Expeditious Syntheses of (±)-*allo*-Sedamine and (±)-*allo*-Lobeline via a Combination of Aza-Sakurai–Hosomi and Hydroformylation Reactions

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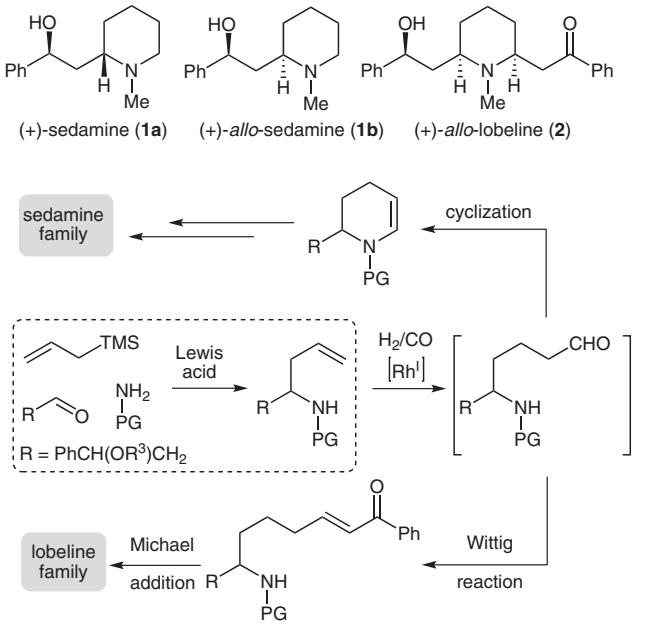
In memory of our late colleague Philippe Klotz (deceased 9 June 2005)

Abstract: The expeditious preparation of *allo*-sedamine and *allo*-lobeline via 1,3-diastereoselective aza-Sakurai–Hosomi reaction followed by hydroformylation is reported.

Key words: alkaloids, multicomponent reaction, diastereoselectivity, hydroformylation

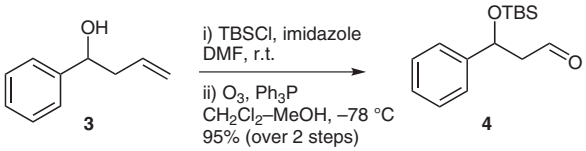
A large body of work has been devoted to the preparation of homoallylamines,[1] the main substrates for the construction of piperidines which are privileged scaffolds for biomolecules. Indeed, homoallylamines have a great chemical potential due to the presence of a terminal double bond enabling a number of chemical manipulations, such as metathesis, oxidative hydroboration or hydroformylation. Several syntheses of naturally occurring piperidines are performed with functionalized hydroxy homoallylamines including sedamine (**1a**) or *allo*-sedamine (**1b**). Most of them are based on the following classical strategy: a multistep preparation of the 1,3-hydroxy homoallylamine and a heterocyclization either by a ring closure metathesis or an internal nucleophilic displacement.[2] Herein we report the synthesis of (±)-*allo*-sedamine (**1b**) and of the unknown (±)-*allo*-lobeline (**2**) based on a new strategy (Scheme 1): (i) an improved method for the preparation of 1,3-O-protected homoallylamines via an aza-Sakurai–Hosomi three-component reaction (aSH-R3C), (ii) a linear hydroformylation of a terminal alkene, yielding an aldehyde that collapses to an internal enamine that is easily convertible into sedamine analogues or which, in a one-pot sequence, can be converted into an enone undergoing an intramolecular aza-Michael reaction yielding lobeline analogues.

In recent years multicomponent reactions have been refined into powerful tools in organic synthesis,[3] exemplified by the preparation of homoallylamines from any kind of aldehyde via the aSH-R3C.[4] In this one-pot reaction the acyliminium produced in situ from an aldehyde and a carbamate reacted with an allylsilane in the presence of a Lewis acid, to afford homoallylamines.[4] In the past, we have reported that the aSH-R3C performed on 1,2-O-protected hydroxy aldehydes provided *syn* 1,2-diastereoselectivity.[5] For the construction of lobeline and sedamine analogues, the hydroformylative end game required the homoallylamines derived from the corresponding 1,3-amino alcohols. Therefore at the onset of our work we had to explore the diastereoselectivity of the aSH-R3C of 1,3-O-protected aldehydes. For the assignment of the stereochemistry of the diastereomers resulting from this aminoallylation step, the subsequent syntheses of lobeline or sedamine analogues were helpful.



