Natural Products

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Asymmetric Total Synthesis of Leucosceptroid B**

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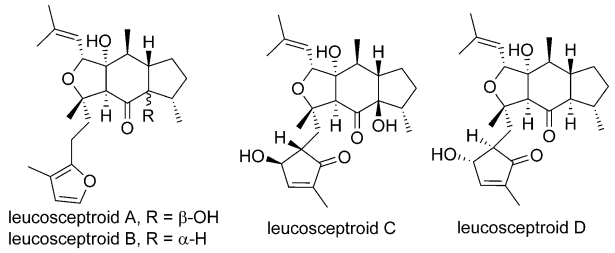
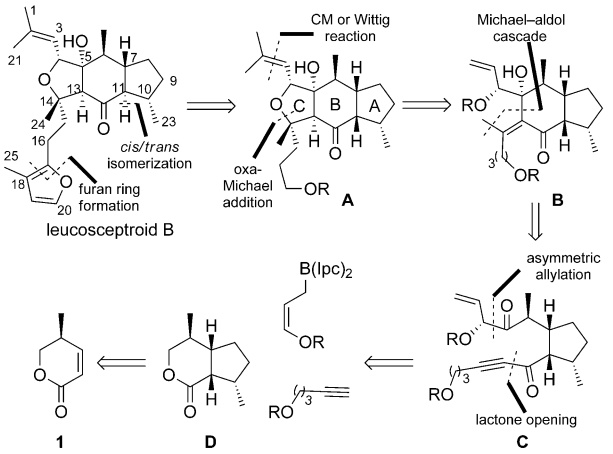
In memory of Wei-Shan Zhou

Most sesterterpenoids feature unprecedented structural complexity and fascinating bioactivities,[1] which continue to inspire synthetic chemists to develop elegant approaches for their synthesis.[2] Since 2010, leucosceptroids A–D, as well as their natural siblings, have been isolated and identified from *Leucosceptrum canum*.[3] These sesterterpenoids exhibit interesting bioactivities, including potent antifungal and antifeedant effects, impressive antiangiogenic activity, and inhibition of prolyl endopeptidase. Leucosceptroids A–D consist of a tricyclic system that contains a fully functionalized tetrahydrofuran ring and eight contiguous stereogenic centers (Scheme 1). With a carbonyl group present in the six-membered ring, the corresponding *cis*-fused 5/6 carbon ring system is thermodynamically more stable than the *trans*-fused one,[4] thus increasing the interest of chemists in the stability of the *trans*-fused 5/6 bicyclic motif in natural leucosceptroids B and D. In 2011, Horne and co-workers reported the asymmetric synthesis of the core structure of leucosceptroids.[5] Here, we would like to present our efforts toward the asymmetric total synthesis of leucosceptroid B.



Scheme 1. Structures of leucosceptroids A–D.

In order to rule out the potentially troublesome epimerization at C11 during the synthesis, we planned the *cis*/*trans* epimerization of the A/B ring system for the final stage (Scheme 2). We also preferred to install the sensitive furan segment late in the synthesis.[6] The chiral oxygenated prenyl group could be derived from intermediate **B** through cross metathesis (CM) or Wittig olefination. The densely functionalized tetrahydrofuran (ring C) could be formed through an intramolecular *oxa*-Michael addition within intermediate **B**, which might be accessible through a copper-mediated Michael–aldol cascade from ynone **C**. Intermediate **C** could be produced by opening of the lactone ring and applying the organoborane chemistry described by Brown et al. to intermediate **D**,[7] which is available from known chiral compound **1**.



Scheme 2. Retrosynthetic analysis of leucosceptroid B. R = protecting group.

