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The First Total Synthesis of Calbistrin A, a Microbial Product Possessing Multiple Bioactivities

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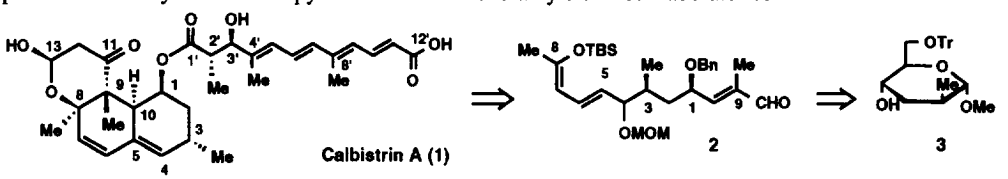
Abstract: The octahydronaphthopyranone moiety is synthesized from methyl α-D-mannopyranoside through the intramolecular Diels-Alder reaction, and the tetraenedicarboxylic acid moiety is from the enzymatically prepared anti-compound. Both moieties were coupled to accomplish the total synthesis of calbistrin A and to disclose its absolute structure.

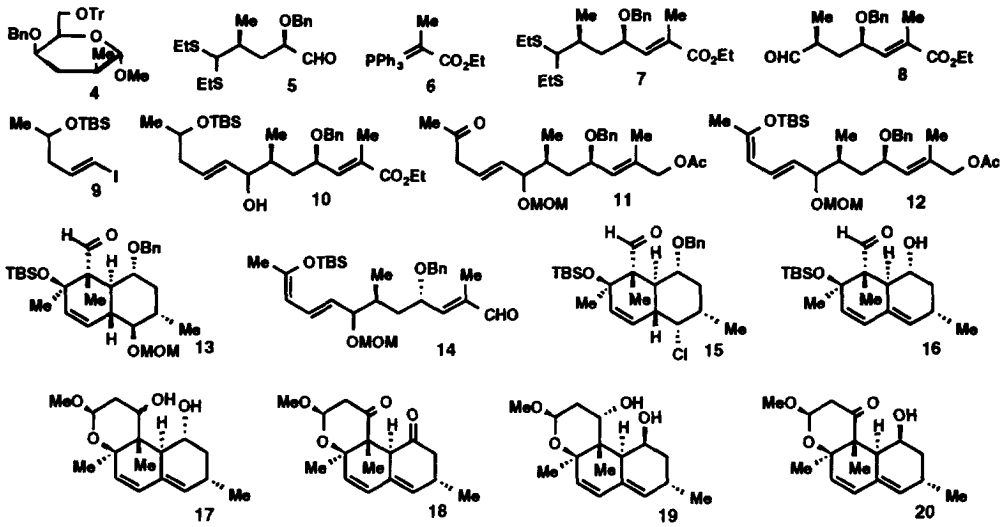
Calbistrin A (**1**) was isolated independently by four groups [1] as an antifungal agent, a promoter of nerve growth factor production, and a cholesterol lowering agent. Although the structure was disclosed to be the ester of an octahydronaphthopyranone with a tetraenedicarboxylic acid, the absolute structure remained undetermined.

Herein we report the first total synthesis of calbistrin A (**1**) by the enantiospecific synthesis of both moieties.

From the retrosynthetic perspective, the octahydronaphthopyranone skeleton is expected to be accessible by the intramolecular Diels-Alder reaction of the silyl dienol ether **2**, possessing the unnatural configuration at C-1 [2]. When the isomer having a natural configuration is used, a strong repulsion between the substituents at C-1 and C-9 is expected in the transition state. The key intermediate **2** is synthesized from **3**, which has been prepared from methyl α-D-mannopyranoside in 47% overall yield in our laboratories [3].



