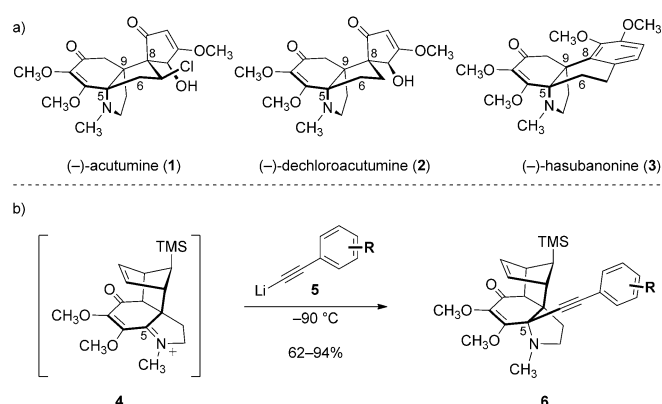


Total Syntheses of (–)-Acutumine and (–)-Dechloroacutumine**

Sandra M. King, Nicholas A. Calandra, and Seth B. Herzon*

(–)-Acutumine (**1**) is a tetracyclic alkaloid that was first obtained from the roots of *Sinomenium acutum* by Goto and Sudzuki in 1929 (Scheme 1a).^[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.

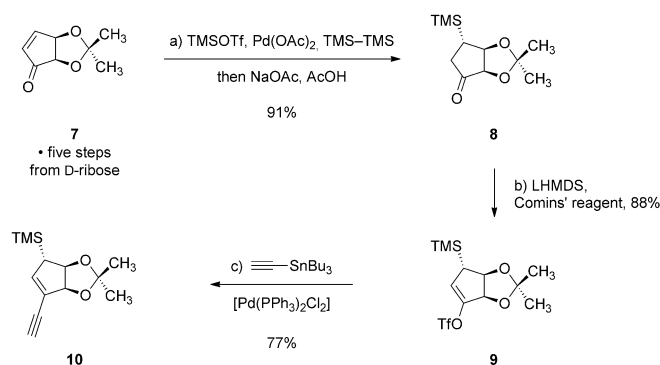
Herein we disclose a concise, unified pathway to (–)-acutumine (**1**) and (–)-dechloroacutumine (**2**). Our routes build on our syntheses of various hasubanan alkaloids, including (–)-hasubanonine (**3**).^[8,9] Central to the success of this earlier work was the stereoselective and site-selective addition of arylacetylide nucleophiles (represented by the generalized structure **5**; Scheme 1b) 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



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**.

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.

Ultimately, the spirocyclopentenone ring was derived from the acetone **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%; ¹H 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%).

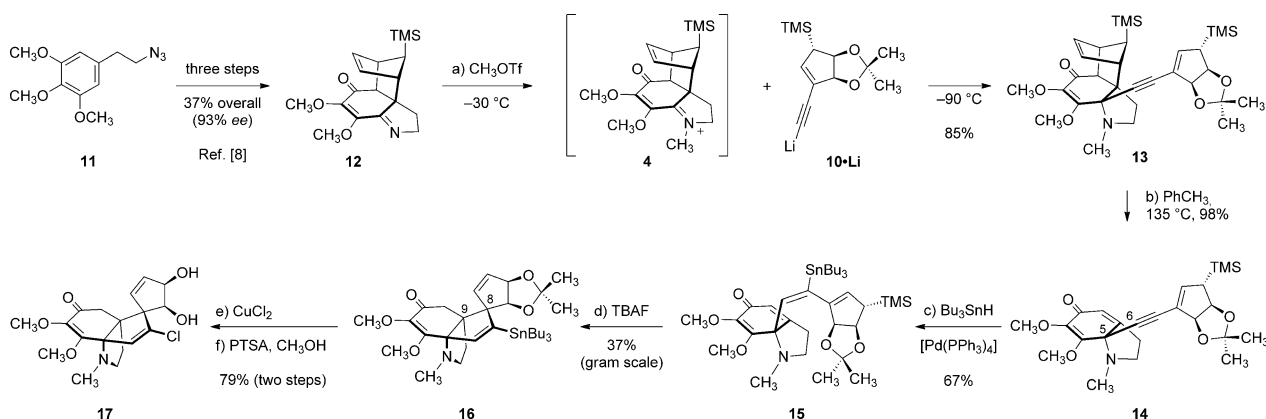


Scheme 2. Synthesis of the enyne **10**. Reaction conditions: a) TMSOTf, Pd(OAc)₂, TMS–TMS, PhCH₃, 0 °C, then NaOAc, then AcOH, 91%. b) LHMDS, Comins reagent, THF, –78 → 0 °C, 88%. c) Ethynyl tributylstannane, [Pd(PPh₃)₂Cl₂], LiCl, THF, 24 °C, 77%. LHMDS = lithium bis(trimethylsilyl)amide, THF = tetrahydrofuran, TMS = trimethylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