Scheme 1 General strategy

In our synthetic plan, the starting homoallylic alcohol **3** was prepared by allylation of benzaldehyde in 96% yield (Scheme 2). Then the secondary alcohol was protected with TBSCl in quantitative yield and subjected to ozonolysis leading to the corresponding racemic 1,3-O-protect-



Scheme 2 Preparation of aldehyde **4**

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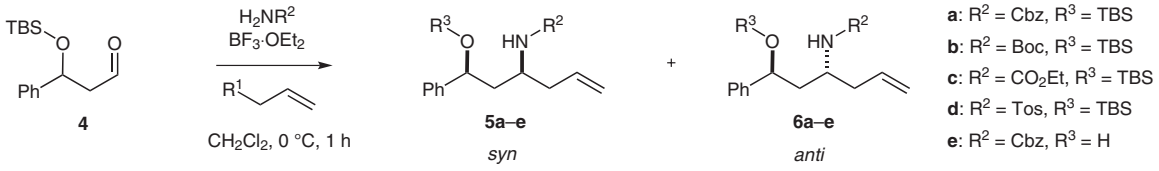
ed aldehyde **4**, the starting material for performing the aSH-R3C.

Then, based on our previous work on the aSH-R3C, different solvents, carbamates and allylating agents were screened. As Lewis acid, $BF_3{\cdot}OEt_2$ was retained, only its stoichiometry was modified. Orientating experiments have revealed that the TBS group on the benzylic alcohol function was the best choice as the protecting group.[6] The results of the chemical screening are depicted on Table 1.

According to the reaction conditions different O-silylated (**5a–d/6a–d**) or O-desilylated homoallylamines (**5e/6e**) were obtained. In dichloromethane, it appeared that the aSH-R3C was operative with allylsilane, $BF_3{\cdot}OEt_2$ and several carbamates including $TsNH_2$, and indeed homoallylamines **5a–d/6a–d** were obtained in acceptable yields as mixtures of diastereomers (Table 1, entries 1, 3–5, and 7–9). However conducting the same experiment in MeCN, O-desilylated adducts **5e** and **6e** were obtained in equal amount (entry 2). As the reaction produces a stoichiometric amount of H_2O, it is conceivable that in acetonitrile, a basic solvent, fluorine is liberated from the Lewis acid, being at the origin of a fast desilylation of the benzylic hydroxyl. As a result, no facial discrimination was obtained. Finally with allyltin a Sakurai–Hosomi reaction occurred with or without carbamate (entries 6 and 11) yielding the corresponding homoallylalcohols with the expected *anti* diastereoselectivity.[7] The same scenario was observed when the carbamate was omitted during the reaction with allylsilane (entry 10); the Sakurai–Hosomi adducts were obtained with a similar diastereomeric ratio. The use of a more hindered allylsilane had no impact either on the yield or on the diastereomeric ratio (entry 5). When $TiCl_4$ was used as Lewis acid compound **4** was converted into cinnamaldehyde (data not shown) via a dehydration pathway, an observation that excluded further investigations with bidendate Lewis acids. The nature of the nitrogen protecting group had little impact on the diastereomeric ratio (entries 7–9). The Boc group showed good diastereoselectivity (entry 7; **5b/6b** = 16:84) although with an eroded yield due to its sensitivity to acidic conditions, even on lowering the amount of the Lewis acid to 0.5 equivalent. Urethane gave good diastereoselectivities (entry 8; **5c/6c**: 19:81) and excellent yields whereas the tosyl group showed a modest yield and moderate diastereoselectivity (entry 9; **5d/6d** = 30:70). From the ^1H NMR spectra of the crude mixtures, it was determined that the diastereomeric ratio always favored the same diastereomer (**6a–d**) with unknown relative stereochemistry. Therefore the major diastereomer **6a**[8] (entry 1) was en-

