Terpenoid Synthesis

DOI: 10.1002/anie.201407788

A General Entry to Antifeedant Sesterterpenoids: Total Synthesis of (+)-Norleucosceptroid A, (−)-Norleucosceptroid B, and (−)-Leucosceptroid K**

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Dedicated to Professor Johann Mulzer and Professor Andrew G. Myers

Abstract: *The first asymmetric total synthesis of the antifeedant terpenoids (+)-norleucosceptroid A, (−)-norleucosceptroid B, and (−)-leucosceptroid K has been accomplished. This highly concise synthetic route was guided by our efforts to develop a platform for the collective synthesis of a whole family of antifeedant natural products. The synthesis features a Hauser–Kraus-type annulation followed by an unprecedented, highly efficient intramolecular dilactol aldol-type condensation reaction to produce the 5,6,5 skeleton. The developed synthetic route proceeds for norleucosceptroid A and B in 16 steps (longest linear sequence) from known compounds.*

The cotton bollworm (*Helicoverpa armigera*) and the beet armyworm (*Spodoptera exigua*) are among the most destructive agricultural pests in nature and they affect vegetables and other crops worldwide.[1] Protection against them has been achieved by the use of sex-pheromone traps, insecticides, and transgenic crops. However, resistance to insecticides has developed over the last decade and new chemical agents are necessary to prevent further crop damage from these pests. *Leucosceptrum canum* Smith ("Bird's Coca Cola tree")[2] and *Colquhounia coccinea* var. *mollisa,* plants found in China and Nepal, are remarkably resistant to herbivores and pathogens. Extraction and isolation of the trichomes, flowers, and whole leaves recently led to the discovery of novel sesterterpenoids, designated leucosesterterpenone and leucosesterlactone,[3] leucosceptroids A–O,[4] colquhounoids A–C,[5] and norleucosceptroids A–C, which are classified as pentanor-sesterterpenoids.[6] In general, these compounds display potent antifeedant activity against the cotton bollworm and the beet armyworm and are the first natural sesterterpenoids with biological activity against plant-feeding insects and pathogens. The concept of employing nontoxic antifeedant compounds to protect plants from insect herbivores could emerge as an alternative to conventional synthetic pesticides since the former exhibit high specificity, quick degradation, and lack of impact on nontarget organisms.[7]

The biological properties and novel chemical scaffolds of leucosceptroids and many other sesterterpenoids[8] make these natural products highly attractive targets for chemical synthesis. Recently, Liu and co-workers[9] disclosed the first total synthesis of leucosceptroid B, and Horne and co-workers[10] reported an approach to the core of the leucosceptroids. To date, a general and modifiable strategy that would allow the collective synthesis of this natural product class (comprising 23 members) is not yet available. Structurally, all members of the leucosceptroid family of natural products share a highly functionalized, synthetically challenging 5,6,5 framework that differs in the oxidation state at C11 (OH, H) and the substitution of the C14 ethyl linkage. These attributes were an essential consideration in our initial retrosynthetic analysis of the common ABC core structure and led us to focus on disconnection of the central six-membered ring.

Herein, we describe an enantioselective synthetic route to (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**) that proceeds through the convergent assembly of two building blocks of similar complexity (Scheme 1). Our initial synthetic target was fragment **4**, which could be traced back to **5** through disconnection of the substituents at C4, C5 and C6. The ABC tricycle **5** contains the full retron for a simplifying formal Diels–Alder reaction of the AB dienolate **6** and the C-ring butenolide **7**. We envisaged that both coupling partners could be accessed from simple, readily available building blocks.

In the forward sense, the absolute configuration of fragment **7** was set through a Sharpless asymmetric dihydroxylation reaction starting from **8** (Scheme 2).[11] As shown by Corey, the *p*-methoxyphenyl directing group determined the enantiofacial selectivity and was essential to provide **9** in high enantiomeric excess (> 97 % *ee*).[12] Oxidation of diol **9** using Parikh–Doering conditions[13] and homologation with Bestmann's ylide ($Ph_3P{=}C{=}C{=}O$)[14] formed the butenolide **7** in good overall yield.

