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Total Synthesis of (−)-Blepharocalyxin D and Analogues

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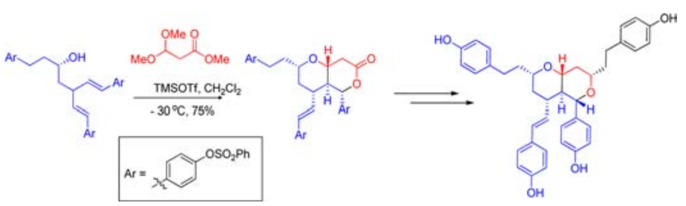
ABSTRACT



An efficient strategy for the total synthesis of (−)-blepharocalyxin D and an analogue is described. The key step involves an acid-mediated cascade process in which reaction of methyl 3,3-dimethoxypropanoate with γ,δ-unsaturated alcohols possessing diastereotopic styrenyl groups gives *trans*-fused bicyclic lactones with the creation of two rings and four stereocenters in one pot.

Kadota and co-workers have reported the isolation of a family of related polyphenolic compounds from extracts of the seeds of *Alpinia blepharocalyx*.[1] Their structures were determined originally using spectroscopic methods. More recent synthetic studies by Rychnovsky and co-workers have led to structural reassignment of some of these compounds.[2] We were drawn to one particular diarylheptanoid blepharocalyxin D (**1**), which was isolated in very small quantities from seeds of *A. blepharocalyx*. Blepharocalyxin D exhibits potent antiproliferative activity against murine colon 26-L5 carcinoma and human HT-1080 fibrosarcoma cells.[3] It has an unusual structure assembled upon a *trans*-2,8-dioxabicyclo[4.4.0]decane adorned by four side chains each in an equatorial position (Figure 1). We now describe a flexible strategy for the synthesis of *trans*-2,8-dioxabicyclo[4.4.0]decanones in which two rings and four stereocenters are created in a one-pot cascade process and culminates in the total synthesis of blepharocalyxin D and an analogue of the natural product.

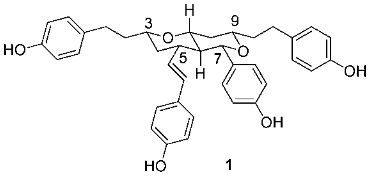


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Figure 1. (−)-Blepharocalyxin D.

Lee and co-workers have reported the only previous total synthesis of blepharocalyxin D in which they employed two separate Prins cyclizations to construct each of the oxane rings.[4] However, introduction of the C-5 equatorial side chain proved challenging. An interesting Prins-pinacol reaction gave predominantly an unwanted axial aldehyde at C-5 which was epimerized prior to a Julia chain extension to the required styrenyl group. Our goal was to develop a new synthetic strategy to blepharocalyxin D in which both rings of the *trans*-fused bicyclic framework would be generated in one-pot with all side chains equatorial. The approach was to be versatile to provide analogues of potential biological interest.

Our retrosynthetic analysis of **1** is shown in Scheme 1. The C-9 side chain would be introduced via a Grignard addition to lactone **2** followed by reduction of the resultant lactol. An advantage of using the lactone is that various

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(1) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208.

(2) (a) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176. (b) Tian, X.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4955.

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

(4) (a) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Org. Lett.* **2007**, *9*, 141. (b) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 5797.

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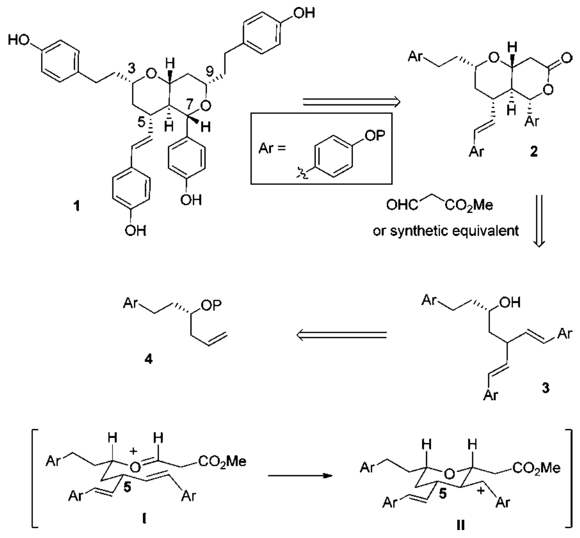
Grignard reagents could be used to prepare analogues of the natural product.