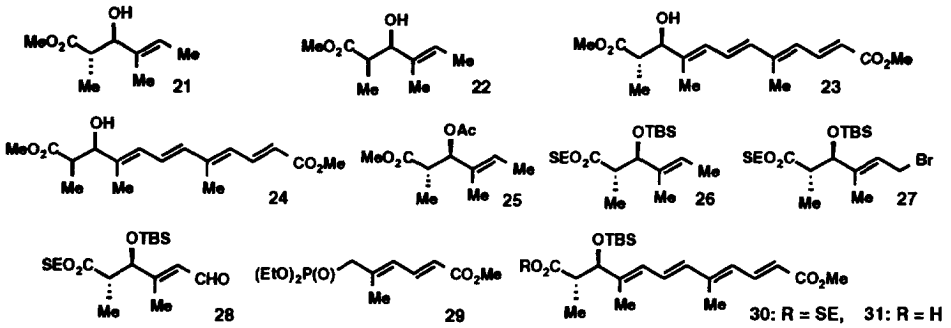
Compound **3** was transformed to **4** [4][80%: mp 92°C(hexane)] by oxidation (PDC, Zeolite/ CH_2Cl_2), reduction (L-Selectride/THF, -78°) and *O*-benzylation(BnBr, NaH/DMF). Treatment of **4** with EtSH and BF_3•Et_2O, and cleavage of the resulting diol with $Pb(OAc)_4$ (K_2CO_3/PhMe) gave the aldehyde **5**, which reacted with Wittig reagent **6** to give α,β-unsaturated ester **7** [72%: syrup, $[\alpha]_D$ -93° (MeOH)]. Deprotection of **7** with CuO and $CuCl_2$ (aq Me_2CO) [5] afforded the aldehyde **8**, which reacted with the vinyl lithium prepared from **9** and *s*-BuLi (Et_2O, -100°) to give quantitatively a diastereomeric mixture (3 : 1) of **10**. Without separation, the mixture was converted into **2**, as it was anticipated that only the proper isomer would undergo Diels-Alder reaction. Thus, **10** was converted into the ketone **11** (48%: syrup) in 5 steps: 1) MOM-Cl, DIPEA/CH_2Cl_2; 2) DIBAL/CH_2Cl_2; 3) Ac_2O/Py; 4) TBAF/THF; 5) PCC, Zeolite/CH_2Cl_2. The ketone **11** was silylated (TBSOTf, lutidine/CH_2Cl_2) to give the silyl dienol ether **12** (90%: syrup), which was de-*O*-acetylated (NaOMe/MeOH) and oxidized (PDC, Zeolite/CH_2Cl_2) to the α,β-unsaturated aldehyde **2** (62%: syrup). The intramolecular Diels- Alder reaction of **2** was assayed under a range of conditions and the best result



was realized by heating in PhMe in a sealed tube for 3 days to give exclusively the adduct **13** [62%; mp 89°C(hexane), $[\alpha]_D$ -78° (MeOH)] with the unreacted diastereomer **2** (19%). The structure **13** was supported by ^{1}H-NMR studies ($J_{3,4}$=10.5Hz, $J_{4,5}$=10.5Hz, $J_{5,10}$=10.5Hz) showing NOE enhancements between H-1 and Me-9 (4.6%), H-5 and Me-9 (4.5%), and H-10 and Me-8 (3.9%). The diastereomer **14**, which was prepared from **3** in a similar manner, gave no Diels-Alder adduct as expected.

De-*O*-methoxymethylation of **13** (2% HCl-EtOH), followed by chlorination ($SOCl_2$/Py) gave the chloro compound **15** [80%: mp 132°C(hexane)], which was hydrogenated (H_2, Pd-C/EtOAc) and heated with KOAc (DMF, 100°) to give the diene **16** [94%: mp 118°C(hexane), $[\alpha]_D$ -51° (MeOH)]. This was converted into the glycosidic β-methyl ether **17** (54%: syrup) in 5 steps: 1) CH_2=$CHCH_2$-Li/Et_2O, -78° ; 2) OsO_4, NMO/aq Me_2CO; 3) $NaIO_4$/aq Me_2CO; 4) aq AcOH; 5) HCl-MeOH, 0°. Dess-Martin oxidation (Py/CH_2Cl_2, 1 day) of **17** gave the diketone **18** [72%: syrup, $[\alpha]_D$ +22° (MeOH)], which was reduced by $Zn(BH_4)_2$ (DME) to give the diol **19** [42%: syrup, $[\alpha]_D$ -57° (MeOH)]. Although the selective reduction of **18** to **20** failed, selective oxidation of the diol **19** with Dess-Martin reagent (Py/CH_2Cl_2, 50min) led to the desired alcohol **20** [80%: $[\alpha]_D$ +6.0° (MeOH)] corresponding to the major skeleton of **1**. Both compounds **19** and **20** were identical with the naturally derived samples, confirming the absolute structure of the natural skeleton as described below.

