Natural Products

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Total Syntheses of (−)-Acutumine and (−)-Dechloroacutumine**

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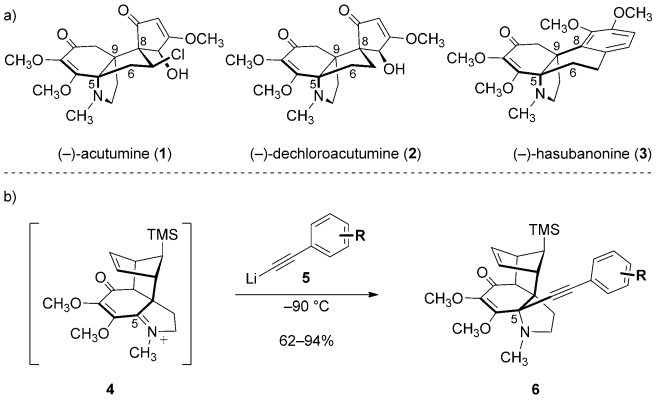
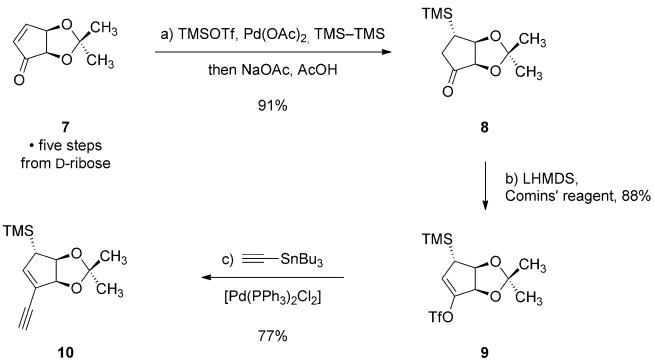
(−)-Acutumine (**1**) is a tetracyclic alkaloid that was first obtained from the roots of *Sinomenium acutum* by Goto and Sudzuki in 1929 (Scheme 1 a).[1] The related metabolite (−)-dechloroacutumine (**2**) was isolated from a chlorine-deficient culture of *Menispermum dauricum* in 1998.[2] The acutumines share some structural homology to the hasubanan alkaloids (e.g., (−)-hasubanonine (**3**)), which are produced by plants of the genus *Stephania*.[3] The stereogenic, heavily oxidized spirocyclopentenone rings of **1** and **2**, dense array of heteroatom-containing functional groups, and secondary alkyl chloride functional group of **1** define these metabolites as challenging targets for synthesis. Additionally, (−)-acutumine (**1**) inhibits human T-cell proliferation[4] and improves object and social recognition in the Wistar rat model,[5] yet the mechanisms underlying these phenotypes have not been elucidated. Although many groups have initiated studies toward the synthesis of (−)-acutumine (**1**),[6] only a single complete route has been reported, in a landmark publication by Castle and co-workers.[7] Studies toward the synthesis of (−)-dechloroacutumine (**2**) have not been described, to our knowledge.

Herein we disclose a concise, unified pathway to (−)-acutumine (**1**) and (−)-dechloroacutumine (**2**). Our routes build on our syntheses of various hasubanan alkaloids, including (−)-hasubanonine (**3**).[8,9] Central to the success of this earlier work was the stereoselective and site-selective addition of arylacetylide nucleophiles (represented by the generalized structure **5**; Scheme 1 b) to the complex, thermally unstable iminium ion **4** (formed in situ by N-methylation of the corresponding imine at −60 °C). A similar strategy could conceivably be employed to form the C5–C6 bond in **1** and **2**, however a number of additional issues complicated this approach. First, our hasubanan studies did not readily accommodate the chloride substituent (or a suitable handle) of (–)-acutumine (**1**). In addition, this work did not establish methods for the stereoselective construction of the C8–C9 bonds of **1** and **2** (in our hasubanan work, this bond was formed by an electrophilic aromatic substitution reaction, see Ref. [8]). An additional issue involved identification of a suitable precursor to the stereogenic, highly oxidized spirocyclopentenone ring of the targets.