Our synthesis commenced with known chiral lactone **1** (Scheme 3), which is easily prepared by an established procedure that we improved.[8] Copper-mediated Michael addition and ozonolysis of the introduced terminal alkene afforded compound **3**. Subsequent TsOH-mediated intramolecular condensation provided compound **4**, while basic condensation and the use of other acids, such as TFA, H_2SO_4, or $BF_3{\cdot}Et_2O$, failed.[9] Using 10 mol% loading of Pd/C (5%) in ethyl acetate afforded the known lactone **5** in 99% yield, minimizing the double bond migration to compound **4a**.[10] The spectral data of our synthetic compound **5** are indistinguishable from the reported data and the signs of optical rotation are opposite,[9a] confirming its proper stereochemistry.

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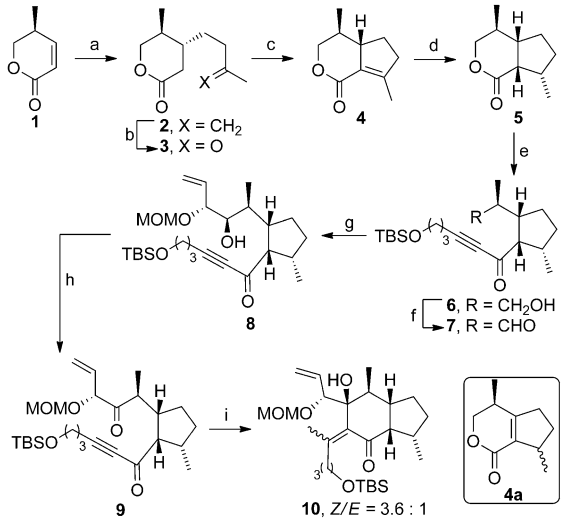


Scheme 3. Reaction conditions: a) 4-iodo-2-methyl-butene, Mg, $CuBr{\cdot}Me_2S$, ether, −78 °C, 67%; b) O_3, $MeOH/CH_2Cl_2$ (1/4), −78 °C; c) TsOH, PhH, Dean–Stark trap, 85% over two steps; d) Pd/C, H_2 (balloon), ethyl acetate, RT, 99%; e) *tert*-butyldimethyl(pent-4-ynyloxy)-silane, *n*BuLi, THF, −78 °C; f) cat. TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 63% over two steps; g) 3-(methoxymethoxy)propene, *s*BuLi, (−)-$(Ipc)_2BOMe$, $BF_3{\cdot}Et_2O$, THF, 90%, d.r. > 20:1; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 76%, i) MeMgBr, CuI, THF, −78 °C, 69% for (*Z*)-**10**, 19% for (*E*)-**10**. Ipc = isopinocampheyl, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl, Ts = 4-toluenesulfonyl.

Mixing *n*BuLi and TBS-protected 4-pentyn-1-ol to generate nucleophilic alkynyl lithium and its reaction with compound **5** led to ketone **6**. Interestingly, compound **6** was found to be sensitive to oxidizing reagents, furnishing a large amount of by-product. Fortunately, reacting **6** with TEMPO/$PhI(OAc)_2$ led efficiently to the desired aldehyde **7**. Asymmetric allylation based on the methodology described by Brown et al. gave compound **8** with excellent diastereoselectivity.[7]

The chemistry of Michael addition to ynoates, which is based on the stability of the corresponding *cis*-alkenylcuprate, is well developed and widely applied.[11] However, few examples of applying Michael addition to ynone have been documented in natural product synthesis,[12] mainly because of the formation of allenylcuprate intermediate.[13] The equivalent Michael-aldol cascade reactions, involving organozinc reagents, ynones, and aldehydes have proved elusive, although some efforts have led to moderate *Z*/*E* ratios.[14] However, no *Z*/*E* selectivity has been achieved for the cascade Michael-aldol reaction involving Grignard reagents, ynones and ketones.[15] In contrast to these failed intermolecular reactions, we envisioned that intramolecular capture of an ynone-derived allenylcuprate by ketone would probably afford some *Z*/*E* stereoselectivity.

