Natural Products

DOI: 10.1002/anie.200701584

Enantioselective Synthesis of Arglabin**

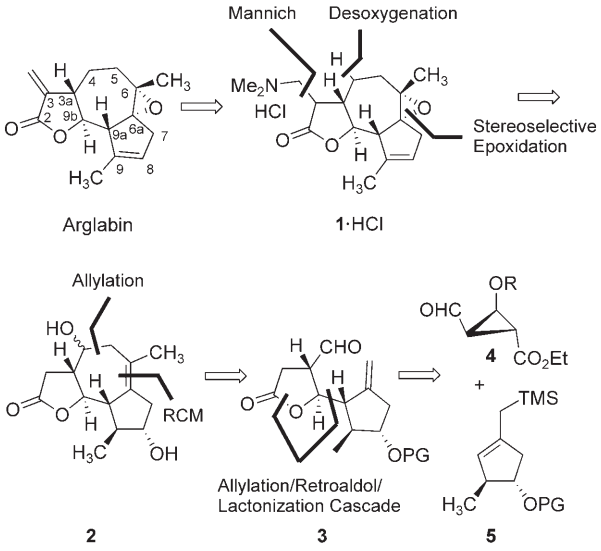
*Srinivas Kalidindi, Won Boo Jeong, Andreas Schall, Rakeshwar Bandichhor, Bernd Nosse, and Oliver Reiser**

Dedicated to Professor Lutz-F. Tietze on the occasion of his 65th birthday

A prominent member of the widely distributed class of guaianolides is arglabin,[1] which inhibits farnesyl transferase and thus activation of the RAS proto-oncogene, a process that is believed to play a pivotal role in 20–30% of all human tumors. The natural product shows promising antitumor activity and cytotoxicity against different tumor cell lines (human tumor cell lines $IC_{50} = 0.9–5.0\ \mu g\,mL^{-1}$).[2] Arglabin is isolated from *Artemisia glabella* and is transformed into the hydrochloride salt of the dimethylamino adduct **1**·HCl to increase bioavailability. This compound **1**·HCl has been successfully used in Kazakhstan for the treatment of breast, colon, ovarian, and lung cancers.[3,4]

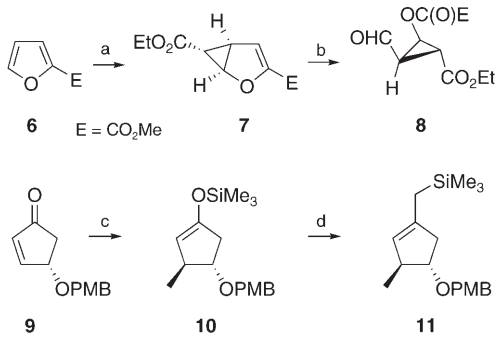
The heart of arglabin consists of a cycloheptane ring with five contiguous stereocenters, to which two five-membered rings are *trans*-annulated. The resulting strain can be released by ring opening of the γ-butyrolactone at C-2, which makes arglabin and its derivatives prone to attack by nucleophiles—a mode of action that plays an integral role in its biological activity.[2,5]

The absence of other control factors should cause the planned epoxidation of **2** described in our retrosynthetic analysis (Scheme 1) to preferably occur from the top face of the tricycle to afford a less-strained but undesirable *cis* junction between the five- and seven-membered rings. Considering this, we reasoned that a hydroxy function at C-8 could direct a suitable epoxidation reagent to the desired lower face, and subsequently allow the installment of the double bond between C-8 and C-9 by elimination of water. Compound **2** should be accessible from **3** by allylation and subsequent ring-closing metathesis (RCM); the latter requires the formation of a tetrasubstituted double bond within a medium-sized seven-membered ring. Following the strategy developed in our research group for the enantioselective synthesis of *trans*-4,5-disubstituted γ-butyrolactones,[6,7] the allylation of cyclopropane **4** with the allylsilane **5** should lead to the first key intermediate **3**.



Scheme 1. Retrosynthetic analysis of arglabin. PG = protecting group, TMS = trimethylsilyl.

