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# Total Synthesis of (−)-Blepharocalyxin D

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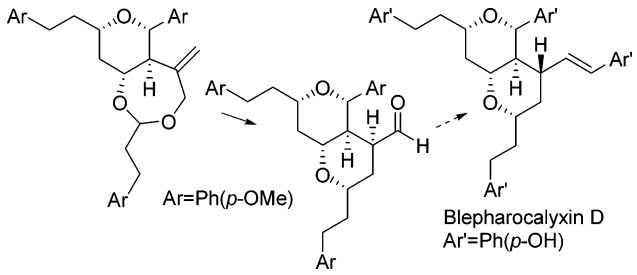
## ABSTRACT




**The Prins cyclization strategy was successfully applied in the total synthesis of (−)-blepharocalyxin D, a cytotoxic dimeric diarylheptanoid isolated from *Alpinia blepharocalyx*.**

Blepharocalyxin D (**1**)[1] is a unique member of dimeric diarylheptanoid natural products isolated from the seeds of *Alpinia blepharocalyx*.[2,3] It is an antiproliferative agent ($ED_{50}$ 3.61 $\mu$M) against murine colon 26-L5 carcinoma cells. The most characteristic feature of blepharocalyxin D (**1**) is a rare 2,8-dioxabicyclo[4.4.0]decane core, to which four *p*-hydroxyphenyl groups are appended.[4] No general strategy has evolved for the generation of this dioxabicyclodecane system, and there have been no advances made toward synthesis of this interesting natural product.[5] In this communication, we describe a concise total synthesis of **1** employing two distinctive Prins cyclization reactions.

In our retrosynthetic analysis, the oxane derivative **A** was considered as a pivotal intermediate in the synthesis of blepharocalyxin D (**1**). A number of different synthetic routes may be considered for the efficient conversion from **A** to **1**. Intermediate **A** may be prepared from homoallylic alcohol **B** and aldehyde **C**. This type of Prins cyclization has already been reported by Willis and co-workers[6] (Scheme 1).

Sulfur trioxide−DMSO oxidation of 3-(*p*-methoxyphenyl)-propan-1-ol (**2**) yielded the corresponding aldehyde, which was converted into homoallylic alcohol **4** (92% ee) via reaction with allyltributylstannane in the presence of the

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(1) (a) Tezuka, Y.; Ali, M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Lett.* **2000**, *41*, 5903−5907. (b) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491−496.

(2) A large number of bioactive diarylheptanoid natural products were isolated recently by Kadota and co-workers from the seeds of *Alpinia blepharocalyx* K. Schum, a member of the Zingiberaceae family: (a) Kadota, S.; Prasain, J. K.; Li, J. X.; Basnet, P.; Dong, H.; Tani, T.; Namba, T. *Tetrahedron Lett.* **1996**, *37*, 7283−7286. (b) Prasain, J. K.; Tezuka, Y.; Li, J. X.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *Tetrahedron* **1997**, *53*, 7833−7842. (c) Prasain, J. K.; Li, J.-X.; Tezuka, Y.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 212−216. (d) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733−1736. (e) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208−213. (f) Ali, M. S.; Tezuka, Y.; Awale, S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 289−293.

(3) More recently, synthetic investigations by Rychnovsky and co-workers led to revised structures of some of the diarylheptanoids, calyxins L, F, M, and G: Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176−3183.

(4) As far as we know, blepharocalyxin D (**1**) is the only natural product known to possess a 2,8-dioxabicyclo[4.4.0]decane core.

(5) There is one reference claiming to be a model study for synthesis of blepharocalyxin D (**1**): Li, W.; Mead, K. T.; Smith, L. T. *Tetrahedron Lett.* **2003**, *44*, 6351−6353.

(6) (a) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429−2432. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577−580.