After oxidation of **8** to **9**, we attempted the Michael-aldol cascade (Table 1). The best *Z*/*E* selectivity (3.6:1) and yield were obtained with methyl magnesium bromide and copper(I) iodide (Table 1, entry 6). The relative stereochemistry of (*Z*)-**10** and (*E*)-**10** was established through extensive 2D NMR experiments.[16] Notably, unlike the known reactions, in which an aldehyde serves as the electrophilic reagent,[14] the Ni^0 or Cu^I catalysts showed no reactivity in the presence of the organozinc reagent (Table 1, entries 7 and 8).[17]

Table 1: Optimization of the Michael–aldol cascade from starting material **9** to product **10**.

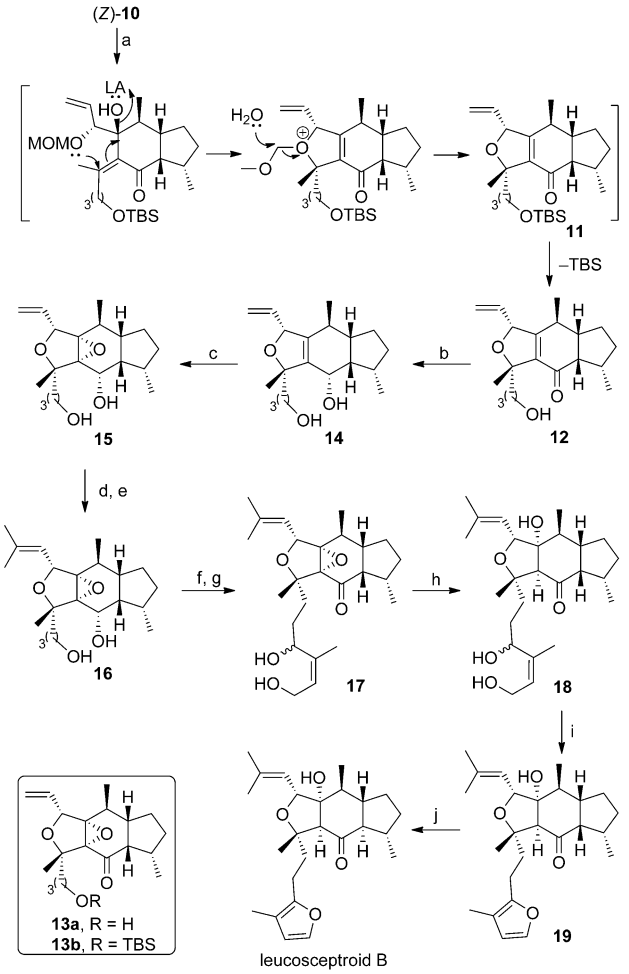
Entry	Conditions	Yield[a]	*Z*/*E*[b]
1	MeLi, CuCN, THF, −78 °C	c.m.	n.d.
2	MeMgBr, CuCN, THF, −78 °C	c.m.	n.d.
3	MeLi, $CuBr{\cdot}Me_2S$, THF, −78 °C	c.m.	n.d.
4	MeMgBr, $CuBr{\cdot}Me_2S$, THF, −78 °C	55%	1.7:1
5	MeLi, CuI, THF, −78 °C	40%	0.9:1
6	**MeMgBr, CuI, THF, −78 °C**	**88%**	**3.6:1**
7	cat. $Ni(cod)_2$, Me_2Zn, PhMe, −78 °C→RT	n.r.	n.d.
8	cat. CuI, MeZnTFA, CH_2Cl_2, RT	n.r.	n.d.

[a] Combined yield of isolated (*Z*)-**10** and (*E*)-**10**. [b] Determined by ^1H NMR spectroscopy. Entry in bold marks optimized reaction conditions. c.m.: complex mixture of products, n.d.: not determined, n.r.: no reaction, cod = 1,5-cyclooctadiene, TFA = trifluroacetate.

