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SUBSTRATE-CONTROLLED FORMAL SYNTHESIS OF (+)-LAURENYNE BY A CHEMOSELECTIVE CHELATION-CONTROLLED ALKYLATION STRATEGY

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Abstract – A substrate-controlled formal synthesis of (+)-laurenyne has been accomplished featuring a highly stereoselective chemoselective chelation-controlled amide enolate alkylation for synthesis of the α,α'-*syn*-bis-alkene without resorting to use of a chiral auxiliary.

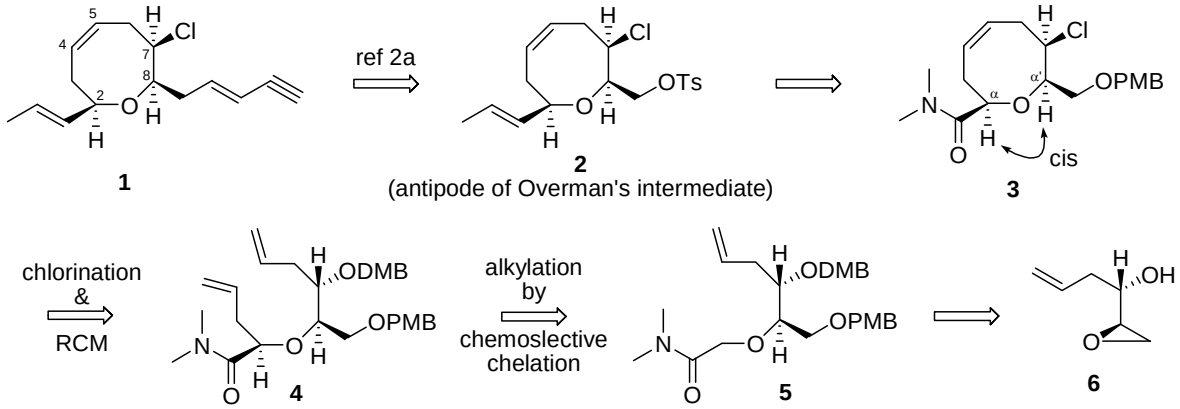
(+)-Laurenyne (**1**), a C_{15} nonisoprenoid metabolite, was isolated from *Laurencia obtusa* collected in the Aegean Sea off the coast of Turkey by Thomson and co-workers in 1980.[1] The structure and absolute stereochemistry of the chlorinated α,α'-*cis*-oxocene marine natural product were proposed by the Thomsom group using X-ray crystallography.[1] The first total synthesis[2] of unnatural (-)-laurenyne by Overman and Thompson using an acetal-initiated cyclization confirmed the constitution and relative stereochemistry of laurenyne but reassigned the absolute stereochemisty as 2*R*,7*R*,8*R*.[2] The recent asymmetric total synthesis of (+)-laurenyne by Boeckman and co-workers features a retro-Claisen rearrangement as a key step to construct the oxocene skeleton.[3] Recently, Clark et al. reported a synthesis of the cyclic ether core of (+)-laurenyne by a ring-closing metathesis.[4] Reported herein is a substrate-controlled synthesis of chloro tosylate **2** employing a highly stereoselective amide enolate alkylation based on a chemoselective chelation process as a key step. The chloro tosylate **2** represents the antipode of a late-stage intermediate in the total synthesis of (-)-laurenyne by Overman and Thompson.

As shown in Scheme 1, we envisioned that chloro tosylate **2** could be elaborated from key α,α'-*cis*-disubstituted chloro oxocene **3**, which in turn could be prepared from α,α'-*syn*-bis-alkene **4** by

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

a chlorination-RCM sequence. We further envisaged that key α,α'-*syn*-diene **4** could be secured in a stereoselective fashion by alkylation[5] of α-alkoxy amide **5** using a chemoselective chelation strategy (vide infra). Further analysis indicated that alkylation substrate **5** should be readily available from epoxy alcohol **6**.

