Stereodivergent Approach to Both C2,8a-*syn* and C2,8a-*anti* Relative Stereochemical Manifolds in the Lepadin Family via a $TiCl_4$-Promoted Aza-[3+3] Annulation

Gang Li, Lauren J. Carlson, Irina K. Sagamanova, Brian W. Slafer, Richard P. Hsung,* Claudio Gilardi, Heather M. Sklenicka, Nadiya Sydorenko

Division of Pharmaceutical Sciences and Department of Chemistry, Wisconsin Center for Natural Products Research, School of Pharmacy, Rennebohm Hall, University of Wisconsin, Madison, WI 53705, USA
Fax +1(608)2625345; E-mail: rhsung@wisc.edu

Received 23 May 2009

Abstract: Details in developing a stereodivergent approach to the lepadin family and establishing an entry to both C2,8a-*syn* and C2,8a-*anti* relative stereochemical manifolds through a common intermediate are described here. This works paves the foundation for constructing all members of the lepadin family, which consists of three subsets based on an array of interesting relative configurations. These efforts underline the prominence of aza-[3+3] annulation as a unified strategy in alkaloid synthesis.

Key words: titanium(IV) chloride, aza-[3+3] annulation, vinylogous amides, iminium ions, alkaloid synthesis, lepadin alkaloids, stereodivergent approach, episulfide contraction

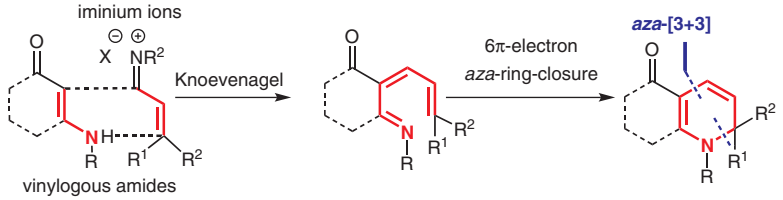
We[1–3] have been embarking on the chemistry of an aza-[3+3]-annulation strategy[4] involving vinylogous amides and vinyliminium ions[5] for the past decade (Scheme 1). This unique aza-annulation has come to represent a unified strategy amenable for de novo syntheses of many alkaloids.[6,7] To ascertain this annulation as a unified strategy to alkaloids, and to establish this imminent concept, the lepadin family attracted out attention.

The lepadin family (Scheme 2), isolated from various sources such as tunicate *Clavelina lepadinformis*,[8a] flatworm *Prostheceraeus villatus*,[8b] tropical marine tunicate *Didemnum* sp,[8c] and Australian great barrier reef ascidian, *Aplidium tabascum*.[8d] is comprised of eight *cis*-decahydroquinoline members and possesses a range of biological activities such as cytotoxicity, antiplasmodial, anti-trypanosomal properties, and antimalarial properties.[8] While all contain a *cis*-1-azadecalin, stereochemically, members of the lepadin family display a highly diversified array of relative configurations at C2, C3, C4a, C5, and C8a.

Consequently, the unique feature of being a small stereochemically diversified library has attracted many synthetic efforts.[9–15] These stereochemical relationships could be categorized into three subsets as shown in Scheme 2. While the most challenging aspect would be the 1,3-stereochemical relationship at C2 and C8a, which can be *syn* as in A–E, and H, and *anti* as in F and G, we envisioned that all three subsets could be accessed from the aza-[3+3]-annulation product **1** in a stereodivergent manner. We report here our efforts in developing a stereodivergent approach to the lepadin family with the focus on the C2,8a-*syn* and C2,8a-*anti* relative stereochemical manifolds.

The unique advantage of developing a stereodivergent approach to the lepadin family featuring the aza-[3+3] annulation product **1** can be seen in Scheme 3. That is, the annulation product **1** could be assembled rapidly from commercially available chiral amino alcohol **2** and cyclohexane-1,3-dione in just three steps. Under standard conditions, the annulation product **1** was attained in 73% yield with a diastereomeric ratio of 96:4. While the iminium ion chemistry has served us well, operationally it has not always been trivial.