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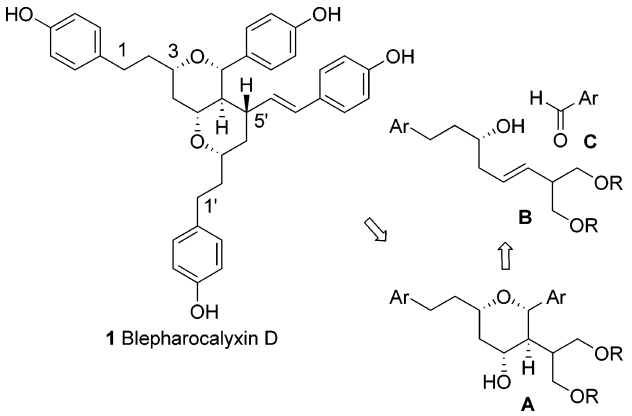
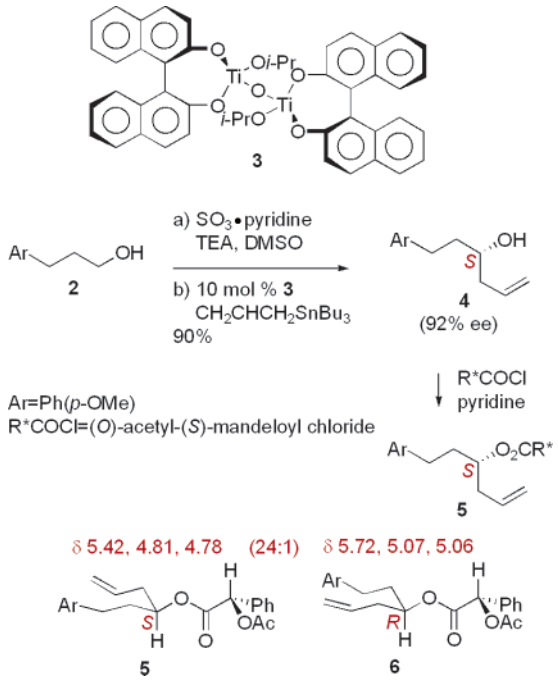
**Scheme 1.** Retrosynthetic Analysis



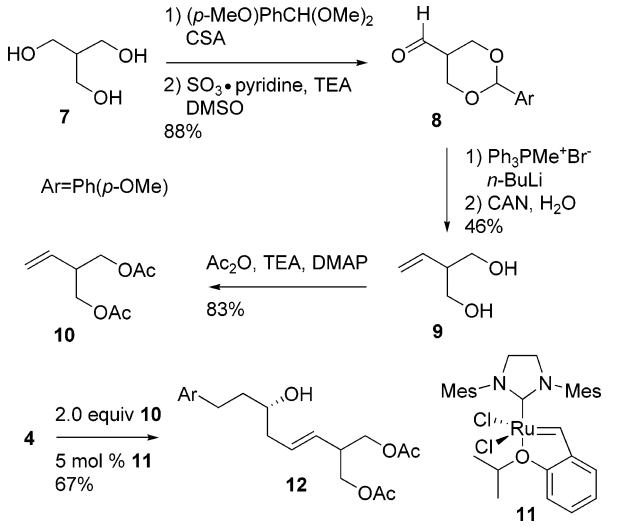

catalyst **3** following the Maruoka protocol.[7] The (*S*)-configuration of homoallylic alcohol **4** was confirmed by NMR analysis of the ester derivative which was produced via reaction with (*O*)-acetyl-(*S*)-mandeloyl chloride.[8] The NMR spectra of the major product **5** exhibited vinylic proton signals at $\delta$ 5.42, 4.81, and 4.78, compared to the signals of the minor isomer **6** at $\delta$ 5.72, 5.07, and 5.06 (Scheme 2).

**Scheme 2.** Asymmetric Allylation




Sulfur trioxide−DMSO oxidation of the cyclic acetal prepared from triol **7** yielded aldehyde **8**.[9] Wittig olefination and oxidative deprotection produced diol **9**, from which diacetate **10** was obtained via acetylation. Cross metathesis reaction of **4** with 2 equiv of olefin **10** in the presence of the second-generation Hoveyda−Grubbs catalyst (**11**)[10] proceeded smoothly producing a new homoallylic alcohol **12** in 67% yield (Scheme 3). Use of the second-generation

**Scheme 3.** Preparation of the **B** Fragment




Grubbs catalyst under identical reaction conditions provided the product **12** in 48% yield. Use of alternative olefin partners, for example, diol **9** or its bis(TBS) ether, led to more sluggish reactions producing the corresponding products in 10∼20% yield in the presence of the second-generation Grubbs catalyst.

For the crucial Prins cyclization of homoallylic alcohol **12** with *p*-anisaldehyde, reaction conditions of Willis and co-workers[6] were modified for maximum efficiency: in our hands, use of 4 equiv of triethylsilyl triflate and 1 equiv of trimethylsilyl acetate in 40 equiv of acetic acid worked best producing the oxane product **13** stereoselectively in 60% yield. No sign of racemization was noticed originating from the oxonia−Cope rearrangement.[11] Use of 2 equiv of boron trifluoride etherate, 4 equiv of trimethylsilyl acetate, and 4 equiv of acetic acid in cyclohexane produced **13** in 18∼26% yield.

