Terpenoids

DOI: 10.1002/anie.201410134

# Total Synthesis of Leucosceptroids A and B**

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***Abstract:*** *Leucosceptroids A and B are sesterterpenoids with potent antifeedant and antifungal activities. A more efficient gram-scale total synthesis of leucosceptroid B and the first total synthesis of leucosceptroid A are presented. The key transformations include an aldol reaction between a substituted dihydrofuranone and an (S)-citronellal-derived aldehyde, a $SmI_2$-mediated intramolecular ketyl–olefin radical cyclization, and final-stage alcohol oxidation.*

In 2010, Li and co-workers reported the isolation of leucosceptroids A and B (Figure 1) from glandilar trichomes of *Leucosceptrum canum*. Preliminary biological evaluation revealed that these two sesterterpenoids have potent antifeedant activity (against the beet armyeorm and cotton bollworm) and antifungal effects (against four strains of agricultural pathogenic fungi, including *Colletotrichum musae* and *Rhizoctonia solani*).[1] In the following years, several additional structurally related sesterterpenoids were isolated by the same group from *Leucosceptrum canum* and *Colquhounia coccinea* var. *mollis,* and these were named leucosceptroids C–O,[2] colquhounoids A–C,[3] and norleucosceptroids A–C.[4] Most of these show significant antifeedant activity, which could explain why the corresponding plant is rarely attacked by herbivores and only occasionally by pathogens. This finding may shed new light on crop protection, and these sesterterpenoids could serve as lead compounds for developing conceptually novel pesticides.

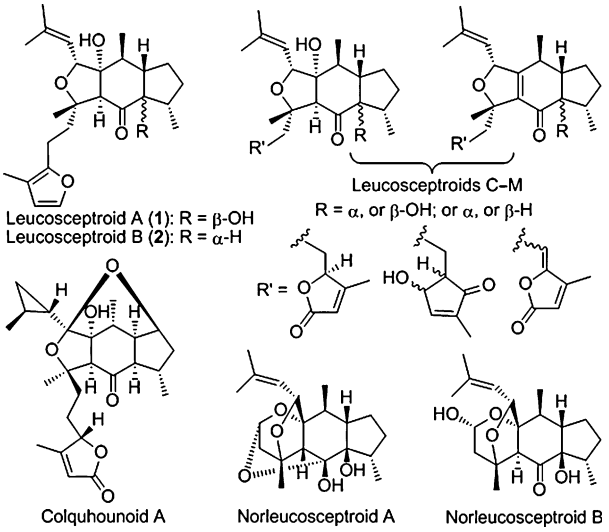


***Figure 1.*** Structures of the leucosceptroids and related sesterterpenoids.

The interesting chemical structures and biological activities of the leucosceptroids and related sesterterpenoids attracted the immediate attention of the synthetic community. In 2011, the Horne group reported synthetic studies toward the core structure of leucosceptroids A–D, with the employment of an intramolecular Diels–Alder reaction to install the fused tricyclic hydrindane ring system.[5] Two years later, Liu and co-workers achieved the first total synthesis of leucosceptroid B in 2.7% overall yield from commerically unavailable (*S*)-5-methyl-5,6-dihydro-2*H*-pyran-2-one.[6] Recently, Magauer and Hugelshofer accomplished the first total synthesis of norleucosceptroids A and B.[7] Herein, we describe a more efficient and scalable route for assembling leucosceptroid B and the first total synthesis of leucosceptroid A.

As outlined in Figure 2, we assumed that **1** could be elaborated from **2** through deprotonation and oxidation. The *trans*-hydrindanone skeleton in **2** offers an additional synthetic challenge because the corresponding *cis* isomer may be the more stable one and the energetic difference between these two isomers is quite low.[8] Indeed, poor conversion for epimerization of the *cis* isomer **2** greatly reduced the synthetic efficiency in the leucosceptroid B synthesis developed by Liu and co-workers.[6] To avoid this problem of isomerization, we planned to obtain a *trans*-hydrindanol intermediate first and