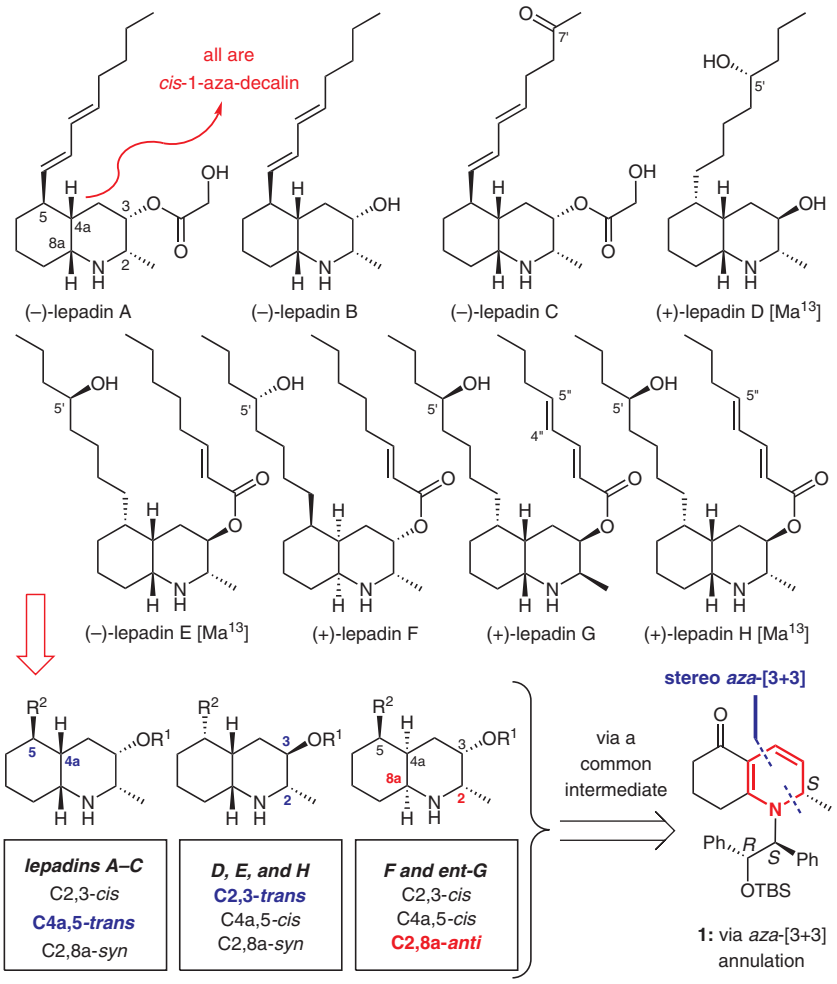
During this exercise, we found that the annulation could also be carried out using 1.0 equivalents of titanium(IV) chloride as a promoter at room temperature to give **1** and 2-*epi*-**1** in 80% yield as a 51:49 isomeric mixture. This isomeric mixture, however, could be thermally equilibrated all to **1** through a sequence of pericyclic aza-ring opening and ring closure.[2a] While most other Lewis acids [i.e., $BF_3{\cdot}OEt_2$. $SnCl_4$. $AlCl_3$. TMSOTf. $Cu(OTf)_2$.



Scheme 1 An aza-[3+3]-annulation strategy

SYNTHESIS 2009, No. 17, pp 2905–2914
Advanced online publication: 30.07.2009
DOI: 10.1055/s-0029-1216920; Art ID: C01709SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: Queen's University. Copyrighted material.



Scheme 2 A stereodivergent approach to the lepadin family

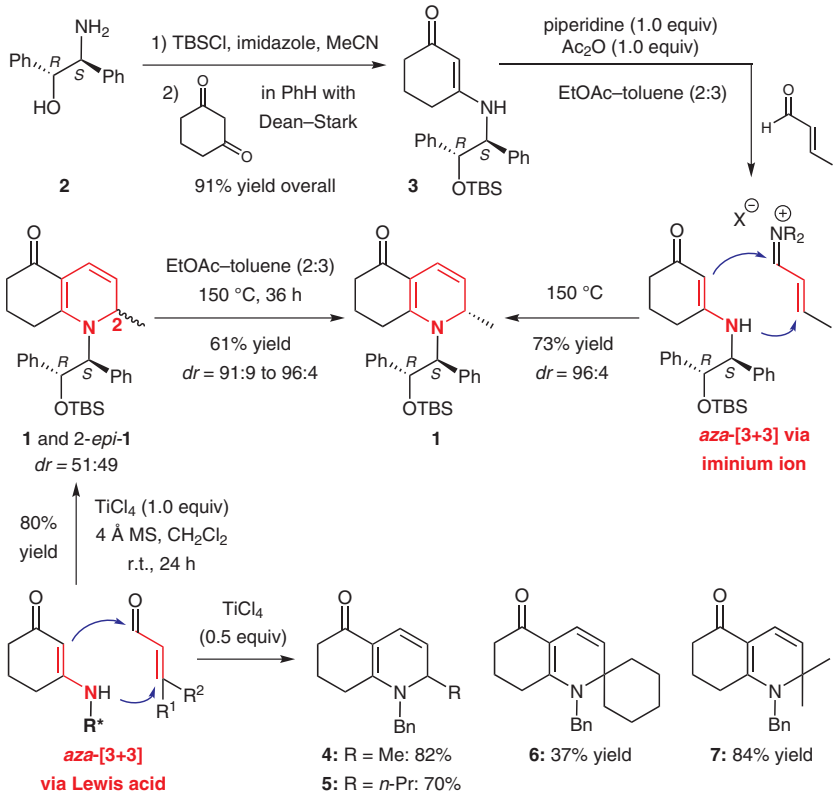
$MgBr_2 \cdot OEt_2$. $ZnCl_2$] were not successful, the titanium(IV) chloride protocol (0.5 equiv used) proved to be general in synthesizing other aza-annulation products **4**–**7**, thereby rendering the aza-[3+3] annulation operatively simpler.

