Published in final edited form as:

Chem Sci. 2013 February ; 4(5): 2262–2266. doi:10.1039/C3SC00056G.

Total synthesis of (±)-leuconolam: intramolecular allylic silane addition to a maleimide carbonyl group

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Abstract

A concise total synthesis of the plant alkaloid (±)-leuconolam (**1**) has been achieved. A regio- and diastereoselective Lewis-acid mediated allylative cyclization was used to establish, simultaneously, two adjacent tetrasubstituted carbon centers. Furthermore, an essential arene cross-coupling to a hindered haloalkene was enabled by the use of a novel 2-anilinostannane.

Introduction

Leuconolam (**1**) is a monoterpenoid bislactam alkaloid that has an interesting and complex polycyclic molecular architecture shown in panel A of Figure 1. Goh and coworkers reported the isolation of **1**¹ from the *Leuconotis* plants *L. griffithii* and *L. eugenifolia* located in Malaysia.² This open-ring indole is a member of the aspidosperma class of anti-mitotic alkaloids.³ Two closely related analogues of **1**, rhazinilam^{4a} and rhazinal,^{4b} are shown in panel B. There has been a significant level of interest in developing synthesis strategies to construct the carbon frameworks of the latter alkaloids.⁵ Leuconolam (**1**) distinguishes itself from these pyrrole embedded natural products by possessing a functionalized α,β-unsaturated carbinolamide subunit (highlighted in gray, panel A). Some of the key structural features of **1** are revealed more explicitly by its single crystal X-ray structure.^{1b} In particular, the styrenyl moiety and the acetanilide functional group are non-coplanar with the benzenoid ring. Therefore, the molecule is axially chiral around the arene-alkene C14b-C14a bond. Moreover, the relative configuration of the two adjacent stereogenic tetrasubstituted carbons presents an additional challenge from the perspective of synthetic chemists.

In 2006 Banwell and co-workers reported the only total synthesis of **1**^{5g} [via the PCC oxidation of rhazinilam, which proceeded to give both **1** and **12a-epi-1** (1:1.7 ratio)]. To establish the complex carbinolamide motif in **1**, we envisioned a Sakurai type⁶ intramolecular 1,2-addition of an allylic silane to a maleimide (see **3** to **2**, Scheme 1). Such a transformation, if achieved in a regio- and diastereoselective fashion, would be an especially

productive disconnection because the two adjacent tetrasubstituted carbon centers as well as the ethylene branch of the monoterpenoid would be formed in a single step. Herein we describe our efforts that led to a concise total synthesis of (±)-leuconolam (**1**). Our strategy for construction of **1** included the following (Scheme 1): Ireland-Claisen rearrangement of **4** followed by Mitsunobu displacement to give maleimide **3**, intramolecular allylative ring closure within **3** to provide **2**, arylation (arene-alkene cross-coupling) of **2**, and macrolactamization.

Results and Discussion

Our synthesis commenced with construction of the Ireland-Claisen rearrangement precursor **4** from methallyl alcohol (**6**, Scheme 2). S_N2-Alkylation occurred at the more reactive allylic position of the dianion of **6**⁷ (the C-terminus) with bromide **5**.⁸ We transformed the primary alcohol **8** to the ester **4** by employing a 3-step procedure: (i) Swern oxidation; (ii) 1,2-addition of (trimethylsilyl)methylmagnesium chloride (**7**, cf. Scheme 1) to the resulting aldehyde; and (iii) acetylation of the secondary alcohol **9**. The acetate **4** was prepared on a ca. 10-gram scale and in 66% overall yield from **8**.

The Ireland-Claisen rearrangement was used to install the desired C-C double bond at the β-position of the silyl moiety. *In situ* trapping of the lithium enolate (LDA/HMPA/THF) with TBSCl⁹ was followed by facile (ambient temperature) [3,3] sigmatropic rearrangement, which gave the TBS-ester **11** after an aqueous workup. The *E*-configuration of the alkene was determined by nOe experiment. One pot ethoxyethyl (EE) cleavage-methyl esterification was done by treatment of **11** with methanolic HCl. Mitsunobu displacement of the resulting alcohol **12** with either of the furan protected maleimide derivatives **13a** or **13b** afforded, following thermolysis, **3a** or **3b**, each in 80% yield. Initial attempts to succeed a direct displacement with the parent maleimides gave considerably lower yields of **3a** (41%) and **3b** (13%), possibly due to their propensity to oligomerize under the somewhat basic reaction conditions.¹⁰