The sequence for the preparation of **6** was initiated with the degradation of inexpensive (*R*)-pulegone (**10**)[15] accord-

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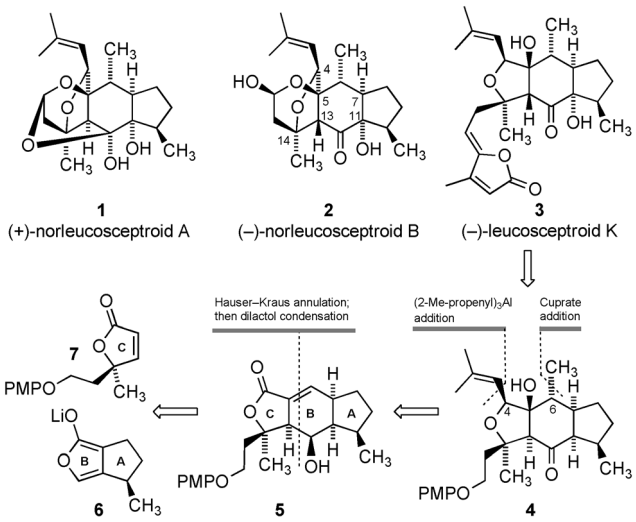
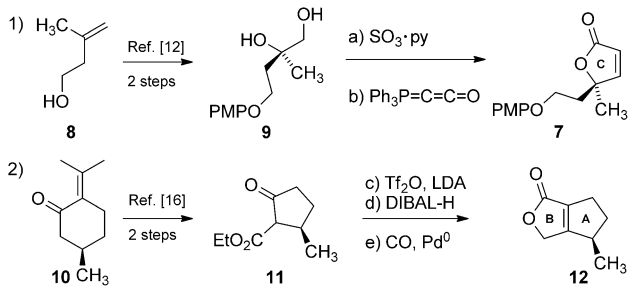
[**] We gratefully acknowledge financial support from the FCI (Liebig Fellowship to T.M. and Kekulé Mobility Fellowship to C.L.H.), the DFG (Emmy-Noether Fellowship to T. M.) and Prof. Dirk Trauner. We thank M. Sc. A. Ahlers and B. Sc. J. Tumpach for preliminary synthetic studies, Dr. Peter Mayer (LMU Munich) for determination of the X-ray structures, and Dr. David Barber, Dr. Jonathan Mortison, and Dr. Ian Seiple for helpful discussions during the preparation of this manuscript.

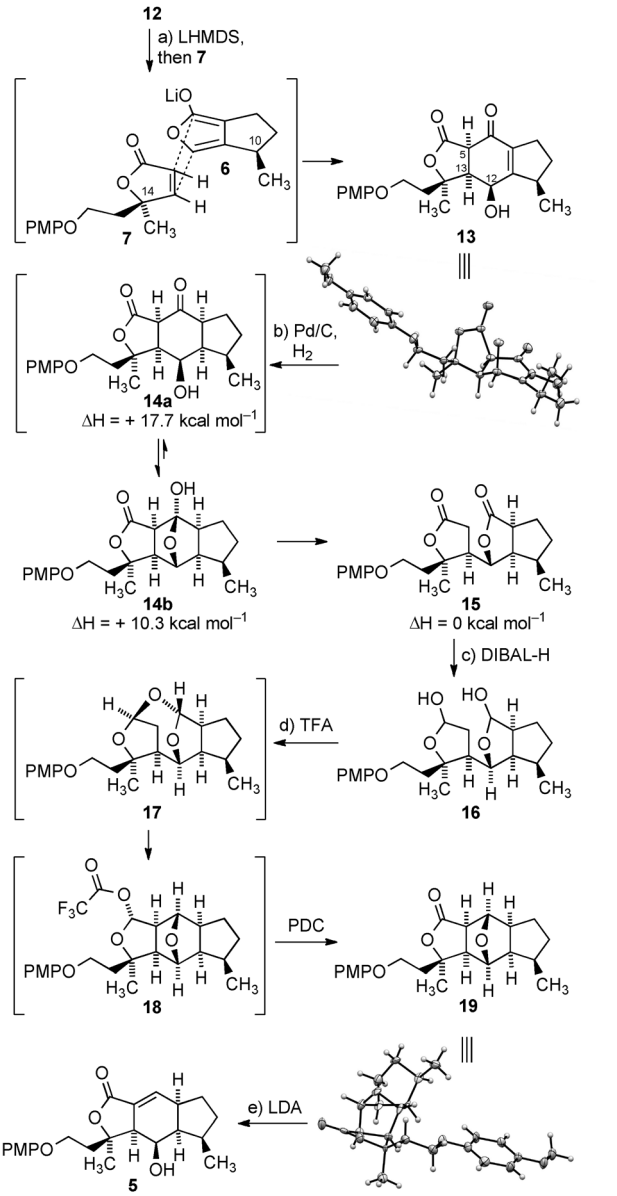
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201407788.