The synthesis of the tetraenedicarboxylic acid moiety began with derivation of (±)-**23** from the racemic *anti* and *syn* isomers **21** and **22** to determine the relative configuration in a similar manner as described below. The racemic tetraene (±)-**23** derived from the *anti* isomer **21** proved to be identical with the naturally derived compound **23** in NMR studies, while the derivative **24** of the *syn* isomer **22** was clearly different. Consequently, the optically active *anti* compound **25** [$[\alpha]_D$ -13° ($CHCl_3$)] was prepared from the acetate of **21** according to Oishi's lipase method (lipase Amano A-6, phosphate buffer, at 33°, 5 days) [6]. The sign of the optical rotation of **25** was in agreement with that of the naturally derived tetraene **23**, indicating that **25** would be suitable for the synthesis of **23**. Thus, **25** was converted into **26** [68%: syrup, $[\alpha]_D$ +2.1° ($CHCl_3$)] in 4 steps: 1) K_2CO_3/MeOH; 2) 1M aq LiOH/MeOH; 3) trimethylsilyl ethanol (SE-OH), Ph_3P, DEAD/THF; 4) TBSCl, imidazole/DMF. Bromination of **26** (NBS/CCl_4, 80°) to give **27** followed by treatment with Ag_2CO_3 in DMSO[7] (90°, 20min) afforded the aldehyde **28** [60%: syrup, $[\alpha]_D$ -28° ($CHCl_3$)]. This was treated with the



Horner-Wittig reagent **29** (LiN(TMS)$_2$/THF), which was prepared from the corresponding bromide by a usual way, to give the tetraene **30** [66%: syrup, $[\alpha]_D$ -105° ($CHCl_3$)], which was desilylated with TBAF in THF and esterified ($TMSCHN_2$/MeOH-THF) to the dimethyl ester **23** [60%: syrup, $[\alpha]_D$ -123° (MeOH)]. This ester was identical with a sample of **23** derived from natural calbistrin A in all respects. Selective desilylation (TBAF/THF, 1 h) of **30** gave the carboxylic acid **31** [67%: syrup, $[\alpha]_D$ -141° ($CHCl_3$)].

Authentic samples of **19**, **20** and **23** were obtained from the natural product **1** as follows. Esterification ($TMSCHN_2$/EtOH) followed by treatment with 2-methoxypropene (CSA/DMF) gave the bis-(1-methyl-1-methoxyethyl)ether, which was reduced by $LiAlH_4$ (THF) to remove the side chain. Methanolysis (1% HCl-MeOH) of the resulting product gave the diol **19** [quant: syrup, $[\alpha]_D$ -55° (MeOH)], which was selectively oxidized with Dess-Martin reagent (Py/CH_2Cl_2, 50min) to give the alcohol **20** [80%: syrup, $[\alpha]_D$ +8.0° (MeOH)]. Saponification of **1** (1M aqNaOH/dioxane, 50°, 4 h) followed by esterification ($TMSCHN_2$ /EtOH) gave the dimethyl ester **23** [syrup, $[\alpha]_D$ -115° (MeOH)] in 42% overall yield.