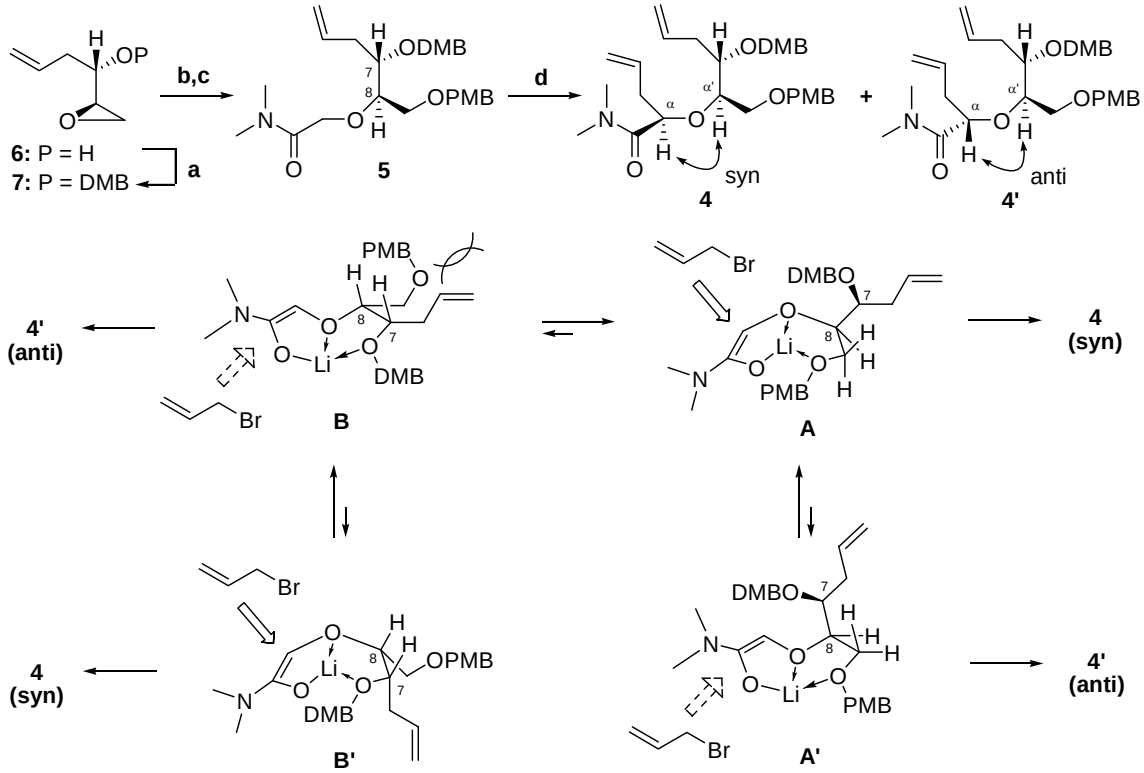
Scheme 1. Retrosynthetic Plan



To commence the synthesis, (2*R*,3*S*)-1,2-epoxy-5-hexen-3-ol (**6**) was prepared by exposure of racemic, commercially available 1,5-hexadien-3-ol to a standard Sharpless asymmetric epoxidation[6] [(+)-DIPT, Ti(O-*i*-Pr)$_4$, cumene hydroperoxide, 4 Å molecular sieves, 98% ee, 33% conversion]. As shown in Scheme 2, regioselective opening of DMB-protected epoxide **7** with PMB alcohol using potassium *t*-butoxide as base, followed by *O*-alkylation of the resulting alcohol with *N*,*N*-dimethyl-α-bromoacetamide, provided α-alkoxy amide **5** in 53% overall yield for the three steps from **6**, setting the stage for the crucial amide enolate alkylation.

We were intrigued by the possibility that electrophilic attack on the sterically more exposed convex *β*-face of the cup-shaped PMBO-chelated bidentate enolate intermediate **A** might produce the requisite α,α'-*syn*-bis-alkene **4** in a stereoselective fashion.[7] The alternative cup-shaped DMBO-chelated bidentate intermediate **B** experiences a destabilizing interaction between the two *cis*-oriented substituents at C(7) and C(8). It is noteworthy that cup-shaped bidentate models **A'** and **B'** are disfavored compared to **A** and **B** since their substituents are disposed on the sterically hindered concave faces. To our satisfaction, treatment of α-alkoxy amide **5** with LiHMDS followed by allyl bromide gave rise to the desired α,α'-*syn*-diene **4** in 80% isolated yield with 11:1 *syn*/*anti* selectivity.