Scheme 1. Selected members of the leucosceptroids family of natural products: (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**); and retrosynthetic analysis. PMP = *p*-methoxyphenyl.



Scheme 2. 1) Preparation of C-ring butenolide **7**. Reagents and conditions: a) SO_3·pyridine, DMSO, NEt_3, CH_2Cl_2, 23 °C, 87%; b) $Ph_3P{=}C{=}C{=}O$, THF, 60 °C, 56%. 2) Preparation of AB segment **12**. Reagents and conditions: c) Tf_2O, LDA, THF, −78 °C to 0 °C; d) DIBAL-H, CH_2Cl_2, −78 °C to 23 °C, 58% over two steps; e) H_2SO_4/HCO_2H, $Pd(PPh_3)_4$, LiCl, $(nBu)_3N$, MeCN, 70 °C, 98%. DIBAL-H = diisobutylaluminium hydride, DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide.



Scheme 3. Fragment coupling to give the ABC tricycle **5**. Reagents and conditions: a) LHMDS, THF, then **7**, −78 °C to −30 °C, d.r. = 3:1; b) Pd/C, H_2, MeOH, 57% over two steps; c) DIBAL-H, CH_2Cl_2, −78 °C; d) TFA, CH_2Cl_2, 4 Å molecular sieves, 23 °C, then PDC, 23 °C; e) LDA, THF, −78 °C, 69% over three steps. LHMDS = lithium hexamethyldisilazane, PDC = pyridinium dichromate, TFA = trifluoroacetic acid.

ing to a reported procedure.[16] A combination of lithium diisopropylamide and triflic anhydride was superior to all other investigated conditions (KHMDS/Tf_2O; NEt_3/Tf_2O; DIPEA/Tf_2O; LDA/$PhNTf_2$; LDA/Comins' reagent) for the triflation of the known β-keto ester **11**. Selective reduction of the ester group was readily accomplished with diisobutylaluminium hydride to afford the allyl alcohol in 57% yield over two steps. Palladium(0)-catalyzed insertion of carbon monoxide,[17] generated in situ from the reaction of formic acid with sulfuric acid,[18] gave the AB bicycle **12** in 98% yield.

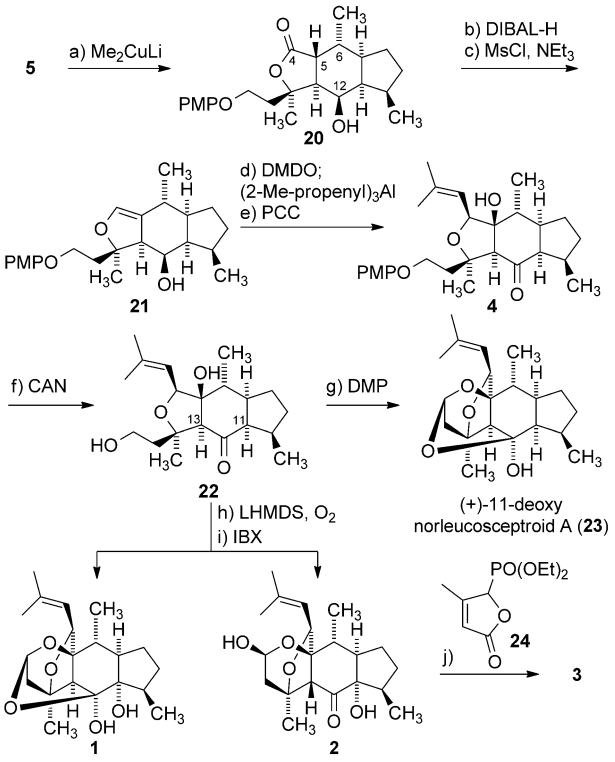
Having developed scalable routes to both ring fragments, we concentrated our efforts on uniting **7** and the AB component **12**-derived lithium isofuran-1-olate **6**, through a Hauser–Kraus-type annulation (Scheme 3).[19,20] Predicting that the reaction would proceed via the transition state shown in Scheme 3, we expected the stereochemical outcome depicted for the ABC tricycle **13**. Although the stereodiscriminating effect of the quaternary center at C14 in **7** was highly uncertain at this stage, we hypothesized that the methyl group at C10 of the AB segment **6** could reinforce the stereofacial selectivity by approaching **7** with its sterically less-hindered bottom face. Indeed, treatment of a solution of **6** in tetrahydrofuran, prepared from **12** using lithium hexamethyldisilazane (2.2 equiv), with equimolar amounts of **7** (−78 °C to −30 °C) led to the formation of enone **13** as a 3:1 mixture of diastereomers. The proposed structure and relative stereochemistry of **13** was unambiguously validated by single-crystal X-ray diffraction. It was necessary to employ excess base to trap **13** as the enolate in order to prevent a retro-Claisen reaction from occurring. The formation of the minor diastereomer can be rationalized by an *exo* approach of **6** from the

