

Total Synthesis of Lobatoside E, A Potent Antitumor Cyclic
Triterpene Saponin

Chunsheng Zhu, Pingping Tang, and Biao Yu*

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of
Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Received March 5, 2008; E-mail: byu@mail.sioc.ac.cn

Lobatoside E (**1**) is a member of the triterpene saponins named cyclic bisdesmosides,^{1,2} which have two oligosaccharides flanked on a pentacyclic triterpene and bridged with 3-hydroxy-3-methyl glutarate. Thus far, only 10 such compounds have been disclosed, from two Chinese medicinal plants, that is, *Bolbostemma paniculatum*¹ and *Actinostemma lobatum* (Cucurbitaceae).² Cyclic bisdesmosides are cytotoxic^{3,4} and might induce apoptosis of tumor cells.⁴ Removal of the glutarate bridge kills the activity, thus the novel cyclic structure of these saponins is crucial to their antitumor activity.³ Lobatoside E (**1**)² shows the highest potency among its congeners against the growth of tumor cells and is especially sensitive toward the lung cancer cell A549, colon cancer cell SW-620, and melanoma SK-MEL-5, with GI₅₀ values at 0.14–0.36 μ M.³ Herein we report the first synthesis of Lobatoside E (**1**).

The successful synthetic route toward Lobatoside E (**1**) employed modular assembly of the building blocks **2**–**7** (Figure 1).⁵ Benzyl group was chosen as the permanent protecting group, knowing that it could be removed by hydrogenolysis without affecting the alkene function within the triterpene unit.⁶ The acetyl, chloroacetyl, benzoyl, *tert*-butyldiphenylsilyl, and 4-methoxybenzyl groups were temporary protecting groups to facilitate the sequential assembly of the units. Additionally, the neighboring participating acyl groups on the 2-OH of the gluco- and galactosyl trichloroacetimidates **4** and **5** effected formation of the required 1,2-*trans*-glycosidic linkages. Use of the L-arabinosyl β -bromide **3** (for a S_N2-type coupling with the triterpene 28-carboxylate)⁷ and the armed thiorhamnoside **6** as glycosylation donors ensured the stereoselective formation of the native α -L-arabino- and -rhamnosyl linkages.⁸

The synthesis of the bayogenin derivative **2** commenced with oleanolic acid **8**, the most abundant triterpene in Nature (Scheme 1). Thus, benzylation of the 28-COOH, oxidation of the 3-OH,⁹ and subsequent oxime formation provided compound **9** (82%). Selective hydroxylation of the C-4 equatorial methyl group was then achieved by Baldwin's method^{10,11} to afford the 23-acetoxy **10** (72%), involving (1) cyclopalladation of the methyl group from the 3-one oxime with Na₂PdCl₄, (2) acetylation of the oxime hydroxyl group, and (3) oxidation with Pb(OAc)₄ and pyridinium acetate followed by reductive workup with NaBH₄. Hydrolysis of **10** with Na₂CO₃/MeOH and then with TiCl₃/NH₄OAc¹¹ followed by protection of the resulting 23-OH with a Bn group gave **11** (86%). Introduction of the 2- α -OH was achieved by the Rubottom oxidation,¹² via a sequence of (1) silyl enol ether formation (LDA, TMSCl), (2) epoxidation (mCPBA), and (3) desilylation (TBAF) to afford **12** (84%). The benzylic CH₂ at the 28-ester moiety (in **11**) was also deprotonated by LDA, thus the benzyl group was transformed into a PhCHTMS moiety and was recovered during the subsequent

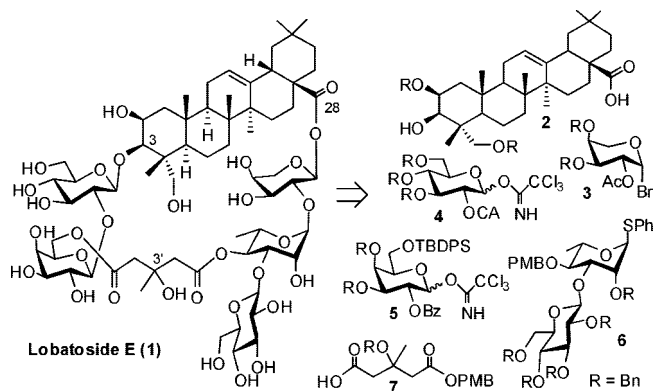
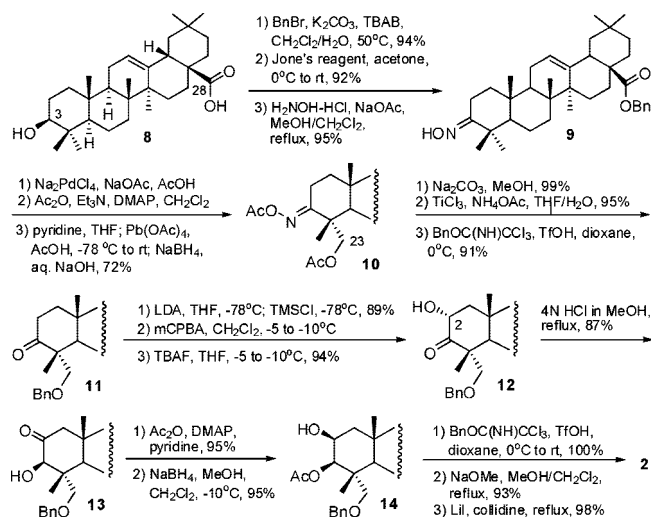