For the formation of the densely functionalized tetrahydrofuran motif, we planned to remove the MOM protection from the hydroxy group at C5, and then to attempt an intramolecular *oxa*-Michael addition, followed by reversal of the stereochemistry at C4. Boron trifluoride turned out to be the best reagent to promote a one-pot rearrangement–deprotection cascade giving compound **12** (Scheme 4),[18] the relative stereochemistry of which was confirmed by NOESY experiments.[16] A tentative mechanism for the formation of **12** is proposed in Scheme 4. First, activation of the tertiary allylic hydroxy group with Lewis acid facilitates its removal through an S_N2' process, when the electron-deficient double bond is attacked by the MOM ether. The MOM protecting group on the resulting oxonium is then cleaved in the presence of adventitious water. Subsequently, the primary *tert*-butyldimethylsilyl ether is cleaved by Lewis acid. An alternative mechanism involving MOM-deprotection/*oxa*-Michael addition/elimination can be ruled out, given the observed facile transformation of (*Z*)-**10** into **11** on silica gel during purification by column chromatography.

We then carried out extensive trials to install the tertiary chiral hydroxy group at position C5 in leucosceptroid B. All efforts to directly transform **11** or **12** into epoxide **13** using peroxide or peracid in a basic environment failed, probably because of the neighboring steric hindrance. Thus, we resorted to a hydroxy-directed epoxidation strategy. Highly stereoselective reduction of the carbonyl group with DIBAL-H, followed by chemo- and stereoselective epoxidation, furnished compound **15**.[19] Ozonolysis of the terminal double bond in **15** and subsequent Wittig olefination installed the prenyl group, giving compound **16**.[20] Then both hydroxy groups in compound **16** were oxidized and the aldehyde selectively reacted with vinyl lithium, affording compound **17**. Epoxide opening with lithium naphthalene generated the tertiary hydroxy group at C5 with proper stereochemistry.[21]

The furan ring was formed after a one-pot oxidation–cyclization–dehydration sequence, producing compound **19**, the C11 epimer of leucosceptroid B. In order to minimize elimination of the hydroxy group at C5, many bases were screened for use with **19**, such as Et_3N, *t*BuOK, K_2CO_3, DBU,



Scheme 4. Reaction conditions: a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C, 91 %; b) DIBAL-H, CH_2Cl_2, −78 °C; c) cat. $VO(acac)_2$, anhydrous *t*BuOOH, CH_2Cl_2, RT, 94 % over two steps; d) O_3, MeOH, −78 °C; e) *i*PrPPh$_3$I, KHMDS, THF, 0 °C, quantitative over two steps; f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT; g) *Z*-3-iodo-2-buten-1-ol, MeMgBr, *n*BuLi, THF, −78 °C, 91 % from **16**, mixture of stereoisomers with d.r. = 1:1; h) Li, naphthalene, THF, −78 °C, quantitative, mixture of stereoisomers with d.r. = 1:1; i) Dess–Martin periodinane, CH_2Cl_2, RT, quantitative; j) Et_3N, MeOH, 50 °C, 21 % or 60 % (brsm).
acac = acetylacetonate, brsm = based on recovered starting material, DIBAL-H = diisobutylaluminum hydride, KHMDS = potassium bis(trimethylsilyl)amide, LA = Lewis acid.

Me_4NOH, and $NH_3{\cdot}H_2O$. The best results were obtained by treating compound **19** with Et_3N in methanol at 50 °C. After the reaction reached equilibrium, leucosceptroid B was obtained in 21 % yield (or 60 % yield based on recovered **19**). All characterization data of our synthetically obtained leucosceptroid B are in agreement with the data reported for the natural compound.[16] Our synthesis demonstrates that leucosceptroid B with a *cis,trans*-fused 5/6/5 tricycle is indeed not as thermodynamically stable as its C11 epimer with a *cis,cis*-fused tricycle, in agreement with previous work.[4] This is another curious example showing that Nature does not always prefer the more stable isomer in biosynthesis.

In conclusion, we report here the first asymmetric total synthesis of leucosceptroid B, which paves the way for the chemical synthesis of other siblings in this fascinating family.

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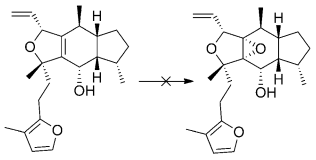

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