Scheme 1. a) Structures of (−)-acutumine (**1**), (−)-dechloroacutumine (**2**), and (−)-hasubanonine (**3**). b) Addition of the arylacetylide **5** to the iminium ion **4** to form the 1,2-addition product **6**.

Ultimately, the spirocyclopentenone ring was derived from the acetonide **7**, itself prepared in five steps and > 10 g scale from D-ribose (Scheme 2).[10] Palladium-catalyzed 1,4-disilylation,[11] followed by in situ cleavage of the resulting enoxysilane (not shown), formed the β-trimethylsilyl ketone **8** as a single detectable *exo* diastereomer (91 %; ^{1}H and NOE NMR analysis). Deprotonation with lithium bis(trimethylsilyl)amide and trapping of the resulting enolate with *N*,*N*-bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine (Comins reagent)[12] generated the vinyl triflate **9** (88 %).



Scheme 2. Synthesis of the enyne **10**. Reaction conditions: a) TMSOTf, $Pd(OAc)_2$, TMS–TMS, $PhCH_3$, 0 °C, then NaOAc, then AcOH, 91 %. b) LHMDS, Comins reagent, THF, −78→0 °C, 88 %. c) Ethynyl tributylstannane, $[Pd(PPh_3)_2Cl_2]$, LiCl, THF, 24 °C, 77 %. LHMDS = lithium bis(trimethylsilyl)amide, THF = tetrahydrofuran, TMS = trimethylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

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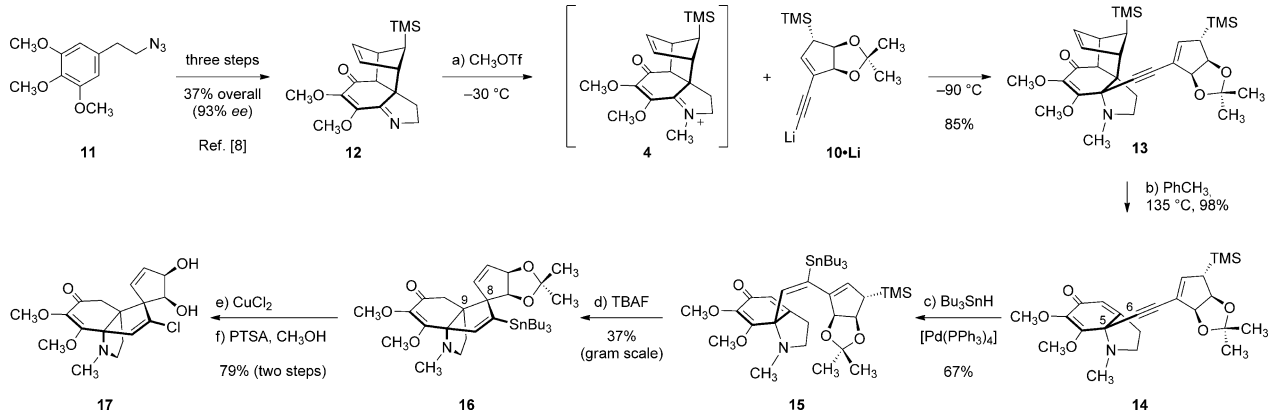
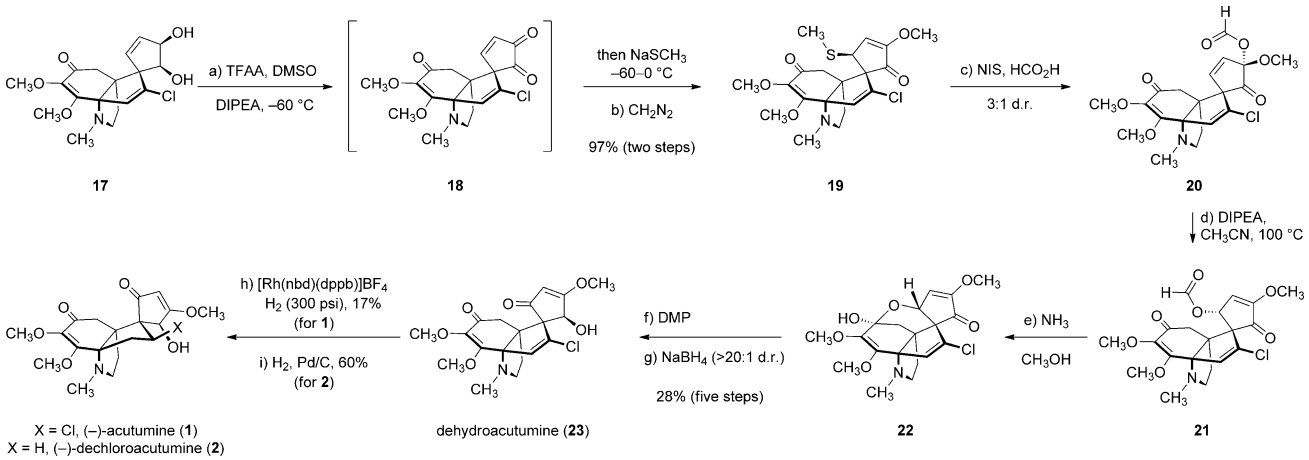