Table 1 Study of the 1,3-Diastereoselective Aza-Sakurai–Hosomi Reaction



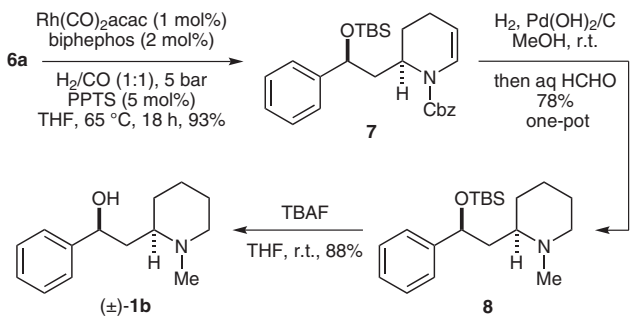
Entry	R^1	R^2	$BF_3{\cdot}OEt_2$[a]	Products	*syn*/*anti*[b]	Yield[c]
1	TMS	Cbz	1 equiv[d]	**5e/6e**	18:82	89%
2	TMS	Cbz	1 equiv[d,e]	**5e/6e**	50:50	93%
3	TMS	Cbz	1 equiv, 1 M[f]	**5a/6a**	17:83	84%
4	TMS	Cbz	0.5 equiv, 1 M[f]	**5a/6a**	15:85	89%
5	$SiMe_2Ph$	Cbz	1 equiv, 1 M[f]	**5a/6a**	16:84	75%
6	$SnBu_3$	Cbz	1 equiv, 1 M[f]	–[g]	ND	90%
7	TMS	Boc	0.5 equiv, 1 M[e]	**5b/6b**	16:84	68%
8	TMS	CO_2Et	1 equiv, 1 M[f]	**5c/6c**	19:81	95%
9	TMS	Tos	1 equiv, 1 M[f]	**5d/6d**	30:70	51%
10	TMS	–[h]	1 equiv, 1 M[f]	–[g]	30:70	76%
11	$SnBu_3$	–[h]	1 equiv, 1 M[f]	–[g]	25:75	94%

[a] Freshly distilled $BF_3{\cdot}OEt_2$ was used.
[b] Determined by GC–MS, except for entries 10 and 11 that were determined by ^1H NMR.
[c] Isolated after column chromatography.
[d] Added neat.
[e] Reaction was performed in MeCN.
[f] Diluted in CH_2Cl_2.
[g] Sakurai products.
[h] Reaction was performed without carbamate.

gaged in subsequent transformations towards the preparation of sedamine or *allo*-sedamine depending on if **6a** had the *syn* or *anti* configuration. We expected that the correlation with the reported physical data of sedamine (**1a**) would not only solve the structural ambiguity but also provide some rationale about the observed 1,3-diastereoselectivity in the aSH-R3C.

As mentioned before homoallyamine **6a** was submitted to a hydroformylation on the terminal alkene in THF as solvent. This reaction is an attractive synthetic transformation as a new carbon–carbon bond is formed by addition of H_2 and CO to an alkene catalyzed by Rh(I). Furthermore an aldehyde function is introduced under generally mild conditions allowing the direct use of this highly important group into a wide variety of reactions, making this process a prototype of an atom economic transformation.[9] In our case, the linear aldehyde was desired for the subsequent construction of a piperidine ring; we, thus, selected the bulky diphosphite biphephos as ligand for hydroformylation (Scheme 3).[10] As a nucleophilic nitrogen is embedded in substrate **6a**, the hydroformylation step is followed by the desired cyclohydrocarbonylation to give the six-membered heterocycle **7**[11] in 93% isolated yield, formed via a transient aminal and the assistance of catalytic amount of PPTS.[12] The conditions for the conversion of **6a** into **7** were very mild using low loading of Rh(I) and reasonable *syngas* pressure, demonstrating that the cyclohydrocarbonylation is a viable alternative to metathesis for the transformation of homoallylamines to piperidines.[13] Regarding the presence of functional groups on the substrates, the catalytic mixture Rh(I)–biphephos used for the hydroformylation reaction is less demanding than the Ru(II)-based catalyst, used for metathesis. Then the final steps were carried out in one pot under hydrogen reductive conditions in the presence of Pearlman's catalyst: (i) the enamide of the tetrahydropyridine was reduced, (ii) the Cbz group was deprotected, (iii) the presence of formaldehyde furnished by reductive amination yielded the sedamine analogue **8** in 78% yield. Finally cleavage of the TBS protecting group with TBAF gave the hydroxypiperidine in 88% yield after purification by column chromatography.

The ^1H and ^{13}C NMR data of this compound clearly matched those of reported *allo*-sedamine (**1b**). This chemical correlation (**6a** with *allo*-sedamine) revealed that the



Scheme 3 Preparation of (±)-**1b**

anti stereochemistry could be assigned to the major adduct **6a** or its analogues **6b–d**. Consequently the aSH-R3C performed on 1,3-O-protected aldehyde followed an *anti* bias. To account for the observed *anti*-preferred diastereoselectivity, a nonchelated transition state is suggested. Therefore, the model proposed by Evans and Reetz[14] for the nucleophilic attack on aldehydes possessing a β stereocenter (Figure 1) could be transposed to the corresponding iminiums (**A**), intermediates in the aSH-R3C, to explain the observed *anti* selectivity. From this preliminary study we propose an expeditious preparation of 1,3-O-protected homoallylamine from the corresponding aldehyde using a simple R3C reaction and the synthesis of (±)-*allo*-sedamine (**1b**) in seven steps (from benzaldehyde) with an overall yield of 44%. Probably this is one of the shortest syntheses reported to date.[15]