We then turned to a study of the critical cyclization reaction between allylic silane and maleimide moieties. Unimolecular Sakurai-type^{6a} C-C bond forming processes are known, but have rarely been used to construct adjacent (vicinal) tetrasubstituted centers.¹¹ To find robust and functional group tolerant allylative ring closure conditions, we screened various Lewis-acid activators using **3a** as the test substrate (Table 1). This symmetrical imide was particularly useful for analyzing the reaction outcomes because the allylation step was not confronted by any regioselectivity issues, as in the case for the 3-substituted maleimides **3b–e**. One obstacle we encountered during the optimization of the ring closure was the formation of the protodesilylation¹² byproduct **15** (entries 2–4). Gratifyingly, use of MeAlCl₂ (4 equiv, entry 5)¹³ facilitated the desired 1,2-addition of the allylic silane onto the maleimide carbonyl group in excellent yield (88%) and diastereoselectivity (42:1 by ¹H NMR). Subsequent cyclizations on the substituted analogs **3b–e** also proceeded with good to excellent levels of diastereoselectivity (Scheme 3). The relative configuration of the major diastereomer, although not confirmed until the completion of the synthesis and correlation with the leuconolam structure, was predicted to be that shown in structures **14a–e** by the transition state geometry **16** in panel D of Scheme 3.¹⁴

We initially explored a retrosynthetic plan slightly different from that shown in Scheme 1. In particular, we investigated whether the allylative cyclization could be effected on a substrate already having the arene appended to the maleimide. Accordingly, we prepared the 2-nitrophenyl and 2-aminophenyl substrates **3c** and **3d** (cf. Scheme 2) by Stille coupling of bromide **3b** with *o*-(tributylstannyl)nitrobenzene¹⁵ or *o*-(tributylstannyl)aniline,^{16a} respectively. The first of these cyclized under the action of MeAlCl₂ in excellent yield, but gave, exclusively, a carbinolamide having the undesired regioisomeric relationship (i.e., **iso-14c**, Scheme 3, panel A). Similarly, the anilino substrate **3d** gave mostly the unwanted constitutional isomer although some of the desired **14d** (Scheme 3, panel B) was observed at room temperature. Presumably, the bulky aromatic substituent inhibits allyl addition in the desired trajectory. The ratio of **14** to **iso-14** was determined by the well-separated ¹H NMR signals of the α- and β-protons of the enone system (cf. δH_α= 6.17 vs δH_β= 6.86 ppm, respectively). Therefore, we turned our attention to cyclization of the halogenated maleimide substrates **3b** and **3e**, the latter of which was prepared from the former by treatment with NaI in refluxing acetone¹⁷ (cf. Scheme 2). Each of these substrates efficiently closed to the desired β-halocarbinolamide **14b** or **14e**, respectively, in ca. 85% yield and, more importantly, with high levels of both regio- and diastereoselectivity (Scheme 3, panel B). As mentioned earlier, the geometry depicted in panel C serves to rationalize the preferred mode of addition. We speculate that σ-inductive effect of the halogen substituent activates the adjacent carbonyl.

We next focused on the arylation of the hindered halides **14b** and **14e** with the Stille cross-coupling partners **17–20** (Scheme 4). The bromide **14b** proved to be an ineffective substrate under all conditions we examined. Similarly, the iodide **14e** failed to provide any of the nitro- or BocHN-derivative **14c** or **14f** using the known organostannanes **17**¹⁵ and **18**,¹⁸ respectively. A trace of the required aniline product **14d**¹⁹ was observed using the more electron-rich anilino-stannane **19**.¹⁶ Gratifyingly, using the sterically less bulky Stille donor *o*-(trimethylstannyl)aniline (**20**),¹⁶ which we expressly designed for this application, we were successful in arylation of **14e** to furnish **14d** in 74% yield. The near-neutral conditions used for this cross-coupling [Pd₂(dba)₃·CHCl₃/AsPh₃ at room temperature] were tolerant of the base-sensitive iodo-carbinolamide **14e**. This novel organostannane (**20**) allowed for direct introduction of the ortho-aminophenyl substituent in unprotected form, a transformation of broader interest.

To prepare **14d** for the macrolactamization, it was necessary to saponify the methyl ester. Reagents used previously to perform late-stage methyl ester hydrolysis in rhazinilam syntheses [namely, NaOH^{5c,e,j}, KOH^{5g}, Ba(OH)₂5h] or potassium trimethylsilanolate (KOTMS) proved ineffective, presumably because of the base sensitivity of the carbinolamide in **14d**. Gladly, use of a limited amount of LiOH-monohydrate (3 equiv) in aqueous THF served to effect this transformation cleanly, furnishing the corresponding amino acid in excellent yield (>90%, Scheme 5). Although carbodiimide mediated lactamization (EDCI·HCl) proved inefficient, we successfully achieved the desired lactam formation in 71% isolated yield by treating a DMF solution (0.05 M) of the amino acid derived from **14d** with HATU, DIPEA, and DMAP. The resulting macrolactam **21** was

smoothly converted by chemoselective hydrogenation with H₂ (50 psi) over Pd/C to provide the target alkaloid leuconolam (**1**) in 95% yield.