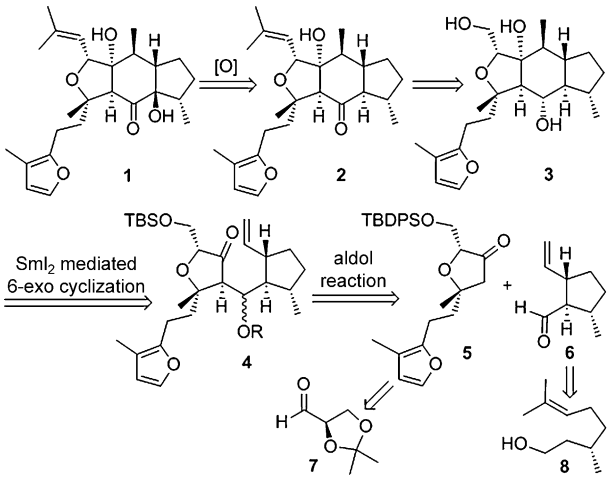


***Figure 2.*** Retrosynthetic analysis of leucosceptroids A and B.

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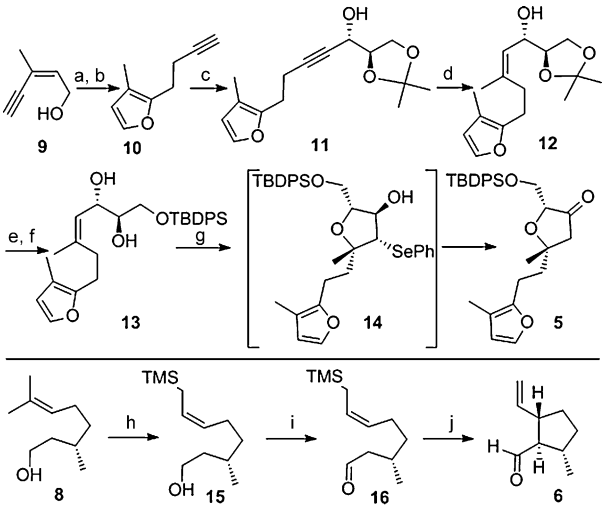
[**] We are grateful to the National Basic Research Program of China (973 Program, grant 2010CB833200), Chinese Academy of Sciences and the National Natural Science Foundation of China (grant 21132008 & 20921091) for their financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201410134.

subsequently convert it into **2** at the final step. Consequently, triol **3,** which could be assembled by a $SmI_2$-mediated 6-*exo* cyclization of ketone **4**, became our next synthetic target . The installation of **4** could be achieved by an aldol reaction of dihydrofuranone **5** and aldehyde **6**, which could be prepared by using aldehyde **7** and (*S*)-citronellal (**8**), respectively, as the chiral pools.

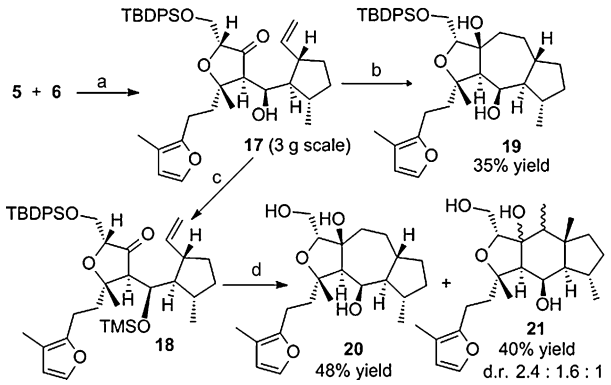
We commenced our total synthesis by assembling the required dihydrofuranone **5** and aldehyde **6** (Scheme 1). The




***Scheme 1.*** Reagents and conditions: a) EtMgBr, CuCl, 50 °C, then 3-bromoprop-1-yne; b) $AuPPh_3Cl$, AgOTf, 85 % for 2 steps; c) *n*BuLi, THF, −78 °C, then $(iPrO)_3TiCl$; then (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **7**, 78 %; d) $Fe(acac)_3$, MeMgBr, THF, 85 %; e) Dowex 50 W/$H^+$ acid resin, MeOH, 78 %; f) TBDPSCl, Imidazole, DMF, 88 %; g) PhSeCl, $K_2CO_3$, THF, −78 °C, then HOAc/NaOAc, $H_2O_2$, 78 %; h) $O_3$, MeOH, $Me_2S$, −78 °C then $Ph_3P{=}CHCH_2TMS$, 59 %; i) Dess–Martin periodinane, $CH_2Cl_2$, 87 %; j) 5 % (2*S*,6*S*)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazoildinone trifluoroactate, CAN, $NaHCO_3$, $H_2O$, DME, 89 %, d.r. = 33:2:1. THF = tetrahydrofuran, TBDPS = tert-butyldiphenylsilyl, DMF = *N*,*N*-dimethylformamide, TMS = trimethylsilyl, CAN = ceric ammonium nitrate, DME = 1,2-dimethoxyethane.