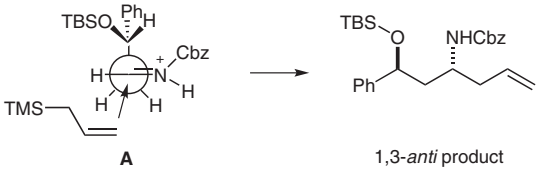
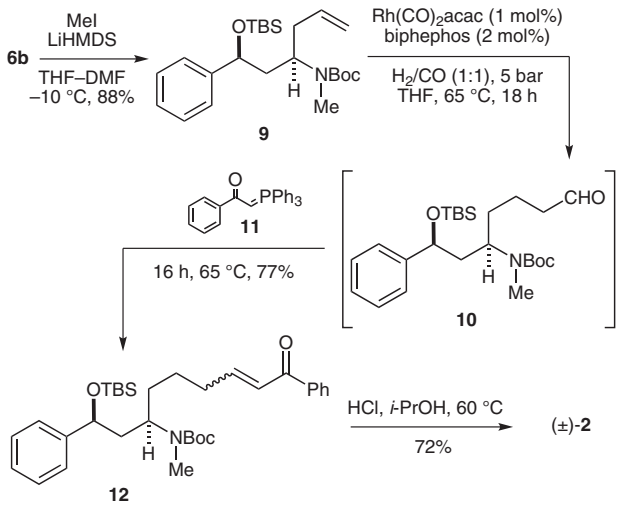


Figure 1 Rationale for the 1,3-diastereoselectivity

Now that we had secured the relative stereochemistry of allylamines **6a–d**, we envisioned the preparation of (±)-*allo*-lobeline (**2**) starting from **6b**, a compound that has never been prepared before. Therefore, we targeted intermediate **12**, an epimer of a late stage intermediate reported by Lebreton, towards the synthesis of (–)-lobeline.

As the hydroformylation proved to be useful in the preparation of *allo*-sedamine, we decided to exploit the same sequence towards the synthesis of *allo*-lobeline with some new sophistication. The synthesis started with the Boc-protected allylamine **6b** (Scheme 4). To prevent the cyclohydrocarbonylation, that would inevitably follow the hydroformylation of the terminal double bond, and to meet the structural requirements, substrate **6b** was reacted with methyl iodide in the presence of LiHMDS to produce the *N*-methylated compound **9**. For the access to enone **12**, we first opted for a domino hydroformylation–Wittig olefination, a sequence initially described by Breit et al.[16] But under the hydroformylative conditions the conjugated double bound was reduced, precluding the possible aza-Michael reaction. Therefore the reaction sequence was modified in the following way: after hydroformylation of **9** the pressure was released, ylide **11** was added in the same pot yielding enone **12** in 77% isolated yield, as a mixture of *E*- and *Z*-isomers. The final steps were adapted from the reported synthesis of lobeline. Heating **12** under hydrolytic condition in isopropanol allowed *N*-Boc deprotection followed by the aza-Michael reaction and desilylation affording a *cis*-2,6-piperidine identified as (±)-*allo*-lobeline (**2**). As the intramolecular Michael addition in **12** is reversible, the stereochemistry of the double bond in the enone **12** has no influence on the 1,4-addition because the thermodynamic more stable 2,6-*cis*-piperidine is the fa-



Scheme 4 Preparation of (±)-**2**

vored diastereomer.[17] Finally (±)-*allo*-lobeline was prepared for the first time in seven steps (from benzaldehyde) with an overall yield of 25%.

Thus we have reported that implementation of the aza-Sakurai–Hosomi three-component reaction (aSH-R3C) on 1,3-O-protected aldehydes delivered homoallylamines in good yields and with moderate *anti* 1,3-diastereoselectivities in an acyclic stereocontrol. The *anti*-allylamines **6a** and **6b** were used for the expeditious syntheses of two piperidine alkaloids (±)-*allo*-sedamine (**1a**; 7 steps) and (±)-*allo*-lobeline (**2**; 7 steps), respectively, by using a cyclohydrocarbonylation or a one-pot hydroformylation–Wittig reaction. We are currently focusing our efforts on the rapid access to other biomolecules using hydroformylation.

Acknowledgment

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(6) Orientating experiments with different protecting groups on the alcohol were performed with TBS (**5e**/**6e** = 85:15), Bn (**5e**/**6e** = 75:25), Me (**5e**/**6e** = 70:30) using conditions from Table 1, entry 1.

