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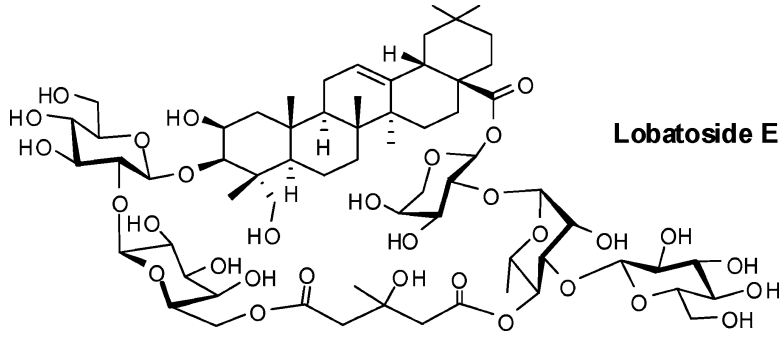


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# Total Synthesis of Lobatoside E, A Potent Antitumor Cyclic Triterpene Saponin

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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 $GI_{50}$ values at 0.14−0.36 $\mu$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 $\beta$-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 $Na_2PdCl_4$, (2) acetylation of the oxime hydroxyl group, and (3) oxidation with $Pb(OAc)_4$ and pyridinium acetate followed by reductive workup with $NaBH_4$. Hydrolysis of **10** with $Na_2CO_3$/MeOH and then with $TiCl_3$/$NH_4OAc$[11] 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 $CH_2$ 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

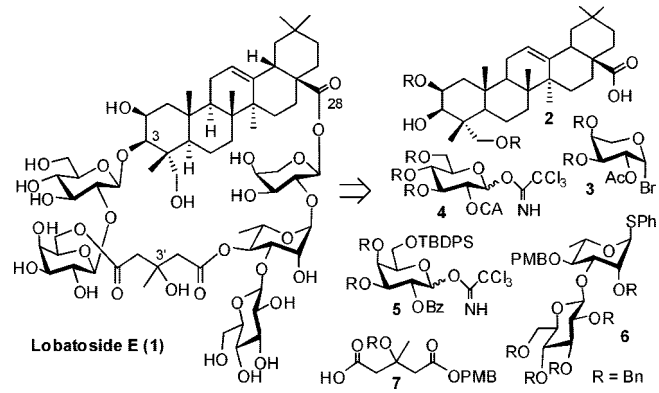
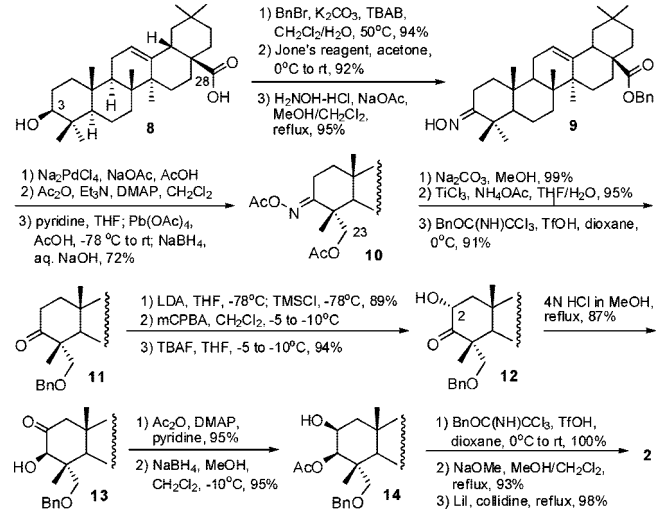



***Figure 1***

***Scheme 1***

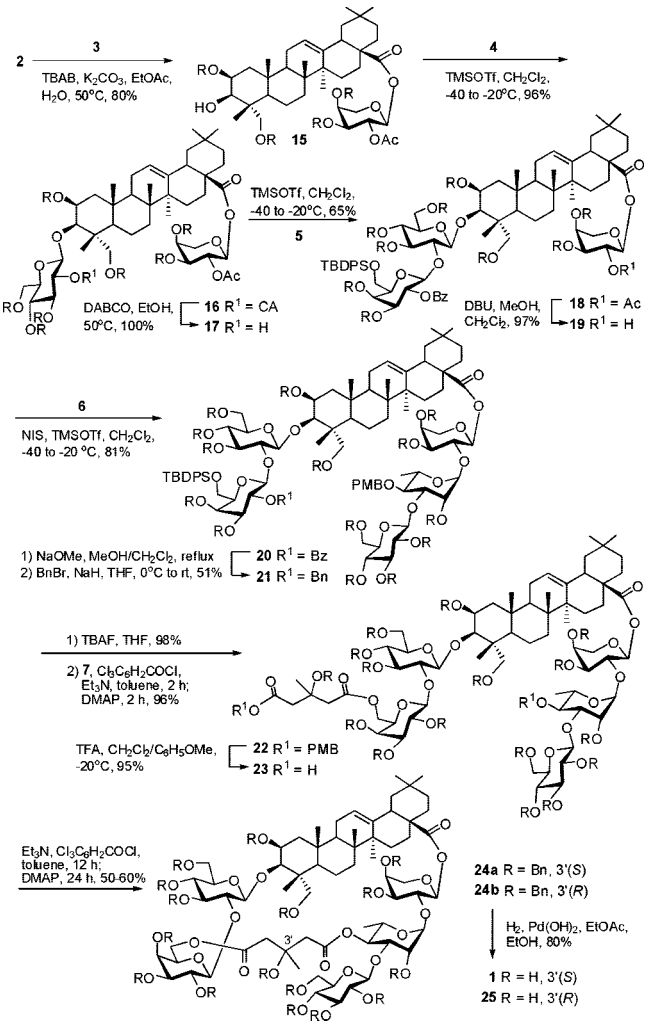



mCPBA and TBAF treatment. Isomerization of **12** with 4 N HCl in MeOH provided 2-one-3-$\beta$-ol **13** (87%), where the concentration of the acid was found to be critical.[13] The nascent 3-$\beta$-OH was protected with an Ac group and the 2-keto reduced with $NaBH_4$ (at −10 °C) to afford the desired 2$\beta$,3$\beta$-ol derivative **14** (90%).[14] Adjustment of the protecting groups in **14**, that is, benzylation of the 2$\beta$-OH, removal of the 3-*O*-Ac group, and cleavage of the 28-benzyl ester (LiI, $\gamma$-collidine),[15] accomplished the synthesis of the triterpene derivative **2** (91%).

Coupling of the 3-ol-28-carboxylic acid **2** with the newly prepared $\beta$-arabinosyl bromide **3**[5] under optimized phase transfer conditions[7] 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


10.1021/ja801669r CCC: $40.75 

***Scheme 2***




−20 °C provided the $\beta$-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 −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 $\beta$-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 conditions[18] 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 (∼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 $^1$H NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For the synthesis of the building blocks **3**−**7**, see Supporting Information.

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(20) The *S* configuration at C3′ has been determined in two congeners of Lobatoside E.[1a,c]

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