[*] S. M. King, N. A. Calandra, Dr. S. B. Herzon
Department of Chemistry, Yale University
225 Prospect Street, New Haven, CT 06520-8107 (USA)
E-mail: seth.herzon@yale.edu
Homepage: <http://www.chem.yale.edu/herzongroup>

[**] Financial support from the National Science Foundation (CHE-1151563), the Department of Defense (NDSEG fellowship to S.M.K.), the Division of Organic Chemistry of the American Chemical Society (Graduate Research Fellowship to N.A.C., sponsored by Boehringer Ingelheim), the Searle Scholars Program, and Yale University is gratefully acknowledged. S.B.H. is a fellow of the Alfred P. Sloan and David and Lucile Packard Foundations, and is a Camille Dreyfus Teacher-Scholar.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201210076>.



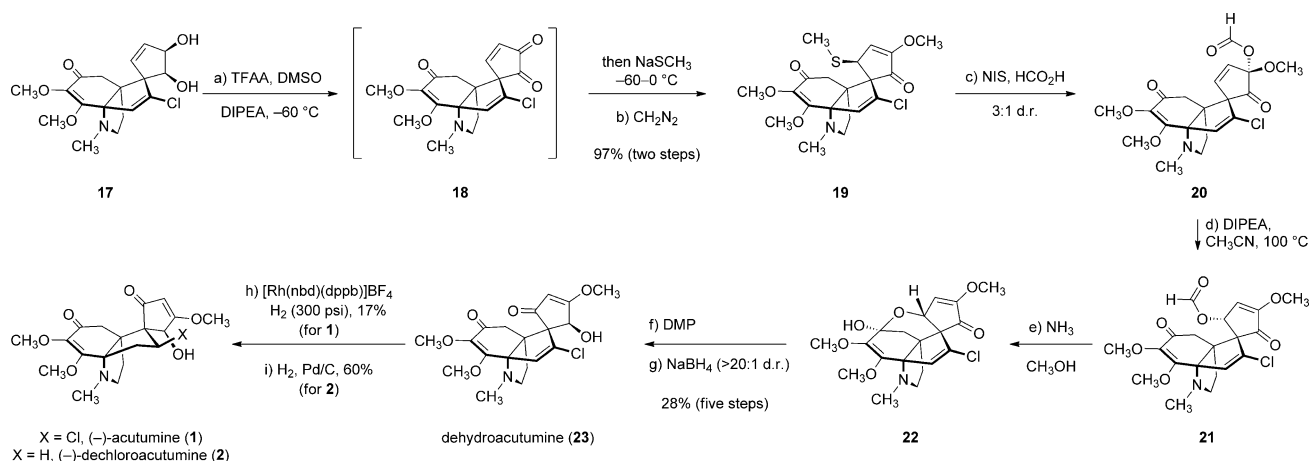
Scheme 3. Synthesis of the diol **17**. Reaction conditions: a) CH_3OTf , THF, $-78 \rightarrow -30 \rightarrow -90^\circ\text{C}$, then **10-Li**, $-90 \rightarrow 24^\circ\text{C}$, 85%. b) PhCH_3 , 135°C , 98%. c) Bu_3SnH , $[\text{Pd}(\text{PPh}_3)_4]$, THF, 24°C , 67%. d) TBAF, DMF, -10°C , 37%. 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%, ^1H NMR analysis).^[13] Thermal extrusion of the silylcyclopentene fragment (toluene, 135°C) produced the cyclohexanediene **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%, ^1H 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 acetone (*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, ^1H 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 , $-60 \rightarrow 0^\circ\text{C}$. b) CH_2N_2 in ether, THF, 24°C , 97% (two steps). c) NIS, HCO_2H , CH_2Cl_2 , $0 \rightarrow 24^\circ\text{C}$. 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) $[\text{Rh}(\text{nbd})(\text{dppb})]\text{BF}_4$, 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., ¹H NMR analysis) to yield the penultimate intermediate dehydroacutumine (**23**, 28 % over five steps). Homogeneous hydrogenation^[21] of **23** ([Rh(nbd)(dppb)]BF₄, 300 psi H₂) provided synthetic (–)-acutumine (**1**, 17 %), which was identical to a natural sample^[22] by ¹H and ¹³C NMR spectroscopy, IR spectroscopy, HRMS, TLC in eight solvent systems, UPLC/MS coinjection, and optical rotation. Alternatively, heterogeneous hydrogenation of **23** (H₂, Pd/C) provided synthetic (–)-dechloroacutumine (**2**, 60 %), which was identical to natural material^[2] by ¹H and ¹³C 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 cyclohexanedieneone. 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