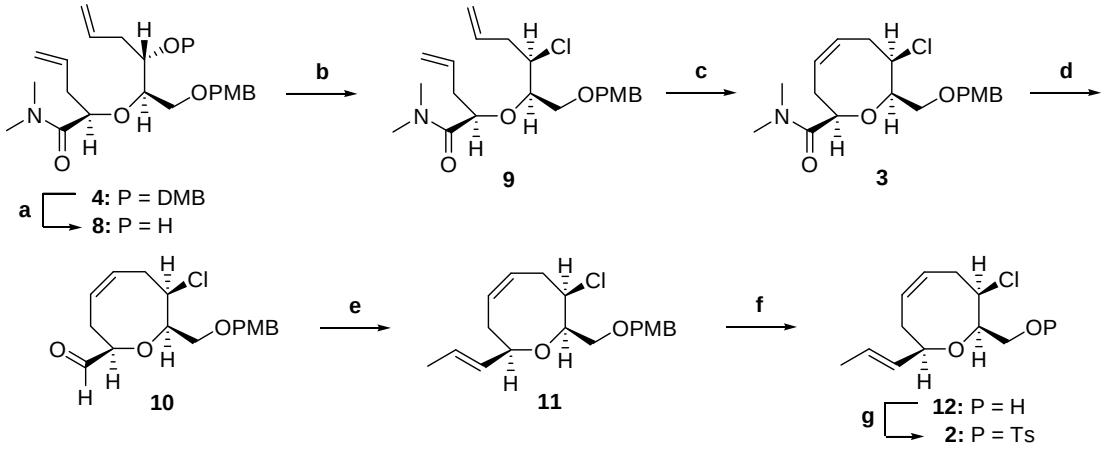
Scheme 2. Synthesis of α,α'-*syn*-bis-Alkene 4 by Alkylation[a]



[a]*Reagent and Conditions*: a) DMB-Cl, NaH, DMF, rt, 3 h, 71%; b) PMB-OH, *t*-BuOK, *t*-BuOH, 90 °C, 4 h, 78%; c) NaH, $BrCH_2CONMe_2$, THF, 0 °C to rt, 3 h, 95%; d) LiHMDS, allyl bromide, -78 °C, 1.5 h, 80%.

With key α,α'-*syn*-bis-alkene **4** in hand, we proceeded to address construction of the chloro oxocene core **3** (Scheme 3). In view of the difficulties associated with halogenation of α,α'-*cis*-7,8-*anti*-oxocene alcohol system,[3,8] chlorination of acyclic homoallylic alcohol **8**, prepared from diene **4** by exposure to wet DDQ,[9] was carried out under the conditions of Hooz[10] to furnish chloro diene **9** (52%, two steps). Ring-closing metathesis[11] of chloro diene **9** using Grubbs first generation catalyst then afforded the desired chloro oxocene **3** in good yield (80%). We next turned our attention to assembly of the *trans* propenyl side-chain appendage at C(2). For this purpose, reduction of α-alkoxy amide with an ate complex,[12] followed by Takai olefination[3,13] of the resultant aldehyde **10**, delivered chloro alkene **11** as an inseparable 15:1 *E*/*Z* mixture in 68 % yield for the two steps. Finally, removal of the PMB group of chloro oxocene **11** under the Yonemitsu conditions[8] and tosylation of the resulting primary alcohol **12** delivered the desired chloro tosylate **2**.[14] The spectral and optical rotation data of our synthetic material were in good agreement with those previously obtained except for the sign of the optical rotation: $[\alpha]^{25}_D$ -51.1 (*c* 0.10, $CHCl_3$) [lit.,[2] $[\alpha]^{20}_D$ +47.1 (*c* 0.97, $CHCl_3$)].