Ways for preparation of the dioxabicyclodecane system were examined, and a prominent possibility appeared to be a second Prins cyclization. Exhaustive deacetylation of **13** led to the corresponding triol, which was converted into thionocarbonate **14** in 67% yield. Cyclic acetal formation of **14** with 3-(*p*-methoxyphenyl)propanal was accomplished using ionic liquid [SOClMIm]Cl,[12] and thermal elimination

(7) Hanawa, H.; Uraguchi, D.; Konishi, S.; Hashimoto, T.; Maruoka, K. *Chem. Eur. J.* **2003**, *9*, 4405−4413.
(8) For extensive use of (*O*)-acetylmandelate NMR correlation, see: Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444−1456.
(9) Kim, E. J.; Ko, S. Y. *Bioorg. Med. Chem.* **2005**, *13*, 4103−4112.
(10) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.
(11) For a recent discussion on oxonia−Cope rearrangement, see: Jasti, R.; Anderson, C. D.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 9939−9945.
(12) Li, D.; Shi, F.; Peng, J.; Guo, S.; Deng, Y. *J. Org. Chem.* **2004**, *69*, 3582−3585.

was carried out in hot diphenyl ether to provide the seven-membered cyclic acetal **16**. The second Prins reaction proceeded smoothly in the presence of boron trifluoride etherate producing a mixture of the axial aldehyde **17** (83%) and the equatorial aldehyde **18** (2%). As far as we know, this type of Prins cyclization using methylidene-substituted seven-membered cyclic acetals is unprecedented. The high stereoselectivity is surprising, as the Prins−pinacol sequence on related diol substrates is known to yield mainly equatorial aldehydes.[13,14] The kinetic preference in our case may be explained by conformational constraints originating from the steric crowding.

Under basic conditions, aldehyde **17** was converted into a mixture favoring the equatorial aldehyde **18** (**18**, 52%; **17**, 25%). Epimerization at C5′ (from **17** to **18**) was accompanied by the diagnostic upfield shift of the aldehyde proton signals in the $^1$H NMR spectra: the aldehyde proton of **17** exhibits a singlet at $\delta$ 9.68 compared to a doublet at $\delta$ 8.38 ($J$ = 4.7 Hz) for the same proton of **18**. The axial aldehyde **17** recovered could be recycled to produce additional samples of **18**. Julia−Julia reaction[15] of the lithiated sulfone **19** with aldehyde **18** proceeded smoothly, and a 77% yield of the (*E*)-olefin **20** was obtained stereoselectively (50:1). Crystals of **20** were obtained from carbon tetrachloride−pentane solution, and the crystallographic data confirmed the assigned structure (Figure 1).

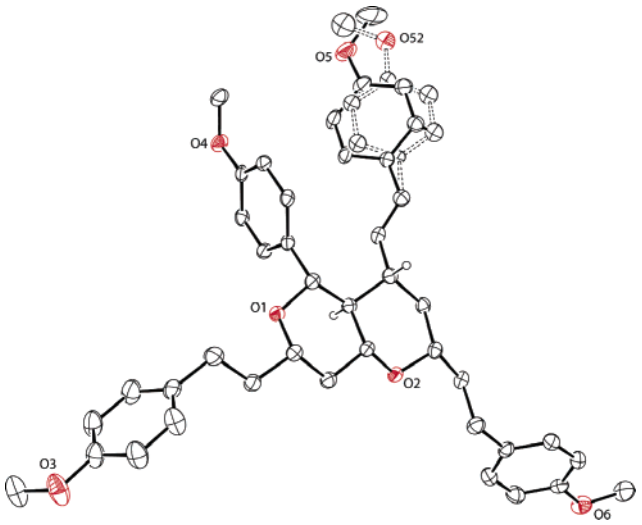
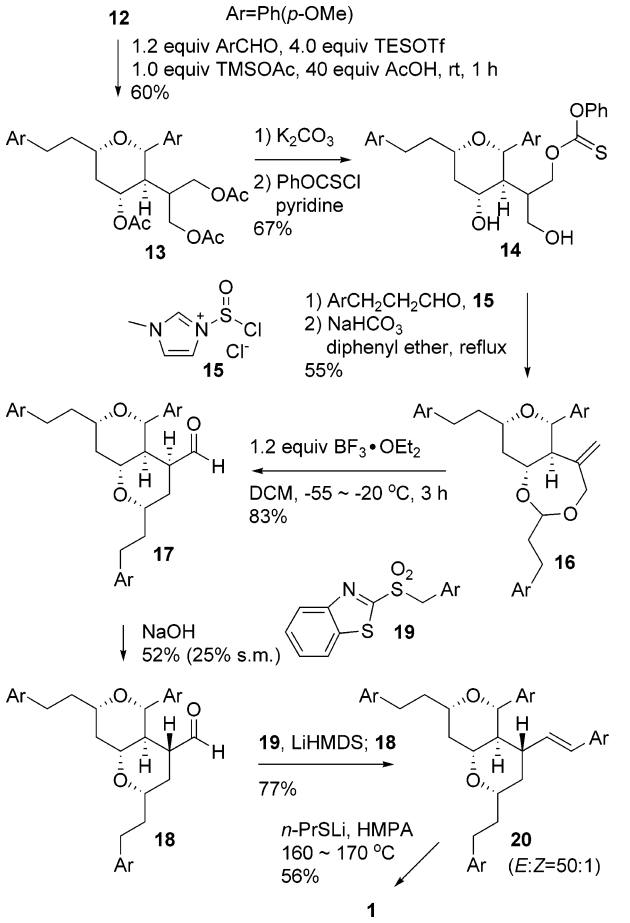