Figure 1

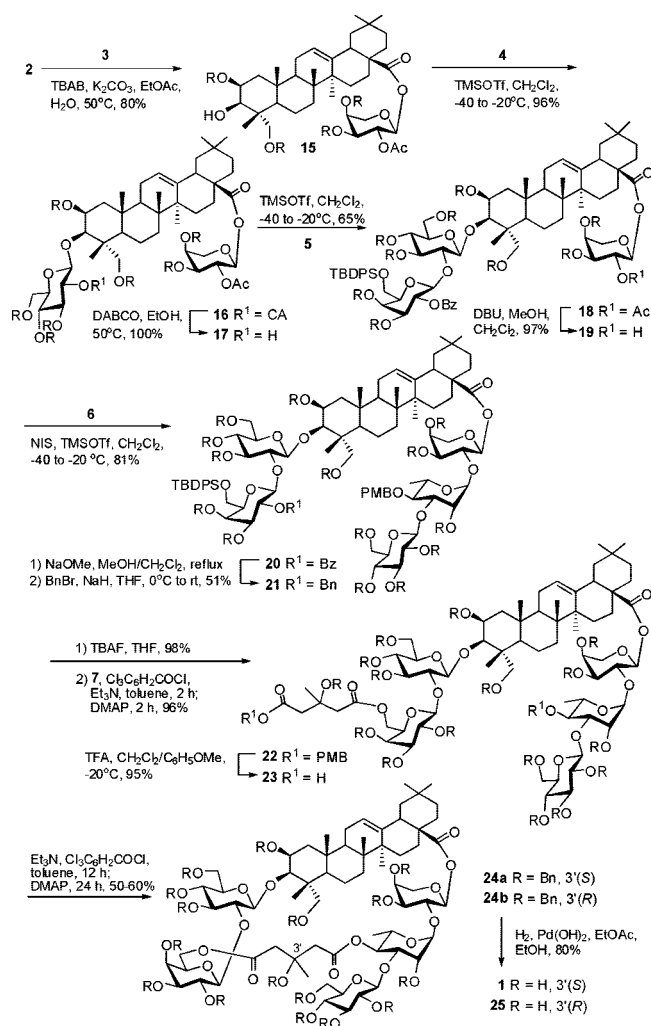
Scheme 1



mCPBA and TBAF treatment. Isomerization of **12** with 4 N HCl in MeOH provided 2-one-3- β -ol **13** (87%), where the concentration of the acid was found to be critical.¹³ The nascent 3- β -OH was protected with an Ac group and the 2-keto reduced with NaBH₄ (at -10 °C) to afford the desired 2 β ,3 β -ol derivative **14** (90%).¹⁴ Adjustment of the protecting groups in **14**, that is, benzylation of the 2 β -OH, removal of the 3-O-Ac group, and cleavage of the 28-benzyl ester (LiI, γ -collidine),¹⁵ accomplished the synthesis of the triterpene derivative **2** (91%).

Coupling of the 3-ol-28-carboxylic acid **2** with the newly prepared β -arabinosyl bromide **3**⁵ under optimized phase transfer conditions⁷ gave the desired ester α -arabinoside **15** (80%) (Scheme 2). Subsequent glycosylation of the remaining 3-OH with the glucosyl imidate **4**⁵ under the catalysis of TMSOTf at

Scheme 2



-20°C provided the β -glucoside **16** (96%). The hindrance of the 2-O-position in the glucose unit (in **16**) raised problems for further elaboration; nevertheless, selective removal of the CA group (vs the Ac group) was finally achieved with DABCO to afford **17** (100%);¹⁶ glycosylation of the resulting $-\text{OH}$ with the galactosyl imidate **5**⁵ (TMSOTf, -20°C) proceeded sluggishly; addition in portions of 5 equiv of the donor **5** led to the β -galactoside **18** in 65% yield. Glycosylation at elevated temperatures (e.g., rt) led to anomerization of the ester arabinosyl linkage. Selective removal of the Ac group (vs the Bz group in **18**) was realized with DBU to give **19** (97%),¹⁷ which was glycosylated with thiodisaccharide **6**⁵ (NIS, TMSOTf) to afford stereoselectively the α -rhamnosyl-linked pentasaccharide **20** (81%). The Bz group in the galactose unit was then replaced by a Bn group, without optimization, to give **21** (51%, 19% recovered).

The availability of the pentasaccharide **21** set a final stage for the elaboration of the target molecule (**1**). Thus, the TBDPS group was removed cleanly with TBAF (98%), and the resulting primary hydroxyl group was condensed with acid **7**⁵ under the Yamaguchi conditions¹⁸ to provide **22** (96%), where protection of the tertiary hydroxyl group of the glutarate was found to be mandatory. Removal of the two PMB groups was effected with CF_3COOH to give **23** (95%).¹⁹ The two oligosaccharide residues in **23** (at 0.001 M) were then bridged by the Yamaguchi

macrocyclization,^{18b} furnishing the cyclic **24** in 50–60% yield. At this stage, the two C3' epimers (**24a** and **24b**, formed without a preference) were able to be separated readily by chromatography on silica gel. Finally, the 16 Bn groups were taken off cleanly by hydrogenolysis over Pd(OH)_2 , leading to the target Lobatoside E (**1**) and its epimer **25**, respectively ($\sim 80\%$). The analytical data of **1** are in good agreement with those reported for the natural product,^{2,20} while the NMR spectra of its epimer **25** show minor differences between signals from the atoms proximal to the epimeric C3'.

In summary, Lobatoside E (**1**), a complex cyclic bisdesmoside showing potent antitumor activities, has been synthesized for the first time. This highly modular synthesis requires a total of 73 steps starting with cheap materials, with the longest linear sequence of 31 steps and in 1.2% overall yield.

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Supporting Information Available: Experimental details, characterization data, and ^1H NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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