Cyclopropanecarbaldehyde **8** was prepared in diastereo- and enantiomerically pure form in two steps from methyl-2-furoate (**6**) on a 50 g scale (Scheme 2) following an analogous



Scheme 2. a) 1. Ethyl diazoacetate (2.67 equiv), $Cu(OTf)_2$ (0.66 mol%), (*R*,*R*)-*i*Pr-box[8] (0.84 mol%), $PhNHNH_2$ (0.70 mol%), CH_2Cl_2, 85–90% *ee*; 2. recrystallization (pentane), >99% *ee*, 38%; b) 1. O_3, CH_2Cl_2, −78 °C 2. dimethylsulfide, 94%; c) CH_3MgCl, TMSCl, CuI, LiCl, THF, −78 °C, 4 h, 90%; d) $TMSCH_2MgCl$, $[Ni(acac)_2]$, Et_2O, reflux, 16 h, 72%. Tf = trifluoromethanesulfonyl, acac = acetylacetonate, PMB = *para*-methoxybenzyl.

[*] M.Sc. S. Kalidindi, Dr. W. B. Jeong, Dipl.-Chem. A. Schall, Dr. R. Bandichhor, Dr. B. Nosse, Prof. Dr. O. Reiser
Institut für Organische Chemie
Universität Regensburg
Universitätsstrasse 31, 93053 Regensburg (Germany)
Fax: (+49) 941-943-4121
E-mail: oliver.reiser@chemie.uni-regensburg.de
Homepage: http://www-oc.chemie.uni-regensburg.de/reiser/index.html

[**] This work was supported by the DAAD (fellowship for S.K. and R.B.), the Studienstiftung des Deutschen Volkes (fellowship for B.N.), and the Fonds der Chemischen Industrie (fellowship for A.S. and Sachbeihilfe). We thank Dr. M. Zabel, Regensburg, for carrying out the X-ray analyses.

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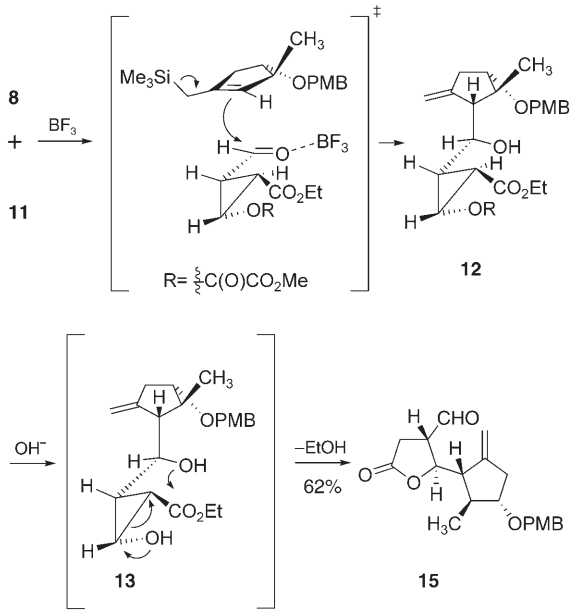
strategy previously developed by us for its enantiomer.[9] The allylsilane **11** was obtained starting from enantiomerically pure **9**,[10] by *trans*-selective methyl cuprate addition and Ni^{II}-catalyzed cross coupling[11] with trimethylsilylmethylenemagnesium chloride.

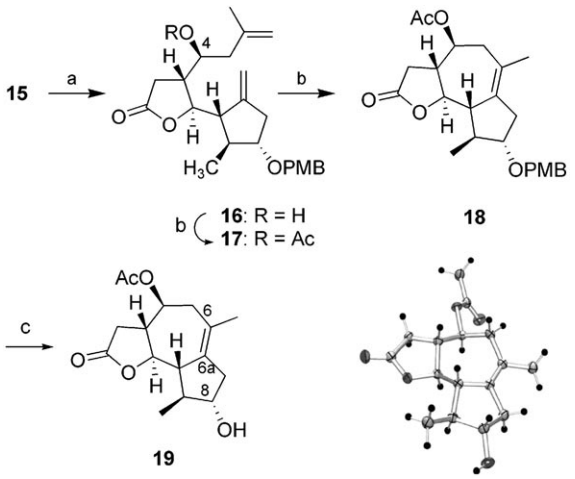
Borontrifluoride-mediated formation of **12** proceeded with excellent double stereocontrol (Scheme 3). The carbonyl group of **8** was attacked in accordance with the Felkin–Anh



Scheme 3. Stereoselective allylation/retroaldol/lactonization cascade for the synthesis of the outer five-membered rings in arglabin. **8** (1.0 equiv), **11** (1.04 equiv), $BF_3{\cdot}OEt_2$, −78 °C, 4 h; $Ba(OH)_2{\cdot}8H_2O$, 0 °C, 2 h.

paradigm[12] by the allylsilane **11**, which reacts from the face opposite its methyl group. Without isolation, **12** was directly subjected to a base, which caused saponification of the labile oxalic ester. As a result, the now-unmasked donor-acceptor cyclopropane[13] underwent ring opening followed by lactonization to give **15** as a single stereoisomer.