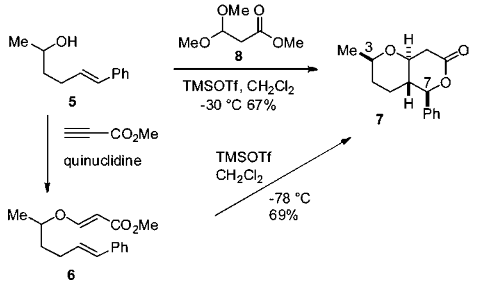
Scheme 1. Retrosynthesis of Blepharocalyxin D



The *trans*-2,8-dioxabicyclo[4.4.0]decanone (**2**) would be assembled from γ,δ-unsaturated alcohol **3** in which the double bond is placed one position further away from the hydroxyl group than in homoallylic alcohols and derivatives commonly used in Prins cyclizations.[5] The success of this strategy relied upon reaction of **3** (to be prepared from (*S*)-homoallylic alcohol **4**) with an electrophile to generate an intermediate oxycarbenium **I** with diastereotopic styrenyl groups. Cyclization was predicted to proceed to give stabilized carbocation **II** with the first of the oxane rings with an equatorial substituent at C-5. Intramolecular trapping of the resultant carbocation with an ester would generate the second heterocycle giving lactone **2** with an equatorial substituent at C-7.[6]

To establish conditions for the proposed cyclization, first the known[7] γ,δ-unsaturated alcohol **5** was converted to enol ether **6** using methyl propiolate and catalytic quinuclidine. Treatment of **6** with TMSOTf gave bicyclic lactone **7** in 69% yield (Scheme 2).[8] The structure was elucidated by NMR spectroscopy and confirmed by X-ray crystallography.

Scheme 2. Synthesis of Bicyclic Lactone **7**



The second approach to **7** involved the direct reaction of γ,δ-unsaturated alcohol **5** with commercially available methyl 3,3-dimethoxypropanoate **8** giving, after optimization, lactone **7** in 67% yield. These studies established an approach for the direct conversion of γ,δ-unsaturated alcohols to *trans* fused bicyclic lactones with equatorial groups at both C-3 and C-7.

For the proposed synthesis of blepharocalyxin D (Scheme 2), a γ,δ-unsaturated dienol **3** was required as the substrate for the key cyclization to generate the bicyclic framework with an equatorial styrenyl group at C-5. Following the studies outlined in Scheme 2, we selected dienol **16** with phenyl groups as the initial target.

Dienol **16** was prepared from the known[9] (*S*)-homoallylic alcohol **9** as shown in Scheme 3. Following protection of the secondary alcohol as TBS ether **10**, the double bond was oxidatively cleaved with OsO_4/$NaIO_4$ to give aldehyde **11**. A Horner–Wadsworth–Emmons chain extension of **11** using phosphonate **12** and K_2CO_3 gave (*E*)-α,β-unsaturated ketone **13** with excellent stereocontrol. The final carbon–carbon bond was formed via a rhodium-mediated 1,4-addition of styrenyl boronic acid to enone **13** under the conditions reported by Hiyashi[10] to give ketone **14** in 94% yield as a 1:1 mixture of diastereomers. The lack of stereocontrol was not a problem as this newly created stereocenter would be destroyed later in the synthesis as the target, dienol **16**, has two identical (*E*)-phenylethenyl side chains.

We envisaged that the second double bond of **15** could be readily generated from ketone **14** via reduction to an alcohol followed by elimination. While reduction of ketone **14** with $NaBH_4$ proceeded smoothly to give the expected benzylic alcohol as a mixture of isomers, the elimination step proved problematic via either the corresponding acetate or mesylate. However, the rarely used xanthate formation/Chugaev elimination in this instance worked well. Thus, conversion of the alcohol to a xanthate using $NaH/CS_2/MeI$ followed by refluxing with $NaHCO_3$ in

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(5) For reviews on Prins cyclizations, see: (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413. (b) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316.