With **20** and **31** in hand, we turned to the esterification. Following the stepwise one-flask conversion of **31** to the mixed anhydride (β-naphthoyl chloride/Et_3N/THF, 0.5 h) and then to the ester by reaction with **20** (DMAP/PhMe, 2 h), subsequent deprotection was carried out in 3 steps: 1) TBAF/THF, 2 h; 2) 0.1M NaOH/dioxane, 0.5 h); 3) 5% H_3PO_4/dioxane, 2 h. Thus, synthetic calbistrin A (**1**) was obtained in 54% yield and was found to be identical with the natural product in all respects [mp 133°C (EtOAc), $[\alpha]_D$ +69° ($CHCl_3$)].

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2. The carbon-numbering protocol parallels conveniently that of the natural product **1**.
3. a) Tatsuta, K.; Koguchi, Y.; Kase, M. *Bull. Chem. Soc. Jpn.*, **61**, 2525 - 2530 (1988). b) Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tamai, T.; Tatsuta, K. *Bull. Chem. Soc. Jpn.*, **65**, 2974 - 2991 (1992).

4. Optical rotations were measured using a 0.5 dm tube at 22°C. Significant ^{1}H-NMR spectral data (270, 300, and 400 MHz, $CDCl_3$, δ; TMS=0, unless otherwise noted) are the following. **1**(CD_3OD): 0.89(3H, d, *J*=7.0Hz), 1.04(3H, d, *J*=7.0Hz), 1.24(3H, s), 1.33(3H, s), 1.77(3H, s), 2.04(3H, s), 2.39(1H, dd, *J*=14.0 & 4.0Hz), 2.87(1H, dd, *J*=14.0 & 8.5Hz), 4.07(1H, d, *J*=9.0Hz), 5.28(1H, dd, *J*=8.5 & 4.0Hz), 5.64(1H, d, *J*=9.9Hz), 5.70(1H, br. s), 5.90(1H, d, *J*=15.0Hz), 5.96(1H, d, *J*=15.0Hz), 6.10(1H, br. s), 6.13(1H, d, *J*=10.5Hz), 6.30(1H, d, *J*=12.0Hz), 6.41(1H, d, *J*=15.0Hz), 6.74(1H, dd, *J*=15.0 & 10.5Hz), 7.70(1H, dd, *J*=15.0 & 12.0Hz). **2**: 0.93(3H, d, *J*=7.3Hz), 1.75(3H, d, *J*=1.1Hz), 1.84(3H, s), 5.18(1H, d, J=10.6Hz), 5.19(1H,dd, *J*=15.5 and 7.9Hz), 6.34(1H, dq, *J*=9.0 & 1.1Hz), 6.43(1H, dd, *J*=15.5 & 10.6Hz), 9.45(1H, s). **4**: 1.14(3H, d, *J*=7.1Hz), 1.89(1H, ddd, *J*=15.5, 6.5, & 4.2Hz), 3.53-3.57(1H, m), 4.42(1H, br s). **7**: 1.07(3H, d, *J*=6.8Hz), 1.87(3H, d, *J*=1.4Hz), 3.76(1H, d, *J*=3.5Hz), 4.23-4.32(1H, m), 6.66(1H, dq, *J*=9.0 & 1.4Hz). **8**: 1.11(3H, d, *J*=7.2Hz), 1.86(3H, d, *J*=1.5Hz), 4.25-4.32(1H, m), 6.66(1H, dq, *J*=8.8 & 1.5Hz), 9.62(1H, d, *J*=1.3Hz). **9**: 