coupling of 3-bromoprop-1-yne and the cuprous salt generated from enynol **9** produced a diyne, which was treated with a gold catalyst in the presence of silver triflate to afford furan **10** in 85 % yield.[9] After the transformation of **10** into a titanium acetylide complex, Felkin–Anh addition of the aldehyde **7** was carried out to provide *anti*-adduct **11** in 78 % yield and with 7:1 diastereoselectivity.[10] Next, iron-catalyzed carbometalation of propargylic alcohol **11** with MeMgBr proceeded smoothly to deliver allyl alcohol **12**,[11] which was deprotected and the liberated primary alcohol reprotected with TBDPSCl to give diol **13**. Finally, PhSeCl-mediated cyclization of **13** led to the diastereoselective formation of substituted tetrahydrofuran **14**,[12,13] the structure of which was confirmed by X-ray crystallography. Without isolation, **14** could be directly oxidized with $H_2O_2$ to furnish dihydrofuranone **5** in 78 % yield. In a parallel procedure, (*S*)-citronellal (**8**) was subjected to oxidative cleavage and subsequent Wittig olefination to produce olefin **15**, which was converted into aldehyde **16** through DMP oxidation. Pleasingly, the intramolecular allylation of aldehyde **16** worked well according to MacMillan's SOMO-organocatalysis procedure,[14] delivering the aldehyde **6** in 89 % yield (6 g scale) and with high diasteroselectivity (33:2:1 for **6** and two other isomers).

We next investigated the aldol reaction of dihydrofuranone **5** with aldehyde **6**. Initially, we attempted to condense the lithium enolate of ketone **5** (with LiHMDS or LDA) with aldehyde **6** and found that no desired aldol product was produced, presumably because of the steric hindrance of the two reactants and the thermodynamically favored retroaldol reaction. After some experimenting, we discovered that treatment of ketone **5** with $(Hex)_2BCl$ and $Et_3N$ at −78 °C[15] followed by the addition of **6** gives the adduct **17** in 78 % yield and with high diastereoselectivity (13:1.5:1 for **17** and two other isomers; Scheme 2). The success of the aldol reaction under these conditions is ascribed to the stability of the




***Scheme 2.*** Reagents and conditions: a) $(Hex)_2BCl$, $NEt_3$, THF, −78 °C to 0 °C, 78 %; b) $SmI_2$, HMPA, THF, *t*BuOH; c) TMSCl, DMAP, imidazole, DMF, 90 %; d) $SmI_2$, HMPA, THF, $H_2O$, then HF·Py. HMPA = hexamethylphosphoramide, DMAP = 4-dimethylaminopyridine, Py = pyridine.

derived ketol borate complexes. With alcohol **17** in hand, the stage was set for the crucial $SmI_2$-mediated intramolecular ketyl–olefin radical cyclization.[16] Accordingly, we treated **17** with $SmI_2$ in THF/HMPA/*t*BuOH and obtained the 5/7/5 tricyclic compound **19**, together with some decomposed products. This result was rather unexpected because similar substrates have been reported to give 6-*exo* cyclization products.[16] We thought that this observation might result from the steric hindrance of the 6-membered ketyl ring unit that was generated from chelation of the $Sm^{III}$ cation by the β-hydroxyl group (conformer **A**, Figure 3), which might inhibit 6-*exo* cyclization and force the reaction to proceed through 7-*endo-trig* cyclization. Based on this assumption, we decided to protect the free hydroxyl group with TMS. After treatment of the resulting silyl ether **18** with $SmI_2$ and subsequent desilylation, we found that the reaction still gave the 7-*endo-trig* cyclization product **20**[13] as the major product, although the 6-*exo* cyclization product **21** could be isolated in 40 % yield and with poor diastereoselectivity (Scheme 2). Since the problem might be caused by strong repulsive interaction between the axial-orientated β-OTMS and the olefin moiety (conformer **B**, Figure 3), we speculated that if ketone **22**, which has an α-OTMS unit, was used, cyclization