(6) For examples of the use of intramolecular trapping using tethered oxygen nucleophiles, see: (a) Fráter, G.; Muller, U.; Kraft, P. *Helv. Chim. Acta* **2004**, *87*, 2750. (b) Elsworth, J. D.; Willis, C. L. *Chem. Commun.* **2008**, *13*, 1587. (c) Yadav, J. S.; Chakravarthy, P. P.; Borkar, P.; Reddy, B. V. S.; Sarma, A. V. S. *Tetrahedron Lett.* **2009**, *50*, 5998. (d) Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B.; Grée, R. *Org. Biomol. Chem.* **2012**, *10*, 1349. (e) Reddy, B. V. S.; Jalal, S.; Borkar, P.; Yadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B. *Org. Biomol. Chem.* **2012**, *10*, 6562.

(7) Bunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3901.

(8) Previous examples of Prins reactions using enol ethers include: (a) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499. (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. L. *Org. Lett.* **2005**, *7*, 2683. (c) Yang, Y.; Jia, P.; Liu, S.; Yu, W. *Chin. J. Chem.* **2012**, *30*, 1439.

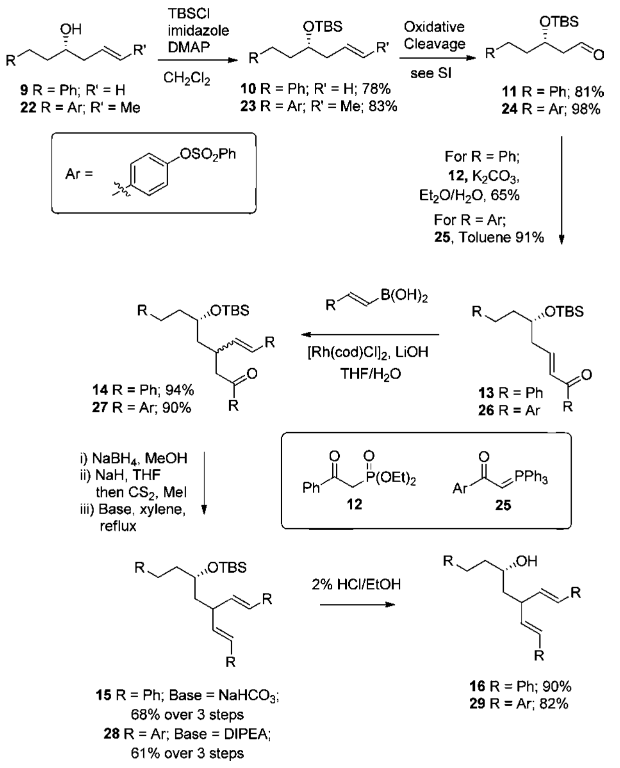
(9) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12.

(10) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(11) Chugaev, L. *Chem. Ber.* **1899**, *32*, 3332. For selected examples of the Chugaev elimination in synthesis, see: (a) Meulemans, T. M.; Stork, G. A.; Macaev, F. Z.; Jansen, B. J. M.; deGroot, A. J. *J. Org. Chem.* **1999**, *64*, 91178. (b) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570. (c) Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Dagneau, P.; Lanver, A.; Jennings, M. P.; Arseniyadis, S.; Faraoni, R.; Lizos, D. E. *J. Am. Chem. Soc.* **2010**, *132*, 7149.

xylene to effect a Chugaev elimination[11] gave the required alkene **15** in 68% overall yield from ketone **14** and with excellent *E*-selectivity. Silyl ether **15** was deprotected using 2% HCl in ethanol to give the required γ,δ-unsaturated alcohol **16**.