**Figure 1.** Crystal structure of **20**. (One of the phenyl groups was statistically disordered: the minor part of the disordered phenyl group is shown in broken lines.)

Global demethylation of **20** was not possible under various reaction conditions using Lewis acids: presumably, oxygen atoms in the dioxabicyclodecane system presented more basic sites. Eventually, blepharocalyxin D (**1**) was obtained in acceptable yield using lithium propanethiolate in hot HMPA[16] (Scheme 4).

**Scheme 4.** Synthesis of Blepharocalyxin D (**1**)




The synthetic sample of blepharocalyxin D (**1**) exhibited variable specific rotation values, particularly in methanol. Some values are $[\alpha]^{22}_D$ −88.1 (*c* 0.43, MeOH), $[\alpha]^{22}_D$ −77.1 (*c* 0.11, MeOH), $[\alpha]^{22}_D$ −89.9 (*c* 0.027, MeOH), $[\alpha]^{23}_D$ −72.9 (*c* 0.32, acetone), and $[\alpha]^{24}_D$ −85.0 (*c* 0.31, MeOH−DCM (1:1)). These values are at odds with the value reported by Kadota and co-workers:[1] $[\alpha]^{25}_D$ +18.5 (*c* 0.025, MeOH). The synthetic sample has (3*S*)-configuration, but at this point, determination of the absolute stereochemistry of the natural product is not possible. Examples of unreliable optical rotation values of related polyphenols have already been reported by Rychnovsky and co-workers.[3]

A synthetic sample of blepharocalyxin D (**1**) was converted back into the tetramethyl ether derivative **20** using iodomethane and potassium carbonate in hot acetone. The specific rotation of this sample ($[\alpha]^{23}_D$ −87.8 (*c* 0.065, $CHCl_3$)) was almost identical with the value of the original

(13) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092−1093.
(14) For more discussions on Prins−pinacol reactions, see: Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.
(15) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178.
(16) For a recent example of the use of lithium alkanethiolate in hot HMPA for aromatic ether demethylation, see: Nakatani, M.; Nakamura, M.; Suzuki, A.; Inoue, M.; Katoh, T. *Org. Lett.* **2002**, *4*, 4483−4486.

sample ($[\alpha]^{14}_D$ −90.4 (*c* 0.32, $CHCl_3$)) of **20**, which confirms the structure of the synthetic sample of **1** beyond any doubt.

In this synthesis, two oxane rings in blepharocalyxin D (**1**) were constructed via two different types of Prins cyclization reactions. The synthetic scheme adopts a highly modular approach, and the strategy may easily be adapted to library synthesis.

**Acknowledgment.** This work was supported by a grant from the Korea Research Foundation (MOEHRD) (KRF-2005-070-C00073) and a grant from the Center for Bioactive Molecular Hybrids (Yonsei University and KOSEF). Brain Korea 21 graduate fellowship grants to H. M. Ko, D. G. Lee, M. A. Kim, and H. J. Kim are gratefully acknowledged. The authors thank Prof. Kadota of Toyama Medical and Pharmaceutical University for providing spectroscopic data of the natural sample of blepharocalyxin D (**1**).

**Supporting Information Available:** Experimental procedures and $^1H$ NMR and $^{13}C$ NMR spectra of the intermediates and products (42 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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