Scheme 3. Synthesis of the diol **17**. Reaction conditions: a) CH_3OTf, THF, −78→−30→−90 °C, then **10·Li**, −90→24 °C, 85 %. b) $PhCH_3$, 135 °C, 98 %. c) Bu_3SnH, $[Pd(PPh_3)_4]$, THF, 24 °C, 67 %. d) TBAF, DMF, −10 °C, 37 %. e) $CuCl_2$, THF, 24 °C, 83 %. f) PTSA, H_2O, CH_3OH, 60 °C, 95 %. CH_3OTf = methyl triflate, DMF = *N*,*N*-dimethylformamide, PTSA = *para*-toluenesulfonic acid, TBAF = tetrabutylammonium fluoride.

Stille coupling with ethynyl tributylstannane as the nucleophile provided the key enyne **10** (77 %).

The tetracyclic imine **12** was obtained in three steps, 93 % *ee*, and 37 % overall yield from the aryl azide **11**, as previously described (Scheme 3).[8] Treatment of **12** with methyl triflate (−30 °C) to form the *N*-methyliminium ion **4**, followed by cooling to −90 °C and addition of the lithium acetylide **10·Li** (generated by deprotonation of **10** with *n*-butyllithium at −78 °C) provided the 1,2-addition product **13** as a single diastereomer (85 %, ^{1}H NMR analysis).[13] Thermal extrusion of the silylcyclopentene fragment (toluene, 135 °C) produced the cyclohexanedienone **14** (98 %). Palladium-catalyzed regio- and stereoselective hydrostannylation (*tri*-butyltin hydride, tetrakis(triphenylphosphine)palladium)[14] then formed the vinyl stannane **15** (67 %). Activation of the allylic silane functional group of **15** (tetrabutylammonium fluoride) induced a Hosomi–Sakurai allylation,[15] to yield the tetracycle **16** as a single detectable diastereomer (37 %, ^{1}H NMR analysis). Although the yield of this transformation is modest, it was readily conducted on > 1 g scale, and was singularly successful among many other strategies investigated (see below). Copper-mediated chlorodestannylation[16] (cupric chloride), followed by removal of the acetonide (*p*-toluenesulfonic acid, aqueous methanol), provided the diol **17** (79 %, two steps).