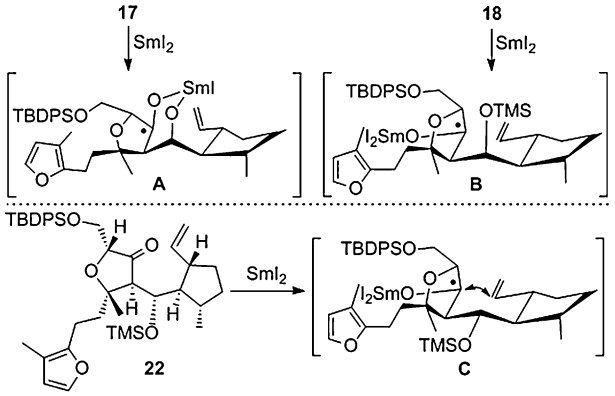
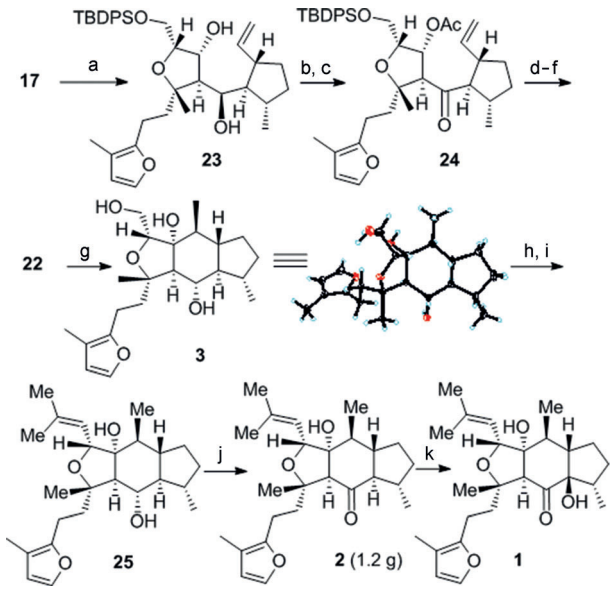



***Figure 3.*** Possible stereochemical outcomes for $SmI_2$-mediated cyclization.

might proceed through conformer **C**, in which the OTMS group in the equatorial position would not affect the 6-*exo* cyclization. Furthermore, this conformer would give the product with correct stereochemistry for synthesizing target molecules at the two newly created stereocenters.

With this idea in mind, we attempted to revise the stereochemistry of the aldol reaction step but we found that none of the desired α-hydroxyl product could be obtained under various conditions. We thus had to reach our goal indirectly, as demonstrated in Scheme 3. Reduction of **17** with $Me_4NB(OAc)_3H$ afforded diol **23**, which was subjected to regioselective acylation and subsequent oxidation of the remained hydroxyl group to produce ketone **24** in 69% overall yield. $LiBH_4$ reduction of **24** provided the alcohol with the desired stereochemistry and the resultant diol was selectively oxidized with IBX to deliver ketone **22** after protection with TMSCl. To our delight, the $SmI_2$-mediated cyclization of **22** worked well, producing the desired triol **3**[13] in 89% yield as a single product after desilylation. Finally, selective oxidation of the primary alcohol in **3** followed by Wittig olefination gave rise to diol **25**, which was converted into **2** through Swern oxidation. This route is scalable, as evident from the fact that more than 1.2 g of **2** could be obtained. Furthermore, regioselective α-hydroxylation (LDA, then $O_2$ and $P(OEt)_3$)[7,17] of **2** delivered leucosceptroid A in 60% yield.

In conclusion, by using a substituted dihydrofuranone and a (*S*)-citronellal-derived aldehyde, with an $SmI_2$-mediated intramolecular ketyl–olefin radical cyclization and final-stage alcohol oxidation as the key steps, we accomplished a more efficient and scalable synthesis of leucosceptroid B (5.6% overall yield for 18 linear steps from commercially available enynol **9**) and the first total synthesis of leucosceptroid A. Leucosceptroid B could serve as the starting material for synthesizing other members of the leucosceptroid family and our synthetic route could be used for assembling a wide range of leucosceptroid analogues. Our findings thus provide a basis for further structure–activity relationship (SAR) studies of these antifeedant compounds and the subsequent development of new pesticides.




***Scheme 3.*** Reagents and conditions: a) $Me_4NB(OAc)_3H$, AcOH, MeCN, 89%; b) DMAP, AcCl, pyridine; c) IBX, DMSO, 77% for 2 steps; d) $LiBH_4$, THF, 85%; e) IBX, DMSO; f) TMSCl, DMAP, imidazole, 62% for 2 steps; g) $SmI_2$, HMPA, $H_2O$, THF, then HF·Py, 89%; h) IBX, DMSO; i) *i*PrPPh$_3$I, *n*BuLi, THF, −78 °C to RT, 92% for 2 step; j) $(COCl)_2$, DMSO, DIPEA, toluene, −75 °C to RT, 80%;k) LDA, $O_2$, $P(OEt)_3$, −78 to −35 °C, 60%. IBX = 2-iodoxybenzoic acid, DMSO = dimethyl sulfoxide, DIPEA = *N*,*N*-diisopropylethylamine, LDA = lithium diisopropylamide. Crystal structure: red oxygen, blue hydrogen.