lower face of **7** to give the corresponding enone, which possesses the inverse stereochemistry at C5, C12, and C13 compared to **13**, as shown by NMR analysis. We also found that the use of degassed tetrahydrofuran for this transformation suppressed the formation of a *p*-hydroquinone byproduct (see the Supporting Information) and increased the yield of the reaction by approximately 20%.

Initial attempts to directly hydroxylate C5 and introduce the methyl group at C6 were unsuccessful since overoxidation prevailed. However, prior reduction of the enone allowed us to develop an alternative approach that avoided the aforementioned problem. Hydrogenation of **13**[21] using palladium on charcoal under 1 atm of hydrogen occurred exclusively from the convex side of the molecule. After prolonged reaction times or exposure of the crude reaction mixture to triethylamine, we isolated a product with ^{13}C NMR and IR spectra that did not correspond to the expected ketone **14a**. From a molecular model, we concluded that the free hydroxyl group at C12 was well disposed to form hemiacetal **14b**, which could in turn undergo a retro-Claisen condensation to give dilactone **15**. This reaction pathway was also supported by data obtained from density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory with the Gaussian 09 software suite.[22] Although ketone **14a** was never observed experimentally, the intermediate **14b** could be obtained as a single compound and fully characterized. As above, upon exposure of hemiacetal **14b** to mildly basic (NEt_3) or acidic (silica gel) conditions, clean transformation to **15** was observed. To date, more than 4.7 g of dilactone **15** have been prepared in a single batch.

This rather unexpected reaction outcome was taken as a chance to reform the 5,6,5 framework by developing an unprecedented intramolecular dilactol aldol-type condensation within a complex molecular setting.[23] The synthesis of the required dilactol motif through a twofold reduction of **15** (DIBAL-H, CH_2Cl_2, −78 °C) was highly efficient and gave **16** as a mixture of four diastereomers. Careful screening of the reaction parameters (solvent, temperature, reagent) was necessary to realize the intended one-pot condensation–oxidation sequence to give **19**. The optimized procedure involved treating a solution of dilactol **16** in dichloromethane containing 4 Å molecular sieves with trifluoroacetic acid (5 equiv) at 23 °C for 20 min, followed by the addition of pyridinium dichromate to the intermediate 4-*O*-trifluoroacetyl acetal **18**.[24] This afforded the tetracycle **19** as a single diastereomer, the structure of which was unambiguously confirmed by single-crystal X-ray diffraction. Excess acid was required to prevent the reaction from stalling after the intramolecular acetalization of **16** to **17**. The most efficient conditions for the opening of the ether bridge involved the addition of lithium diisopropylamide (1.15 equiv) to a solution of **19** in tetrahydrofuran at −78 °C, which afforded more than 3.0 g of α,β-unsaturated lactone **5** (69% yield over three steps).

Conjugate addition of excess dimethyl cuprate to **5** occurred with excellent diastereoselectivity at C6 and gave rise to **20** as an inconsequential 4:1 mixture of kinetic and thermodynamic epimers at C5 (Scheme 4). Since direct α-hydroxylation followed by lactone reduction proved to be



Scheme 4. Functionalization of the leucosceptroids ABC core and total synthesis of (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**). Reagents and conditions: a) MeLi, CuI, Et_2O, −45 °C to −5 °C, 76%; b) DIBAL-H, CH_2Cl_2, −78 °C; c) MsCl, NEt_3, 1,2-dichloroethane, 75 °C, 53% over two steps; d) DMDO, acetone, CH_2Cl_2, −78 °C to −30 °C, then $AlCl_3$, 2-methyl-1-propenylmagnesium bromide, THF, CH_2Cl_2, −78 °C, 52%; e) PCC, CH_2Cl_2, 4 Å molecular sieves, 23 °C, 87%; f) CAN, pyridine, MeCN, H_2O, 0 °C, 70%; g) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 66%; h) LHMDS, O_2, $P(OEt)_3$, −78 °C to −35 °C; i) IBX, DMSO, 23 °C, 40% **1** and 10% **2** over two steps; j) **24**, KO*t*Bu, THF, 0 °C, then **2**, 0 °C to 23 °C, 70%. CAN = ceric ammonium nitrate, DMDO = dimethyldioxirane, DMP = Dess–Martin periodinane, IBX = 2-iodoxybenzoic acid, MsCl = methanesulfonyl chloride, PCC = pyridinium chlorochromate.