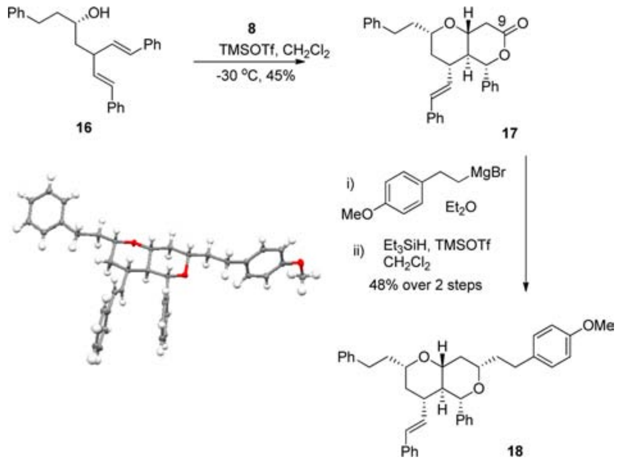
Scheme 3. Synthesis of Dienols **16** and **29**



With dienol **16** in hand, the key cyclization was carried out with acetal **8** and TMSOTf in CH_2Cl_2 at −30 °C giving bicyclic lactone **17** with the creation of four new stereocenters (Scheme 4). The presence of the three equatorial substituents and *trans* ring junction was determined from the ^{1}H NMR spectrum which showed the expected *trans* diaxial couplings for each of the methine protons. It was evident that there was excellent stereocontrol at C-5 with cyclization occurring to give exclusively the equatorial styrenyl side-chain.

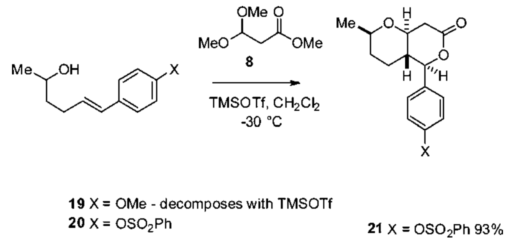
With five out of the six asymmetric centers of the blepharocalyxin D framework intact, the final carbon–carbon bond-forming reaction introduced the side-chain at C-9. Treatment of **17** with 2-(*p*-methoxyphenyl)ethylmagnesium bromide followed by reduction of the resultant lactol with TMSOTf, Et_3SiH gave **18** in 48% yield over the two steps. The NMR data were consistent with the side chains all being in equatorial positions and was confirmed by X-ray crystallography. It is interesting to note the π stacking between the 7-phenyl ring and the styrenyl side chain at C-5 in the crystal structure.

Scheme 4. Completing the Synthesis Blepharocalyxin D Analogue **18** and Crystal Structure of **18**



Turning to the synthesis of blepharocalyxin D, the first challenge was to prepare a dienol with appropriate *para*-substituted phenyl groups. In their total synthesis, Lee and co-workers[4] had used a *p*-methoxyphenyl group which was deprotected using LiSPr/HMPA. However, the unsaturated *p*-methoxyphenyl derivative **19** has an activated electron-donating aromatic ring and proved unstable to the TMSOTf-promoted cyclization conditions (Scheme 5).[7] In contrast, the acid-mediated reaction of methyl 3,3-dimethoxypropanoate **8** and unsaturated alcohol **20** with the electron-withdrawing *p*-phenylsulfonyl group gave bicyclic lactone **21** in 93% yield. Hence the use of phenylsulfonyl esters was selected for the total synthesis of blepharocalyxin D.

Scheme 5. Reaction of Alkenols with **8**



For the natural product, a similar synthetic strategy was used to dienol intermediate **29** as for the analogue **16** (Scheme 3).[12] The chain extension of aldehyde **24** to **26** was achieved in 91% yield using a Wittig reaction with

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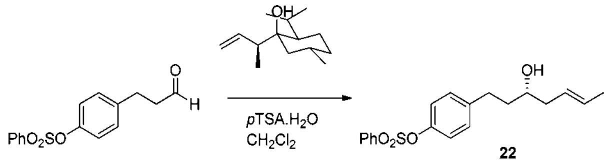
(12) In this case, the synthetic route began with the novel (*S*)-homoallylic alcohol **22** which was prepared in 98% yield via a Nokami crotyl transfer reaction.