Scheme 3. Synthesis of the Antipode of Overman's Intermediate[a]



[a]*Reagent and Conditions*: ; a) DDQ, CH_2Cl_2/pH 7.4 buffer (10/1), 0 °C to rt, 1 h, 70%; b) CCl_4, *n*-Oct_3P, pyridine, 70 °C, 3 h, 74%; c) $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, rt, 2.5 h, 80%; d) *n*-BuLi/Dibal-H, THF, rt, 2 h; e) $CrCl_2$, THF, CH_3CHI_2, rt, 2 h, 68% (2 steps); f) DDQ, CH_2Cl_2/pH 7.4 buffer (10/1), rt, 1 h, 94%; g) TsCl, DMAP, TEA, CH_2Cl_2, rt, 1 h, 78%.

In conclusion, a formal synthesis of (+)-laurenyne has been achieved by synthesizing chloro tosylate **2** in a substrate-controlled fashion in 11 steps in 9% overall yield from readily available epoxide **6**. Highlights of the synthesis include a highly stereoselective amide enolate alkylation for synthesis of the α,α'-*syn*-RCM precursor using a chemoselective chelation strategy without resorting to use of a chiral auxiliary.

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Dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday. We thank Professor L. E. Overman (University of California, Irvine) for providing spectra of (+)-tosylate **2**. This research was supported by the Korea Research Foundation Grant (KRF-2004-015-C00272) and the Brain Korea Project in 2006 and 2007.

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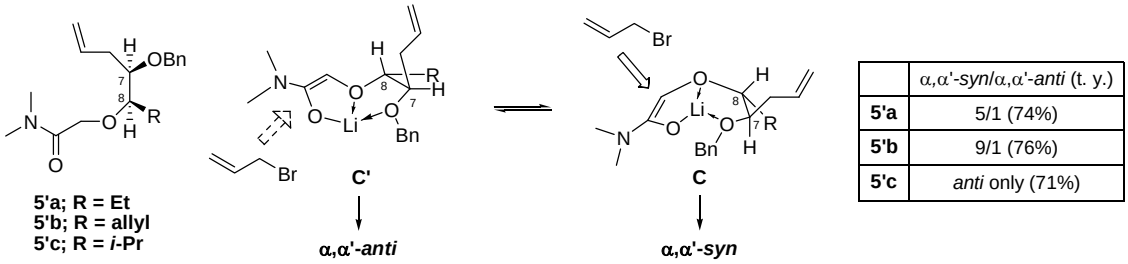
7. Our rationale for the observed *syn*-stereoselectivity in the previously reported alkylation of **5'a** (R = Et), which turned out to be a very subtle case, seems to be insufficient and misleading.[5] Unlike the case of **5**, the C(7) and C(8) substituents in cup-shaped bidentate enolate intermediates **C** and **C'** are *trans*-oriented. Our ensuing studies revealed that the size of the R group at C(8) has a dramatic influence on the stereochemical outcome of alkylation as shown below. Thus, in the case of **5'a** (R = Et) in which the C(7) and C(8) substituents are similar in size (allyl vs ethyl), the C(7) substituent seems to prefer to be disposed on the convex face, leading to the formation of cup-shaped bidentate intemediate **C**. Electrophilic attack from the convex β-face of the cup-shaped bidentate model **C** (described as electrophilic attack from the side opposite to the ethyl group in bidentate model in our original paper) would then produce the corresponding *syn* isomer. We substantiated this argument by introducing the identical allyl group at the C(8) position (**5'b**). However, we find that alkylation of **5'c** (R = isopropyl) proceeds by electrophilic attack from the convex α-face of cup-shaped bidentate model **C'** to give the *anti* isomer exclusively since the branched bulky isopropyl group at C(8) prefers to be located on the less hindered convex face.



	α,α'-*syn*/α,α'-*anti* (t. y.)
5'a	5/1 (74%)
5'b	9/1 (76%)
5'c	*anti* only (71%)

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14. Examination of the spectra of the (-)-chloro-tosylate **2** indicated that the minor (*Z*)-isomer had been lost during purifications in the final two steps.