed a characteristic signal as dd (doublet of doublet) at δ = 5.81 ppm for methine proton attached to xanthate group, a singlet at δ = 2.47 ppm for methyl protons attached to sulfur in the xanthate group. Then it was deoxygenated by tri-*n*-butyltin hydride in the presence of a catalytic amount of AIBN as radical initiator (Barton–McCombie deoxygenation) to afford compound **13** in 92% yield,[12] which was confirmed by ^{1}H NMR analysis. ^{1}H NMR of the compound **13** showed the absence of proton resonance at δ = 5.81 ppm corresponds to methine attached to the xanthate group. Treatment of acetonide **13** with 2 N HCl in THF/H_2O (1:1) afforded the desired 1,3-diol **14** in 80% yield, which was confirmed by the absence of proton resonance at δ = 1.33 ppm corresponds to *gem*-dimethyl group and IR spectrum showed absorption band at 3372 cm^{-1} for O–H stretching frequency (Scheme 2).[13]

Selective oxidation of 1,3-diol **14** using TEMPO-BAIB afforded the β-hydroxy aldehyde, which was used as such in the next step without further purification. Oxidation of β-hydroxy aldehyde under Pinnick's conditions ($NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$)[14] cleanly furnished the acid **3** in 74% yield.[15] ^{1}H and ^{13}C NMR analysis and optical rotation $[\alpha]_D$ = –3.5 were in good agreement with literature.[4b] Yamaguchi macrolactonization (2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) of hemibourgeanic acid under dilute conditions afforded the bourgeanic lactone **2** in 87% yield.[16] This was confirmed by the ^{13}C NMR analysis, which clearly showed only 11 signals (including cyclic ester C=O at δ = 176.4 ppm), indicating that the dilactone possesses C_2 symmetry (Scheme 3).[4]

Notably, the partial hydrolysis of dilactone **2** was observed within 30 min using 1.0 equiv. of LiOH in THF/H_2O (1:1) to afford the target natural product, (+)-bourgeanic acid (**1**) ($[\alpha]_D$ = +7.0) in 54% yield. The complete hydrolysis of dilactone **2** was achieved with extra time and reagent (1.5 h, 2.5 equiv. of LiOH) to furnish (–)-hemibourgeanic acid **3** quantitatively. The spectral and physical data of (+)-bourgeanic acid, bourgeanic lactone and (–)-hemibourgeanic acid were in good agreement with the literature (Scheme 3).

Conclusions

In conclusion, an efficient and highly stereoselective total synthesis of (+)-bourgeanic acid **1** via bourgeanic lactone (**2**) and (–)-hemibourgeanic acid (**3**) has been achieved. The salient features of this strategy are the utilization of our desymmetrization strategy to construct all the asymmetric centers of the natural product **1**. Thus an efficient synthetic route was developed for the remarkably stable lactone **2** using Yamaguchi's macrolactonization of sterically more hindered acid **3** and lithium hydroxide-mediated partial hydrolysis of the eight-membered cyclic dilactone **2**. The synthesis follows 11-step linear synthetic sequence proceeding from the readily available triol **4**, which gave an overall yield of 11%.

Experimental Section

General: All reactions were carried out under an inert atmosphere of argon or nitrogen by applying standard syringe, septa, and cannula techniques unless otherwise mentioned. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded with a Perkin–Elmer 683 spectrometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}. Samples were either scanned neat, in KBr wafers, or in chloroform as a thin film. ^{1}H NMR spectra were recorded in $CDCl_3$ with a Bruker 300, Varian Unit 500 MHz NMR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using tetramethylsilane (TMS) as the reference standard. Column chromatography was performed using silica gel (60–120 mesh) and the column was usually eluted with ethyl acetate/petroleum ether. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates to sulfuric acid/β-naphthol or to ethanolic anisaldehyde/sulfuric acid/acetic acid or to phosphomolybdic acid-sulfuric acid solution and heating the plates at 120 °C. Mass spectra were obtained on a Finnigan MAT1020B or micromass VG 70-70H spectrometer operating at 70 eV using a direct inlet system. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter in 1.0 dm, 1.0 mL cells.

(1*S*,2*R*,4*R*)-1-[(*S*)-1-Carboxyethyl]-2,4-dimethylhexyl (2*S*,3*S*,4*R*,6*R*)-3-Hydroxy-2,4,6-trimethyloctanoate (1): To the eight-membered bourgeanic lactone **2** (16 mg, 43 μmol) in THF/H_2O (1:1) (4 mL) was added LiOH (1.3 mg, 54 μmol) and stirred at room tempera-

ture for 30 min. After the formation of required product (monitored by TLC), the reaction mixture was acidified with 2 N HCl to pH 2 and then tetrahydrofuran was removed under reduced pressure. The combined organic phases were dried with Na_2SO_4, and the solvent was removed under vacuo and the resulting aqueous layer was extracted with ethyl acetate (3 × 10 mL) concentrated under vacuum, and the residue was purified by silica gel chromatography (1:1, ethyl acetate/hexane) to afford **1** (9 mg, 54%) as a white solid. $[a]_D$ = +7.0 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3446, 2923, 2854, 1728, 1639, 1460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.16 (dd, *J* = 9.0, 3.0 Hz, 1 H, 3-H), 3.70 (dd, *J* = 9.8, 2.2 Hz, 1 H, 3-H′), 2.86–2.74 (m, 1 H, 2-H), 2.67–2.54 (m, 1 H, 2-H′), 1.96–1.85 (m, 1 H, 4-H), 1.79–1.59 (m, 2 H, 4-H′, 6-H′), 1.54–1.38 (m, 2 H, 5-H′), 1.34–1.23 (m, 3 H, 5-H, 6-H), 1.18 (d, *J* = 6.7 Hz, 3 H, 9-H), 1.10 (d, *J* = 7.5 Hz, 3 H, 9-H′), 1.14–1.01 (m, 3 H, 7-H, 7-H′), 0.94 (d, *J* = 7.5 Hz, 3 H, 10-H), 0.96–0.90 (m, 1 H, 7-H′), 0.89 (t, *J* = 6.7 Hz, 3 H, 8-H′), 0.87 (d, *J* = 6.0 Hz, 3 H, 10-H′), 0.85 (d, *J* = 6.0 Hz, 3 H, 11-H), 0.84 (t, *J* = 7.5 Hz, 3 H, 8-H), 0.82 (d, *J* = 6.7 Hz, 3 H, 11-H′) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.1, 175.7, 76.5, 74.8, 44.0, 41.9, 41.0, 40.6, 31.2, 30.9, 30.9, 29.4, 29.2, 19.4, 19.3, 14.4, 13.8, 12.7, 11.2, 11.1 ppm. MS (ESI): *m/z* = 385 $[M - H]^-$. HRMS: calcd. for $C_{22}H_{42}O_5$ $[M - H]^-$ 385.2953; found 385.2966.

Supporting Information (see also the footnote on the first page of this article): Synthesis and characterization for compounds **2**–**4** and **8**–**14**.

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