A second Sakurai allylation of **15** with 2-methylallylsilane smoothly yielded **16** as a 4:1 mixture of diastereomers (Scheme 4). The latter is, in principle, without consequence, since in the synthesis of the target compound the newly created hydroxy group is removed at a later stage in the sequence. Acylation of **16** set the stage for subsequent ring-closing metathesis, which not unexpectedly proved to be challenging because of the medium-size ring and the tetrasubstituted double bond that had to be formed. Nevertheless, the combination of Grubbs second-generation (G-II) catalyst and inert-gas sparging at a reaction temperature of 95 °C gave the desired **18** and its C-4-epimer *epi*-**18** in a total of 86% yield, although 15 mol% of G-II split into 3 portions of 5 mol% each had to be employed to achieve complete conversion. To develop the stereoselective epoxidation on C-6/C-6a it turned out to be advantageous to continue working with only the major diastereomer **18**, which was readily separated from *epi*-**18** by column chromatography.



Scheme 4. Synthesis of the guaianolide core. a) 1. 2-methylallylsilane, $BF_3{\cdot}OEt_2$, −78 °C, 16 h, 70% (4:1 epimeric mixture at C-4); 2. Ac_2O, Et_3N, DMAP, RT, 24 h, 85% (4:1 epimeric mixture at C-4); b) 1. cat. G-II (3×5 mol%), toluene, sparging with Ar, 95 °C, 6 h; 2. separation of C-4 epimers by chromatography: **18** (70%), *epi*-**18** (16%); c) DDQ, CH_2Cl_2, 4 h, RT, 90%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine.

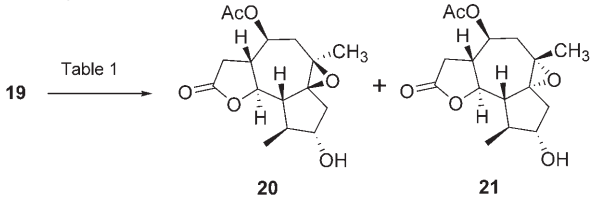
Deprotection of the PMB group was uneventful to give rise to **19** upon treatment with DDQ in 90% yield (Scheme 4).

The X-ray structure of **19**[14] (Scheme 4) revealed that both faces of the seven-membered ring for the subsequently planned epoxidation are equally exposed. In particular, it became clear that for the desired attack from the α face (bottom) the upward but pseudoequatorial-pointing acetoxy group at C-8 would provide little steric shielding. Moreover, the hydroxy group at C-3 that was envisioned to serve as a directing substituent, which is known not only for the epoxidation of allylic but also for homoallylic alcohols,[15] rather unfavorably was in a pseudoequatorial position and pointed away from the double bond that was to be attacked. Furthermore, epoxidation from the β face (top) yielded the product with the more stable *cis* annulation between the five- and seven-membered ring.

Indeed, simple undirected epoxidation of **19** with dimethyldioxirane occurred with a preference of 7:1 (Table 1, entry 1) from the undesired β face to give **20**, which supports the rational put forward above. Disappointingly, *m*-CPBA, which is known to be directed by homoallylic alcohols, still gave the β-epoxide with a ratio of 3:1 (Table 1, entry 4), which again demonstrates the preference for the *cis* annulation of the five- and seven-membered rings.[16]

Consequently, we attempted the epoxidation by initial bromohydrine formation with the rational that the bromonium ion should also be formed from the β face followed by backside attack of water and elimination of HBr. Indeed, by using this strategy, the overall epoxidation took place in high yields without the isolation of intermediates, and gave only one product, although unfortunately again the unwanted β-epoxide (Table 1, entries 2 and 3). However, employing catalytic amounts of $[V(O)(acac)_2]$ and *tert*-butylhydroperoxide (TBHP) as the stoichiometric oxidant[17] gave the desired α-epoxide **21** with a preference of 9:1 (Table 1,

Table 1: Epoxidation of **19**.