1.13(3H, d, *J*=6.0Hz), 6.03(1H, dt, *J*=14.4 & 1.2Hz), 6.52(1H, dt, *J*=14.4 & 7.2Hz). **10**: 1.11 and 1.12 (total 3H, d, *J*=6.2Hz), 1.85(3H, m), 5.40-5.52(1H, m), 5.55-5.65(1H, m), 6.65(1H, dq, *J*=10.8 & 0.6Hz). **11**: 0.90 and 0.93(total 3H, d, *J*=6.8Hz and *J*=6.5Hz), 1.66 and 1.67(total 3H, d, *J*=1.1Hz and *J*=0.8Hz), 2.10(3H, s), 2.15 and 2.16(total 3H, s), 4.51(2H, s), 5.30-5.45(2H, m), 5.65-5.78(1H, m). **12**: 0.89 and 0.93(total 3H, d), 1.65 and 1.66(total 3H, br. s), 1.84(3H, s), 2.10(3H, s), 5.16-5.27(2H, m), 5.32-5.39(1H, m), 6.41 and 6.43(total 1H, dd, *J*=15.7 & 10.6Hz, and *J*=15.1 & 11.2Hz). **13**: 1.06(3H, d, *J*=6.5Hz), 1.06(3H, s), 1.17(1H, ddd, *J*=12.9, 12.9 & 10.5Hz), 1.47(3H, s), 1.95(1H, br. t, *J*=10.5 & 10.5Hz), 2.19(1H, dd, *J*=10.5 & 10.5Hz), 2.85(1H, dd, *J*=10.5 & 10.5Hz), 3.25(1H, ddd, *J*=10.5, 10.5 & 4.1Hz), 5.58(1H, dd, *J*=10.3 & 2.5Hz), 5.74(1H, dd, *J*=10.3 & 1.9Hz), 9.74(1H, s). **14**: 0.87(3H, d, *J*=7.0Hz), 1.73(3H, d, *J*=1.5Hz), 1.83(3H, s), 5.18-5.28(2H, m), 6.36-6.48(2H, m), 9.45(1H, s). **15**: 1.06(3H, s), 1.08(3H, d, *J*=6.6Hz), 1.51(3H, s), 2.31(1H, ddd, *J*=10.5, 4.6 & 2.3Hz), 2.79(1H, dd, *J*=10.5 & 10.5Hz), 3.24(1H, ddd, *J*=10.5, 10.5 & 4.2Hz), 4.18(1H, br. s), 5.37(1H, dd, *J*=10.1 & 1.8Hz), 5.62(1H, dd, *J*=10.1 & 2.8Hz), 9.77(1H, s). **16**: 1.03(3H, s), 1.05(3H, d, *J*=7.0Hz), 1.50(3H, s), 2.92(1H, ddd, *J*=9.2, 2.9 & 2.9Hz), 5.51(1H, d, *J*=9.6Hz), 5.52(1H, br. s), 5.89(1H, d, *J*=9.6Hz), 9.92(1H, s). **18**: 1.20(3H, d, *J*=7.0Hz), 1.22(3H, s), 1.33(3H, s), 2.56(1H, dd, *J*=14.0 & 4.5Hz), 3.02(1H, dd, *J*=14.0 & 8.5Hz), 3.53(3H, s), 4.85(1H, dd, *J*=8.5 & 4.5Hz), 5.73(1H, br. s), 5.75(1H, d, *J*=10.0Hz), 5.97(1H, d, *J*=10.0Hz). **19**: 1.04(3H, s), 1.06(3H, d, *J*=7.0Hz), 1.61(3H, s), 1.77(1H, ddd, *J*=14.0, 3.5 & 3.5Hz), 2.05(1H, ddd, *J*=14.0, 10.0 & 4.0Hz), 2.79(1H, dd, *J*=5.5 & 3.0Hz), 3.49(3H, s), 4.98(1H, dd, *J*=10.0 & 3.5Hz), 5.60(1H, br. s), 5.67(1H, d, *J*=9.5Hz), 5.81(1H, d, *J*=9.5Hz). **20**: 1.08(3H, d, *J*=7.0Hz), 1.26(3H, s), 1.38(3H, s), 2.51(1H, dd, *J*=14.5 & 4.0Hz), 2.90(1H, dd, *J*=14.5 & 8.5Hz), 3.53(3H, s), 4.87(1H, dd, *J*=8.5 & 4.0Hz), 5.68(1H, d, *J*=9.5Hz), 5.70(1H, br. s), 5.95(1H, d, *J*=9.5Hz). **21**: 1.02(3H, d, *J*=7.2Hz), 2.66(1H, dq, *J*=9.3 & 7.2Hz), 4.10(1H, dd, *J*=9.3 & 2.7Hz). **22**: 1.14(3H, d, *J*=7.1Hz), 2.69(1H, dq, *J*=5.4 & 7.1Hz), 4.23(1H, dd, *J*=7.8 & 5.4Hz). **23**: 1.07(3H, d, *J*=7.1Hz), 2.57(1H, d, *J*=4.3Hz), 2.67-2.77(1H, m), 3.73(3H, s), 3.76(3H, s), 4.19(1H, dd, *J*=9.0 & 4.3Hz), 5.91(1H, d, *J*=15.0Hz), 6.16(1H, d, *J*=11.4Hz), 6.22(1H, d, *J*=11.9Hz), 6.34(1H, d, *J*=15.4Hz), 6.65(1H, dd, *J*=15.4 & 11.4Hz), 7.69(1H, dd, *J*=15.0 & 11.9Hz). **24**: 1.13(3H, d, *J*=7.0Hz), 2.57(1H, d, *J*=3.0Hz), 2.70-2.77(1H, m), 3.70(3H, s), 3.75(3H, s), 4.43(1H, dd, *J*=4.5 & 3.0Hz), 5.89(1H, d), 6.21(1H, d), 6.28(1H, d), 6.34(1H, d), 6.67(1H, dd), 7.68(1H, dd). **25**: 1.02(3H, d, *J*=7.0Hz), 1.55(3H, q, *J*=1.0Hz), 1.63(3H, dq, *J*=7.0 & 1.0Hz), 2.78(1H, dq, *J*=10.0 & 7.0Hz), 5.26(1H, d, *J*=10.0Hz), 5.65(1H, br. q, *J*=7.0Hz). **26**: 0.88(3H, d, *J*=7.0Hz), 1.52(3H, br. s), 1.60(3H, dq, *J*=6.5 & 1.0), 2.55(1H, dq, *J*=10.5 & 7.0Hz), 4.07(1H, d, *J*=10.5Hz), 5.43(1H, br. q, *J*=6.5Hz). **27**: 0.91(3H, d, *J*=7.0Hz), 1.68(3H, d, *J*=1.5Hz), 2.58(1H, dq, *J*=9.5 & 7.0Hz), 4.00(2H, d, *J*=8.5Hz), 4.12(1H, d, *J*=9.5Hz), 5.72(1H, tq, *J*=8.5 & 1.5Hz). **28**: 0.96(3H, d, *J*=7.0Hz), 2.12(3H, br. s), 2.65(1H, dq, *J*=9.0 & 7.0Hz), 4.27(1H, d, *J*=9.0Hz), 5.97(1H, dq, *J*=8.0 & 0.6Hz), 10.05(1H, d, *J*=8.0Hz). **29**: 2.05(3H, d like, *J*=4.3Hz), 2.69(2H, d, *J*=23.6Hz), 5.85(1H, dd, *J*=15.2 & 2.7Hz), 6.11(1H, dd, *J*=11.5 & 5.0Hz), 7.56(1H, dd, *J*=15.2 & 11.5Hz). **30**: 0.91(3H, d, *J*=7.0Hz), 0.99(2H, t like, *J*=9.0Hz), 1.76(3H, s), 2.04(3H, s), 2.61(1H, dq, *J*=9.5 & 7.0Hz), 4.18(1H, d, *J*=9.5Hz), 5.90(1H, d, *J*=15.0Hz), 6.08(1H, d, *J*=11.0Hz), 6.22(1H, d, *J*=12.0Hz), 6.32(1H, d, *J*=15.0Hz), 6.63(1H, dd, *J*=15.0 & 11.0Hz), 7.69(1H, dd, *J*=15.0 & 12.0Hz). **31**: 1.04(3H, d, *J*=7.5Hz), 1.78(3H, s), 2.05(3H, s), 2.68(1H, dq, *J*=8.5 & 7.5Hz), 4.17(1H, d, *J*=8.5Hz), 5.90(1H, d), 6.10(1H, d), 6.23(1H, d), 6.34(1H, d), 6.62(1H, dd), 7.69(1H, dd).

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