Extensive experimentation was required to develop a pathway to convert the advanced diol **17** into the target compounds. First, the diol **17** was exhaustively oxidized[17] (trifluoroacetic anhydride, methyl sulfoxide, *N*,*N*-diisopropylethylamine, −60 °C, Scheme 4) to the enedione **18**. The enedione **18** could be isolated, but in practice was trapped in situ by 1,4-addition of sodium thiomethoxide. O-Methylation (diazomethane) of the unpurified addition product provided the methyl ether **19** as a single detectable diastereomer (97 %, two steps, ^{1}H NMR analysis). Treatment of **19** with *N*-iodosuccinimide and formic acid resulted in oxidative elimination of the methanethiol substituent and 1,2-addition to a putative oxocarbenium ion (not shown), to generate the



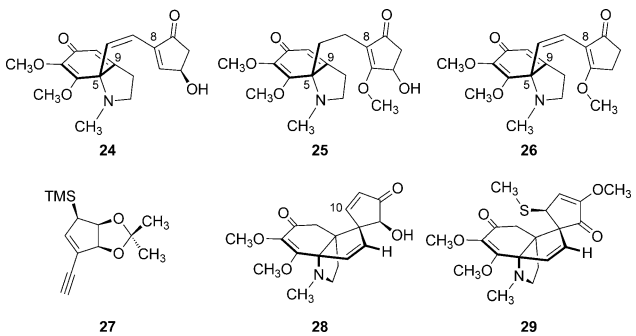
Scheme 4. Completion of the syntheses of (−)-acutumine (**1**) and (−)-dechloroacutumine (**2**). Reaction conditions: a) TFAA, DMSO, CH_2Cl_2, −60 °C, then DIPEA, then $NaSCH_3$, CH_3OH, −60→0 °C. b) CH_2N_2 in ether, THF, 24 °C, 97 % (two steps). c) NIS, HCO_2H, CH_2Cl_2, 0→24 °C. d) DIPEA, CH_3CN, 100 °C. e) NH_3, CH_3OH, 0 °C. f) DMP, CH_2Cl_2, 24 °C. g) $NaBH_4$, EtOH, 0 °C, 28 % (five steps). h) $[Rh(nbd)(dppb)]BF_4$, H_2 (300 psi), DCE, 24 °C, 17 %. i) H_2, Pd/C, CH_3OH, 24 °C, 60 %. DCE = 1,2-dichloroethane, dppb = 1,4-bis(diphenylphosphino)butane, DIPEA = *N*,*N*-diisopropylethylamine, DMP = Dess–Martin periodinane, DMSO = methyl sulfoxide, nbd = 2,5-norbornadiene, NIS = *N*-iodosuccinimide, TFAA = trifluoroacetic anhydride.

addition product **20** (3:1 d.r.).[18] Thermolysis of **20** (*N*,*N*-diisopropylethylamine, acetonitrile, 100 °C) induced [3,3]-rearrangement[19] to provide the formate **21**. The formyl group was cleaved (ammonia, methanol) to produce the hemiketal **22**. Oxidation of **22** (Dess–Martin periodinane)[20] formed a vinylogous α-diketone (not shown) that was selectively reduced (sodium borohydride, ethanol, >20:1 d.r., ^{1}H NMR analysis) to yield the penultimate intermediate dehydroacutumine (**23**, 28% over five steps). Homogeneous hydrogenation[21] of **23** ([Rh(nbd)(dppb)]BF_4, 300 psi H_2) provided synthetic (−)-acutumine (**1**, 17%), which was identical to a natural sample[22] by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, HRMS, TLC in eight solvent systems, UPLC/MS coinjection, and optical rotation. Alternatively, heterogeneous hydrogenation of **23** (H_2, Pd/C) provided synthetic (−)-dechloroacutumine (**2**, 60%), which was identical to natural material[2] by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, HRMS, and optical rotation.

Several steps in these sequences are worthy of additional comment. Acetylide-based nucleophiles were uniquely effective in the iminium ion addition step (**4**→**13**). Alkyl, allyl, and vinyl-based nucleophiles undergo 1,2-addition to the carbonyl group, cleave the *N*-methyl substituent of **4**, or lead to intractable mixtures of decomposition products.