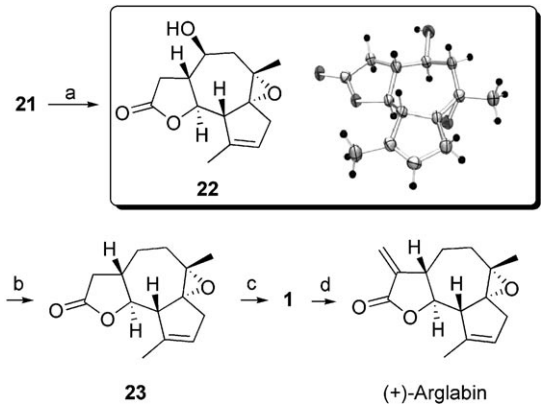


Entry	Method	Conditions[a]	**20**/**21**[b]	Yield [%][c]
1	dimethyl-dioxirane	$KHSO_5$, acetone, CH_2Cl_2/H_2O, pH 7.2 buffer, [18]crown-6, 0 °C, 6 h	88:12	65
2	halohydrine	$NaBrO_3/NaHSO_3$ (1:2), CH_3CN/H_2O (1:2), 48 h, RT	>99:1	80
3	halohydrine	NBS, THF/H_2O (2:1), 15 h, RT	>99:1	72
4	peracid	*m*-CPBA, CH_2Cl_2, −10 °C to RT, 6 h	75:25	85
5	vanadium	$[V(O)(acac)_2]$ (2 mol%), TBHP, CH_2Cl_2, 0 °C to RT, 16 h	10:90	78[d]

[a] NBS = *N*-bromosuccinimide, *m*-CPBA = *meta*-chloroperoxybenzoic acid. [b] Determined by ^{1}H NMR and GC. [c] Yields of isolated products. [d] Yield of isolated purified **21**.

entry 5), which demonstrates the extraordinary affinity for precoordination of the vanadium reagent to hydroxy groups before the epoxidation occurs. Epoxide **21** was isolated in 78% yield after chromatographic separation from the minor β-epoxide product.

Treatment of **21** with trifluorosulfonic acid anhydride and pyridine afforded a clean elimination product **22** as a single regioisomer, which was confirmed by X-ray analysis (Scheme 5).[14] Deoxygenation at C-4 was achieved by acetate deprotection followed by the Barton–McCombie protocol[18] to give rise to **23**. Alkylation with the Eschenmoser salt,[19] yielded **1**, which could then be transformed to arglabin itself by quaternization with methyliodide/trimethylamine elimination. This product corresponded in all spectroscopic data with an authentic sample.[20]



Scheme 5. a) Tf_2O, pyridine, CH_2Cl_2, −10 °C to RT, 18 h, 62%. b) 1. K_2CO_3, MeOH, 0 °C to RT, 4 h, 70%; 2. 1,1′-thiocarbonyldiimadazole, DMAP, CH_2Cl_2, RT, 4 h, 80%; 3. Bu_3SnH, AIBN, toluene, 90 °C, 5 h, 77%. c) 1. LiHMDS, THF, −78 °C; 2. Eschenmoser salt, THF, −78 °C to RT, 4 h, 75%; d) MeI, MeOH, $NaHCO_3$, CH_2Cl_2, 80%. AIBN = azobisisobutyronitrile, LiHMDS = lithium hexamethyldisilazanide.

In conclusion, we have developed the first enantioselective synthesis of the guaianolide arglabin and its dimethylamino adduct **1**. The latter, as its hydrochloride salt, is currently under clinical evaluation for the treatment of various cancers. Key steps to build up the guaianolide framework include a copper(I)-catalyzed asymmetric cyclopropanation, a stereoselective Sakurai allylation followed by a retroaldol/lactonization cascade, a second Sakurai allylation, and ring-closing metathesis. This strategy should also open access to related tricyclic 5,7,5-guaianolide natural products, which we are currently investigating.

Received: April 11, 2007
Published online: July 16, 2007

Keywords: arglabin · asymmetric synthesis · farnesyl transferase · natural products · total synthesis

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