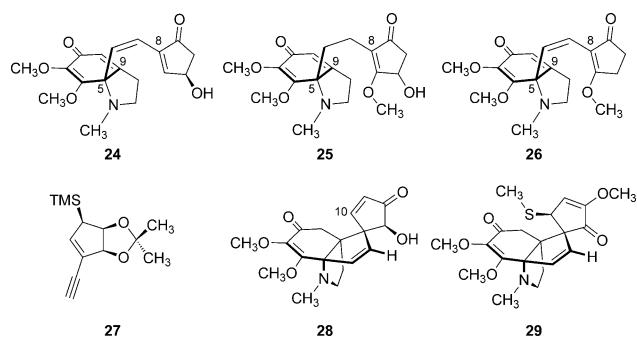
allylations is well-known.^[15b] Accordingly, we prepared the *endo*-trimethylsilyl enyne **27** (Scheme 5); however the cyclization precursor derived from **27** underwent ring closure with similar efficiency (30 %), thus suggesting other factors may influence the efficiency of this transformation.

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 (¹H 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)]BF₄, 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 form 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.



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

Received: December 17, 2012
Published online: February 20, 2013

Keywords: acutumine · alkaloids · dechloroacutumine · hydrogenation · total synthesis

- [1] a) K. Goto, H. Sudzuki, *Bull. Chem. Soc. Jpn.* **1929**, 4, 220; b) K. Goto, M. Tomita, Y. Okamoto, Y. Sasaki, K. Matoba, *Proc. Jpn. Acad.* **1966**, 42, 1181; c) K. Goto, M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, *Proc. Jpn. Acad.* **1967**, 43, 499; d) M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, K. Goto, *Tetrahedron Lett.* **1967**, 8, 2421; e) M. Tomita, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaki, K. Matoba, K. Goto, *Tetrahedron Lett.* **1967**, 8, 2425; for a review, see: f) Y. Sugimoto, R. Hori, in *Alkaloids: Properties, Applications and Pharmacological Effects* (Ed.: N. M. Cassiano), Nova Science Publishers, New York, **2010**, pp. 139.
- [2] a) Y. Sugimoto, S. Inanaga, M. Kato, T. Shimizu, T. Hakoshima, A. Isogai, *Phytochemistry* **1998**, 49, 1293; b) Y. Sugimoto, M. Matsui, H. Takikawa, M. Sasaki, M. Kato, *Phytochemistry* **2005**, 66, 2627.
- [3] Isolation of (–)-hasubanonine (**3**): a) M. Tomita, T. Ibuka, Y. Inubushi, Y. Watanabe, M. Matsui, *Tetrahedron Lett.* **1964**, 5, 2937; for reviews, see: b) M. Matsui in *The Alkaloids*, Vol. 33, Academic Press, New York, **1988**, p. 307; c) A. J. Pihko, A. M. P. Koskinen, *Tetrahedron* **2005**, 61, 8769.
- [4] B.-W. Yu, J.-Y. Chen, Y.-P. Wang, K.-F. Cheng, X.-Y. Li, G.-W. Qin, *Phytochemistry* **2002**, 61, 439.
- [5] “Acutumine and Acutumine Compounds Synthesis and Use”: G.-W. Qin, X.-C. Tang, P. Lestage, D.-H. Calgnard, P. Renard, US Patent 519,418, **2006**.
- [6] a) K. Matoba, N. Karibe, T. Yamazaki, *Chem. Pharm. Bull.* **1982**, 30, 3906; b) K. Matoba, N. Karibe, T. Yamazaki, *Chem. Pharm. Bull.* **1984**, 32, 2639; c) R. J. Moreau, E. J. Sorensen, *Tetrahedron* **2007**, 63, 6446; d) D. L. Waller, C. R. J. Stephenson, P. Wipf, *Org. Biomol. Chem.* **2007**, 5, 58; e) R. Navarro, S. E. Reisman, *Org. Lett.* **2012**, 14, 4354.
- [7] a) F. Li, S. S. Tartakoff, S. L. Castle, *J. Am. Chem. Soc.* **2009**, 131, 6674; b) F. Li, S. S. Tartakoff, S. L. Castle, *J. Org. Chem.* **2009**, 74, 9082.