Conclusion

In summary, we have achieved an efficient total synthesis of (±)-leuconolam (**1**). Key features include: (i) the Ireland-Claisen rearrangement of acetate ester **4** to produce the *E*-trisubstituted alkene in **11**, (ii) the use of furan-protected maleimide **13b** as a superior partner in Mitsunobu installation of the maleimide moiety in **3**, (iii) the regio- and diastereoselective Lewis-acid mediated allylative cyclization of the allylic silane onto the α-halogenated carbonyl group in **3e**, (iv) the use of the novel *o*-(trimethylstannyl)aniline **20**, designed as an effective cross-coupling donor to engage the hindered iodoalkene in **14e**, and (v) the final establishment of the ethyl group by selective hydrogenation of the vinyl unit in **21**, which arose during cyclization of the allylic silane **3e**.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the U.S. Department of Health and Human Services National Institute of General Medical Sciences (GM-65597) and National Cancer Institute (CA-76497).

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Fig. 1.
Structures of leuconolam (**1**) and analogues rhazinilam and rhazinal.

Scheme 1.
Retrosynthetic analysis of **1**.

Scheme 2.

Synthesis of the allylative ring closure precursors. *Reagents and conditions:* (a) *n*-BuLi (2.2 equiv), TMEDA (2.0 equiv), Et₂O, -78 to -10 °C, 12 h; **5** (1.1 equiv), -78 to 0 °C, 12 h, 52%; (b) (COCl)₂ (1.2 equiv), DMSO (1.3 equiv), Et₃N (3.0 equiv), CH₂Cl₂, ca. -65 °C, 85%; (c) **7** (1.3 equiv), Et₂O, -10 °C, 80%; (d) AcCl (1.2 equiv), pyr (1.5 equiv), DMAP (0.2 equiv), CH₂Cl₂, 0 °C, 97%; (e) LDA (1.2 equiv), HMPA (1.0 equiv), TBSCl (1.2 equiv), THF, -78 °C, 85%; (f) AcCl (1.0 equiv), MeOH, rt, 81%; (g) **13a** or **13b** (1.3 equiv), DIAD (1.5 equiv), PPh₃ (1.5 equiv), THF, -10 °C; (h) Toluene, 100 °C, 80–82% over 2 steps. (i) *o*-(Tributylstannyl)nitrobenzene (1.5 equiv), Pd₂(dba)₃·CHCl₃ (0.1 equiv), AsPh₃ (0.4 equiv), DMF, rt, 91%; (j) *o*-(Tributylstannyl)aniline (1.3 equiv), Pd₂(dba)₃·CHCl₃ (0.1 equiv), AsPh₃ (0.4 equiv), DMF, rt, 82%; (k) NaI (5.5 equiv), acetone, reflux, 94%; TMEDA = *N,N,N',N'*-tetramethylethylenediamine, DMAP = 4-(dimethylamino)pyridine, LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, TBSCl = tert-butyldimethylsilyl chloride, DIAD = diisopropyl azodicarboxylate.

Scheme 3.

Panel A. Cyclizations of maleimides containing an aromatic substituent (**3c** and **3d**) proceed with undesired regioselectivity. Panel B. Cyclizations of maleimides containing a halogen substituent (**3b** and **3e**) proceed with desired regioselectivity (and diastereoselectivity).

General procedure for the allylative ring closure: imide (**3b–e**, 1.0 equiv, 0.05 M), MeAlCl₂ (4.0 equiv), CH₂Cl₂, rt, 10–15 min, then NH₄Cl quench. Panel C. Proposed geometry of cyclization for the LA-activated intermediates **16**.

Scheme 4.

Arylation (cross-coupling) studies of the iodoalkene **14e** to provide the anilino esters **14c–d**.

Reagents and conditions for the synthesis of 14d: 20 (1.2 equiv), Pd₂(dba)₃·CHCl₃ (0.1 equiv), AsPh₃ (0.4 equiv), DMF, rt, 74%.

Scheme 5.

Completion of the total synthesis of (±)-**1**. *Reagents and conditions:* (a) LiOH·H₂O (3 equiv), THF/H₂O (2:1), rt, 92%; (b) HATU (1.5 equiv), DIPEA (1.5 equiv), DMAP (0.2 equiv), DMF, rt, 71%; (c) H₂ (50 psi), Pd/C (1 equiv), EtOH, rt, 95%; HATU: 1-[bis-(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, DIPEA = *N,N*-diisopropylethylamine.

Table 1

Screening Lewis acids for the key allylative cyclization.

Entry	LA (equiv)	Time (min)	14a	15
1	Ti(O- <i>i</i> Pr) ₄ (10)	60	no reaction	
2	TiCl ₄ (2)	15	0%	43%
3	TMSOTf (2)	15	0%	95%
4	BF ₃ ·OEt ₂ (2)	15	0%	80%
5	MeAlCl ₂ (4)	10	88% (dr 42:1)	0%