The selectivity of the hydrostannylation step (**14**→**15**) is attributed to more favorable insertion of the alkyne **14** into a palladium hydride to form an intermediate with η^3-allyl character. The steric congestion arising from the fully substituted C5 atom in **14** may also disfavor palladium–carbon bond formation at the 6-position. Attempts to chlorodestannylate the cyclization precursor **15** led to erosion of the exocyclic olefin stereochemistry.

Many different intermediates were examined as substrates for construction of the C8–C9 bond; a selection of these are shown in Scheme 5. These studies revealed a close relationship between the nucleophilicity of the cyclopentenone ring and the products formed. For example, attempts to trigger ring closure by 1,4-addition to the cyclopentenone **24** led to products arising from cleavage of the C5–N bond and aromatization of the cyclohexanedienone. Alternatively, the β-methoxyenone groups of **25** and **26** were not sufficiently nucleophilic to initiate ring closure (thermal or Lewis acid activation). The preference for an *anti* arrangement of the carbon–silicon bond and the electrophile in Hosomi–Sakurai allylations is well-known.[15b] Accordingly, we prepared the *endo*-trimethylsilyl enyne **27** (Scheme 5); however the cyclization precursor derived from **27** underwent ring closure with similar efficiency (30%), thus suggesting other factors may influence the efficiency of this transformation.



Scheme 5. Key intermediates that contributed to the development of the successful syntheses.

The oxidation of **17** to the enedione **18** was attempted only after extensive efforts to effect nucleophilic addition to the C10 position of the dechloroenone **28** (Scheme 5; formed by selective allylic oxidation of the corresponding diol) failed. Oxygen-based nucleophiles (e.g., sodium hydrogen peroxide, various carboxylate salts, primary alcohols, and water) did not add to **28**, and sulfur-based adducts (formed by addition of thiophenol or butanethiol) reverted to **28** on attempted S-functionalization. Presumably, the vicinal dicarbonyl functional group of **18** lowers the kinetic barrier to formation and increases the thermodynamic stability of the C10 addition products.

In exploratory studies, we found that the dechloro intermediate **29** (Scheme 5) underwent stereoretentive *ipso* substitution of the thiomethyl substituent on treatment with mercury acetate in formic acid. However, these conditions failed when applied to the chlorinated substrate **19**, and the oxidative substitution process we developed (**19**→**20**) proceeds with distinct stereo- and site-selectivity. These changes in selectivity may be due to shielding introduced by the chlorine atom; this shielding is apparent on inspection of molecular models, and this same effect also presumably leads to the favorable diastereoselectivity obtained in the borohydride reduction step. The remaining carbonyls in **23** are vinylogous esters, and this may underscore the site-selectivity in the reduction.

Finally, selective hydrogenations of vinyl halides to alkyl halides are known,[23] but are often accompanied by hydrodehalogenation. We found that (−)-acutumine (**1**) was formed exclusively at low conversions of dehydroacutumine (**23**, 17% yield of **1** at 30% conversion of **23**), and other hydrogenation isomers could not be detected (^{1}H NMR analysis). This result suggests that the reduction of **23** is directed by coordination of the amine and/or alcohol groups to the catalyst, as anticipated based on inspection of molecular models. Attempts to achieve higher conversions of **23** by using [Rh(nbd)(dppb)]BF_4, or application of a broad variety of heterogeneous catalysts, led to the formation of (−)-dechloroacutumine (**2**) exclusively.

In summary, we have described a concise and unified pathway to prepare (−)-acutumine (**1**) and (−)-dechloroacutumine (**2**). Notable features of the syntheses include the strategic application of 5-trimethylsilylcyclopentadiene as a stabilization and stereocontrol element, a stereo- and regioselective hydrostannylation of a complex enyne, a Hosomi–Sakurai cyclization to fom the two contiguous quaternary centers of the targets, utilization of an allylic formate rearrangement to establish the oxygenation pattern of the spirocyclopentenone rings, and execution of a selective hydrogenation to construct the alkyl chloride functional group of (−)-acutumine (**1**). The full scope of the chemistry developed in these syntheses, as well as application to other related natural products, will be reported in due course.

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