- [8] S. B. Herzon, N. A. Calandra, S. M. King, *Angew. Chem.* **2011**, 123, 9025; *Angew. Chem. Int. Ed.* **2011**, 50, 8863.
- [9] For contemporaneous studies toward various hasubanan alkaloids, see: K. V. Chuang, R. Navarro, S. E. Reisman, *Angew. Chem.* **2011**, 123, 9619; *Angew. Chem. Int. Ed.* **2011**, 50, 9447.
- [10] A. B. Smith III, Q. Han, P. A. S. Breslin, G. K. Beauchamp, *Org. Lett.* **2005**, 7, 5075.
- [11] S. Ogoshi, S. Tomiyasu, M. Morita, H. Kurosawa, *J. Am. Chem. Soc.* **2002**, 124, 11598.
- [12] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, 33, 6299.
- [13] The contrasting diastereoselectivity in the addition step may be due to unfavorable torsional strain within the pyrrolidine ring in the alternate diastereomer. The relative stereochemistry of **13** was assigned by analogy to related addition products, for which X-ray structures have been obtained (see Ref. 8), and its successful conversion into the targets.
- [14] M. Alami, F. Ferri, *Synlett* **1996**, 755.
- [15] a) A. Hosomi, H. Sakurai, *J. Am. Chem. Soc.* **1977**, 99, 1673; for a review, see: b) D. Schinzer, *Synthesis* **1988**, 263.
- [16] T. Takeda, F. Kanamori, H. Matsusita, T. Fujiwara, *Tetrahedron Lett.* **1991**, 32, 6563.
- [17] a) S. L. Huang, K. Omura, D. Swern, *Synthesis* **1978**, 297; b) C. M. Amon, M. G. Banwell, G. L. Gravatt, *J. Org. Chem.* **1987**, 52, 4851.
- [18] Analytically pure samples of **20–22** could be obtained by flash-column chromatography (see the Supporting Information), but under all conditions we examined significant quantities of decomposition products also formed. In preparative experiments the unpurified product mixtures were advanced directly to dehydroacutumine (**23**). This latter intermediate was amenable to chromatographic purification.
- [19] For a review, see: L. E. Overman, *Angew. Chem.* **1984**, 96, 565; *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 579.
- [20] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, 113, 7277.
- [21] a) J. M. Brown, R. G. Naik, *J. Chem. Soc. Chem. Commun.* **1982**, 348; b) R. H. Crabtree, M. W. Davis, *Organometallics* **1983**, 2, 681; c) G. Stork, D. E. Kahne, *J. Am. Chem. Soc.* **1983**, 105, 1072; d) D. A. Evans, M. M. Morrissey, *J. Am. Chem. Soc.* **1984**, 106, 3866.
- [22] We thank Professor Steven L. Castle (Brigham Young University) for kindly providing a natural sample of (–)-acutumine (**1**).
- [23] Selected recent examples: a) H. Kim, H. Lee, D. Lee, S. Kim, D. Kim, *J. Am. Chem. Soc.* **2007**, 129, 2269; b) X. Sun, L. Zhou, W. Li, X. Zhang, *J. Org. Chem.* **2008**, 73, 1143; c) S. W. Krska, J. V. Mitten, P. G. Dormer, D. Mowrey, F. Machrouhi, Y. Sun, T. D. Nelson, *Tetrahedron* **2009**, 65, 8987; d) I. Gazić Smilović, E. Casas-Arce, S. J. Roseblade, U. Nettekoven, A. Zanotti-Gerosa, M. Kovacevic, Z. Casar, *Angew. Chem.* **2012**, 124, 1038; *Angew. Chem. Int. Ed.* **2012**, 51, 1014.