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(8) **Typical Procedure for an Aza-Sakurai–Hosomi Reaction**: In a dry flask under argon were introduced **4** (0.756 mmol) and R^2NH_2 (0.756 mmol) in anhydrous CH_2Cl_2 (4 mL, 0.2 M). The mixture was cooled to 0 °C by means of an ice bath. Allylsilane (0.765 mmol) was then added followed by a dropwise addition of a 1 M solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.756 mmol). The reaction was stirred for 1 h at 0 °C before addition of sat. $NaHCO_3$. The organic layer was extracted with CH_2Cl_2 (3 ×) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography. Spectroscopic data for **6a**: IR(film): 2952, 2928, 2856, 1696, 1508, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.39 (m, 10 H), 5.70–5.80 (m, 1 H), 5.05–5.21 (m, 5 H), 4.82 (dd, *J* = 2.0, 9.1 Hz, 1 H), 3.80–3.91 (m, 1 H), 2.26–2.40 (m, 2 H), 1.93 (ddd, *J* = 2.9, 10.0, 13.8 Hz, 1 H), 1.68 (br d, *J* = 9.1 Hz, 1 H), 0.88 (s, 9 H), 0.05 (s, 3 H), –0.26 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9 (C), 145.0 (C), 136.9 (C), 134.5 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.3 (CH), 125.9 (CH), 117.8 (CH_2), 72.7 (CH), 66.5 (CH_2), 48.4 (CH), 44.4 (CH_2), 39.7 (CH_2), 25.8 (Me), 18.1 (C), –4.5 (Me), –5.1 (Me). HRMS (ESI, positive, HCOOLi): *m/z* [M + Li] calcd for $C_{23}H_{39}NO_3Si$: 446.2698; found: 446.2690.

(9) For a review on hydroformylation, see: Breit, B.; Seiche, W. *Synthesis* **2001**, 1.

(10) (a) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2066. (b) The structure of Biphephos is shown in Figure 2.

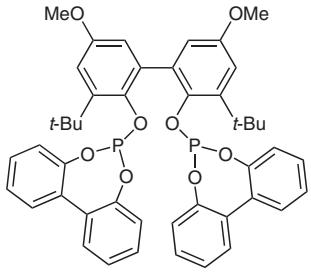

Figure 2

(11) **Typical Procedure for Hydroformylation**: In a dry Schlenk glassware under argon were introduced $Rh(CO)_2acac$ (1 mol%) and anhydrous degassed THF (1 mL). Biphephos (2 mol%) was added and CO evolution was observed. Subsequent addition of homoallylic amide (and PPTS) was performed. The mixture was transferred via a syringe in a dry stainless autoclave under argon. The glassware was rinsed with anhydrous degassed THF (3 ×) to reach a final concentration of 0.04 M. The autoclave was purged (3 ×) with H_2/CO (1:1) before setting the pressure at 5 bar. The autoclave was heated at 65 °C (internal temperature) by means of an oil bath. Once the reaction was

finished, the autoclave was depressurized and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography. Spectroscopic data for **7**: IR(film): 2951, 2927, 2854, 1703, 1651, 1324, 1089, 1060, 833 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.15–7.36 (m, 10 H), 6.79 (br d, *J* = 8.2 Hz, 0.5 H, rotamers), 6.66 (br d, *J* = 8.2 Hz, 0.5 H, rotamers), 5.16 (s, 2 H), 4.94 (m, 0.5 H, rotamers), 4.81 (m, 1 H), 4.65 (m, 0.5 H, rotamers), 4.45 (m, 0.5 H, rotamers), 4.14 (m, 0.5 H, rotamers), 1.72–2.13 (m, 6 H), 0.87, 0.85 (s, 9 H, rotamers), 0.1 (s, 1.5 H, rotamers), –0.03 (s, 1.5 H, rotamers), –0.24, –0.26 (s, 3 H, rotamers). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.2, 152.9 (rotamers, C), 145.3, 144.6 (rotamers, C), 136.5, 136.4 (rotamers, C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.3 (CH), 126.2, 126.1 (rotamers, CH), 124.3, 123.7 (rotamers, CH), 106.2 (CH), 73.8 (CH), 67.4 (CH_2), 49.1, 48.8 (rotamers, CH), 42.7 (CH_2), 26.0 (Me), 25.5, 24.7 (rotamers, CH_2), 18.2 (C), 17.8, 17.4 (rotamers, CH_2), –4.5, –4.8 (rotamers, Me). HRMS (ESI, positive, HCOOLi): *m/z* [M + Li] calcd for $C_{26}H_{37}NO_3Si$: 458.2698; found: 458.2685.

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