Received: October 16, 2014
Published online: December 3, 2014

**Keywords:** aldol reaction · cyclization · natural products · sesterterpenoids · total synthesis

[1] S.-H. Luo, Q. Luo, X.-M. Niu, M.-J. Xie, X. Zhao, B. Schneider, J. Gershenzon, S.-H. Li, *Angew. Chem. Int. Ed.* **2010**, *49*, 4471 – 4475; *Angew. Chem.* **2010**, *122*, 4573 – 4577.
[2] a) S.-H. Luo, L.-H. Weng, M.-J. Xie, X.-N. Li, J. Hua, X. Zhao, S.-H. Li, *Org. Lett.* **2011**, *13*, 1864 – 1867; b) S.-H. Luo, J. Hua, X.-M. Niu, Y. Liu, C.-H. Li, Y.-Y. Zhou, S.-X. Jing, X. Zhao, S.-H. Li, *Phytochemistry* **2013**, *86*, 29 – 35; c) S.-H. Luo, J. Hua, C.-H. Li, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Tetrahedron Lett.* **2013**, *54*, 235 – 237.
[3] C.-H. Li, S.-X. Jing, S.-H. Luo, W. Shi, J. Hua, Y. Liu, X.-N. Li, B. Schneider, J. Gershenzon, S.-H. Li, *Org. Lett.* **2013**, *15*, 1694 – 1697.
[4] S.-H. Luo, J. Hua, C.-H. Li, S.-X. Jing, Y. Liu, X.-N. Li, X. Zhao, S.-H. Li, *Org. Lett.* **2012**, *14*, 5768 – 5771.
[5] J. Xie, Y. Ma, D. A. Horne, *J. Org. Chem.* **2011**, *76*, 6169 – 6176.
[6] X. Huang, L. Song, J. Xu, G. Zhu, B. Liu, *Angew. Chem. Int. Ed.* **2013**, *52*, 952 – 955; *Angew. Chem.* **2013**, *125*, 986 – 989.
[7] C. L. Hugelshofer, T. Magauer, *Angew. Chem. Int. Ed.* **2014**, *53*, 11351 – 11355; *Angew. Chem.* **2014**, *126*, 11533 – 11537.
[8] a) H. L. Gordon, S. Freeman, T. Hudlicky, *Synlett* **2005**, 2911 – 2914; b) G. Yue, X. Huang, B. Liu, *Chin. J. Org. Chem.* **2013**, *33*, 1167.
[9] a) X. Du, F. Song, Y. Lu, H. Chen, Y. Liu, *Tetrahedron* **2009**, *65*, 1839 – 1845; b) C. H. Oh, H. J. Yi, K. H. Lee, *Bull. Korean Chem. Soc.* **2010**, *31*, 683 – 688; c) Y. Liu, F. Song, Z. Song, M. Liu, B. Yan, *Org. Lett.* **2005**, *7*, 5409 – 5412.
[10] a) M. Shimizu, M. Kawamoto, Y. Niwa, *Chem. Commun.* **1999**, 1151 – 1152; b) B. M. Trost, Z. T. Ball, T. Jöge, *Angew. Chem. Int.*

*Ed.* **2003**, *42*, 3415 – 3418; *Angew. Chem.* **2003**, *115*, 3537 – 3540; c) B. M. Trost, Z. T. Ball, K. M. Laemmerhold, *J. Am. Chem. Soc.* **2005**, *127*, 10028 – 10038.

[11] D. Zhang, J. M. Ready, *J. Am. Chem. Soc.* **2006**, *128*, 15050 – 15051.

[12] C. Rodríguez-Escrich, A. Olivella, F. Urpí, J. Vilarrasa, *Org. Lett.* **2007**, *9*, 989 – 992.

[13] CCDC 1028910, 1029134 and 1028909 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] a) R. J. Comito, F. G. Finelli, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 9358 – 9361; b) P. V. Pham, K. Ashton, D. W. C. MacMillan, *Chem. Sci.* **2011**, *2*, 1470 – 1473.

[15] a) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099 – 3111; b) D. A. Evans, B. Cote, P. J. Coleman, B. T. Connell, *J. Am. Chem. Soc.* **2003**, *125*, 10893 – 10898.

[16] a) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1992**, *57*, 3132 – 3139; b) G. A. Molander, J. A. McKie, *J. Org. Chem.* **1995**, *60*, 872 – 882; c) G. A. Molander, J. C. McWilliams, B. C. Noll, *J. Am. Chem. Soc.* **1997**, *119*, 1265 – 1276.

[17] a) E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908 – 6909; b) K. Simon, J. Wefer, E. Schöttner, T. Lindel, *Angew. Chem. Int. Ed.* **2012**, *51*, 10889 – 10892; *Angew. Chem.* **2012**, *124*, 11047 – 11050.