unsuccessful, we envisioned introduction of the C5 hydroxy group via enol ether **21**. The addition of triethylamine (7.5 equiv) to a solution of the crude lactol, derived from **20** by DIBAL-H reduction, and methanesulfonyl chloride (3.5 equiv) in dichloroethane at 75 °C provided **21** in a reproducible manner. These reaction conditions reduced formation of the acetal byproduct that resulted from attack of the C12 hydroxy group on C4 (see the Supporting Information). The epoxide obtained from the reaction of **21** with a solution of dimethyldioxirane in acetone, prepared by the method developed by Taber et al.,[25] was found to be highly unstable and was readily hydrolyzed to the corresponding lactol. We found that the addition of the crude epoxide product as a solution in dichloromethane to a large excess of tris-(2-methyl-1-propenyl) aluminum[26] in tetrahydrofuran at −78 °C delivered the required vinylic appendage from the same side as the epoxide to give the configuration at C4 and C5 depicted in **4**. The observed stereoselectivity of this transformation was attributed to coordination of the organoaluminum reagent to the epoxide to give the alanate and concomitant internal

delivery of the propenyl nucleophile. Introduction of the vinylic appendage at C4 occurred with opposite stereoselectivity when a combination of copper(I) iodide and 2-methyl-1-propenylmagnesium bromide was applied in the analogous reaction.[27]

Subsequent oxidation of the sterically hindered alcohol produced the configurationally stable ketone **4**. We found that H11 and H13 of **4** do not epimerize under basic conditions at 23 °C, however, since the β-hydroxy ketone is perfectly aligned for an E2 elimination, dehydration takes place under more forcing conditions (NEt_3, MeOH, 45 °C). Although *cis*-hydrindanones were calculated to be thermodynamically more stable,[28] and as is corroborated by the structures of most leucosceptroid natural products, (+)-norleucosceptroid A (**1**) features an AB-*cis*-BC-*trans* fusion in which intramolecular hemiacetal formation preserves this conformation from epimerization to the AB-*cis*-BC-*cis* system.

Cleavage of the *p*-methoxyphenyl ether in **4** with ceric(IV) ammonium nitrate followed by oxidation of the primary alcohol **22** with Dess–Martin periodinane afforded (+)-11-deoxynorleucosceptroid A (**23**), which has not yet been isolated from natural sources.[29] Regioselective α-hydroxylation (LHMDS, O_2, $P(OEt)_3$)[30] of **22** afforded two C11 hydroxylated products, which were directly oxidized under mild conditions (IBX, DMSO)[31] without prior purification. NMR analysis of the resulting product mixture revealed that α-hydroxylation had occurred with high stereoselectivity. However, we also recognized that partial epimerization of H13 to the thermodynamically more stable AB-*cis*-BC-*cis* fusion had spontaneously taken place during the α-hydroxylation step. Column chromatography on silica gel thus gave (+)-norleucosceptroid A (**1**), as well as minor amounts of (−)-norleucosceptroid B (**2**). Finally, the union of **2** with phosphonate **24**[32] gave rise to (−)-leucosceptroid K (**3**) in 70 % yield. The spectroscopic data (^1H and ^{13}C NMR, HRMS, $[\alpha]_D$) for **1**–**3**, which are the unnatural enantiomers, were in full agreement with those reported for the naturally occurring substances.

In summary, a general enantioselective synthesis of antifeedant (pentanor-)sesterterpenoids has been developed. This enabled the preparation of three representative antifeedant leucosceptroids; (+)-norleucosceptroid A (**1**), (−)-norleucosceptroid B (**2**), and (−)-leucosceptroid K (**3**); in a convergent manner with a high level of efficiency. The ability to prepare the ABC tricycle **5** on a multigram scale (3.0 g) paves the way for the synthesis of the remaining leucosceptroids. This work also highlights the fact that the intramolecular aldol condensation of dilactols could be a useful method for organic synthesis. A collective synthesis of the leucosceptroid family and unnatural derivatives thereof is currently underway in our laboratories.

Received: July 31, 2014
Published online: September 4, 2014

Keywords: Claisen reaction · leucosceptroids · natural products · terpenoids · total synthesis

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