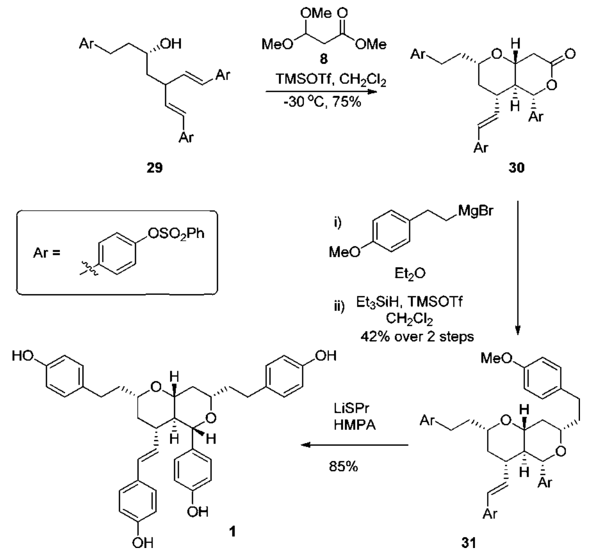
Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

stabilized ylide **25**; this was a significant improvement on the HWE reaction used to prepare enone **13** (65% yield). The rhodium-mediated 1,4-addition to enone **26** using the novel boronic acid (prepared from vinyl boronic acid MIDA boronate and *p*-sulfonylstyrene[13]) gave ketone **27** which was converted to the required dienol **29** using the same reduction/elimination sequence as for analogue **16**.

Reaction of dienol **29** with acetal **8** and TMSOTf gave bicyclic lactone **30** as a single diastereomer with the creation of the two rings and four stereocenters in 75% yield (Scheme 6). The C-9 side chain was introduced via a Grignard addition/reduction protocol giving **31** with the fully assembled carbon framework of our target. Finally deprotection of the phenolic groups with LiSPr/HMPA gave (−)-blepharocalyxin D (**1**) in 85% yield. Interestingly Lee and co-workers[4] reported that their synthetic blepharocalyxin D exhibited variable specific rotation values in methanol (ranging from −77.1 to −89.9 depending on concentration), our synthetic sample $[\alpha]_D$ −79.2 (*c* 0.23, MeOH) was in accord with their data.[15]

In conclusion, a new synthetic strategy to (−)-blepharocalyxin D and an analogue has been developed. The approach proceeds via γ,δ-unsaturated dienols **16** and **29** prepared using an efficient rhodium-mediated conjugate addition to enones **13** and **26** followed by reduction of the resultant ketones and xanthate formation/Chugaev elimination to the required (*E*)-double bond. The key step involves reaction of the dienols with methyl 3,3-dimethoxypropanoate **8** to give bicyclic lactones **17** and **30** via a one-pot cascade to generate two rings and four stereocenters. A Grignard addition/reduction protocol followed by deprotection gave blepharocalyxin D. The bicyclic lactones are flexible intermediates for use as building blocks in organic synthesis and have potential widespread value.

Scheme 6. Completing the Synthesis of **1**



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Supporting Information Available. Preparation and characterization of the compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org

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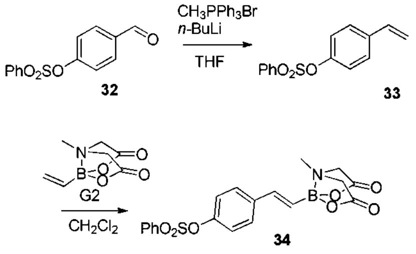
[13] Initial attempts to synthesize boronic acid including the hydroboration of the corresponding alkyne and lithiation of the corresponding β-halostyrene followed by quenching with triisopropylborane were unsuccessful. Instead the required reagent was synthesized in 92% yield from vinyl boronic acid MIDA boronate and *p*-sulfonylstyrene using conditions reported by Burke.[14]



G2 = Grubbs 2nd generation catalyst

[14] Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130.

[15] The optical rotation for the natural product reported by Kadota and co-workers[3] was $[\alpha]_D$ +18.5 (*c* 0.025, MeOH), but Lee reports that the NMR spectra of the natural product contained impurities.[4]

The authors declare no competing financial interest.