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Introduction

Leuconolam (1) is a monoterpenoid bis-lactam alkaloid that has an interesting and complex polycyclic molecular architecture shown in panel A of Fig. 1. Goh and co-workers reported the isolation of 1¹ 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-c} and rhazinal,^{4d} 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.
L In 2006 Banwell and co-workers reported the only total

Total synthesis of (\pm) -leuconolam: intramolecular allylic

A concise total synthesis of the plant alkaloid (\pm) -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

silane addition to a maleimide carbonyl groupt

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haloalkene was enabled by the use of a novel 2-anilinostannane.

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



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

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[†] Electronic supplementary information (ESI) available: Experimental procedures for preparation of, full characterization data for, and copies of NMR spectra of new compounds. See DOI: 10.1039/c3sc00056g



Scheme 1 Retrosynthetic analysis of 1.

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View Article Online View Journal | View Issue 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 (\pm) -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_N 2-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) 1,2addition 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 an *ca.* 10 gram scale and in 66% overall yield from **8**.



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) (COCI)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.), DIAD (1.5 equiv.), PPh₃ (1.5 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*-(Tributyl-stannyl)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.), 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.

The Ireland-Claisen rearrangement was used to install the desired C–C double bond at the β -position of the silvl moiety. In situ trapping of the lithium enolate (LDA/HMPA/THF) with TBSCl⁹ was followed by facile (\leq 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 \geq 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 Lewisacid 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 by-product 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 diasteromer, although not confirmed until the completion of the synthesis and correlation with the leuconolam structure, was predicted to be that shown in





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**.

structures **14a–e** by the transition state geometry **16** in panel C 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.* $\delta H\alpha = 6.17 \nu s. \delta H\beta = 6.86$ 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 -halo-carbinolamide **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 17¹⁵ and 18,¹⁸ respectively. A trace of the required aniline product 14d¹⁹ was observed using the more electron-rich anilinostannane 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)₂^{5h}] 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



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.), $Pd_2(dba)_3 \cdot CHCl_3$ (0.1 equiv.), $ASPh_3$ (0.4 equiv.), DMF, rt, 74%.



Scheme 5Completion of the total synthesis of (\pm) -1. Reagents and conditions:(a) LiOH · H₂O (3 equiv.), THF–H₂O (2 : 1), rt, 92%; (b) HATU (1.5 equiv.), DIPEA (1.5equiv.), DMAP (0.2 equiv.), DMF, rt, 71%; (c) H₂ (50 psi), Pd/C (1 equiv.), EtOH, rt,95%;HATU:O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexa-fluorophosphate, DIPEA = N,N-diisopropylethylamine.

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 (\pm) -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.

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that served as sources of acetaldehyde, which was incorporated into 14d leading to 22. Therefore, use of $\rm Et_3N$ -pre-treated silica gel to purify 14d was avoided.