The annulation product **1** sets the stage for constructing the key 1-azadecalenone **11**. As shown in Scheme 4, the sequence involved essentially a hydration equivalent at the C3–4 olefin via dihydroxylation[16,17] followed by reductive removal of the C4-OH group in the resulting diol **8** using either triethylsilane[18] or alternatively hydrogen as the reductant. This synthetic sequence solidifies an access to the C2,3-*trans* relative stereochemistry. Protection of the C3-OH group in **9** followed by removal of the chiral auxiliary in alcohol **10** via hydrogenolysis gave 1-azadecalenone **11**.

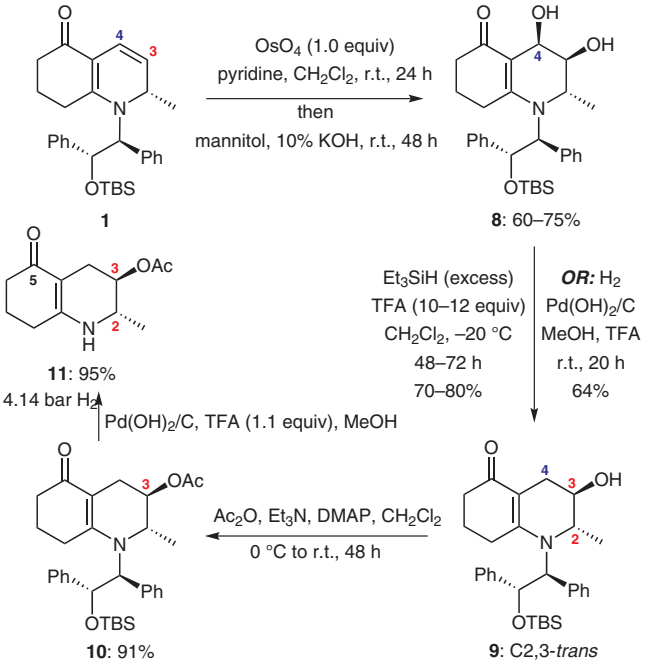
The significance of 1-azadecalenone **11** is revealed in Scheme 5. While the original stereodivergent plan[19] would include: (1) inversion of C3-OH to install the C2,3-*cis* stereochemistry in lepadin A–C, F, and G, and (2) homologation of C5-ketone, the most challenging endeavor would be to identify an appropriate reduction of the C4a–8a olefin in **11** that would give either C2,8a-*syn* or C2,8a-*anti* relative stereochemistry. However, from our earlier work related to pumiliotoxins,[2a] we have reasons to believe that this set of stereochemical manifolds could be attained through manipulations of the N-substituent. Specifically, when **12**-NH was used, the C2-Pr group dictated the facial bias, and the hydrogenation led to the C2,8a-*syn* [see **13**-*syn*] stereochemical outcome. On the other hand, **12**-N-acyl afforded **13**-*anti* because the N-acyl substituent preferred to be axial and *anti* to C2-Pr to alleviate allylic-type strain, thereby shielding the top π-face of the olefin.[2a]

With this initial success, we proceeded to construct a series of N-acylated substrates that can be suitable for setting the C2,8a-*anti* stereochemical manifold. These N-acylated substrates could be prepared starting either from **9** or **11** as shown in Scheme 7. Reductive removal of the chiral auxiliary in **9** via hydrogenolysis gave alcohol **17**. While silylation of **17** would lead to silyl ether **18** that matches Ma's mid-stage intermediate in their efforts toward the lepadin family,[13] a double acylation would lead to N-acylated acetate **19**, which could also be obtained from N-acylating **11**. Acylation of silyl ether **18** using trifluoroacetic anhydride afforded trifluoroacetamide **20**, and finally, acylation using acetic anhydride followed by desilylation gave N-acylated alcohol **21**.

Downloaded by: Queen's University. Copyrighted material.



Scheme 3 A de novo titanium(IV) chloride promoted aza-[3+3] annulation



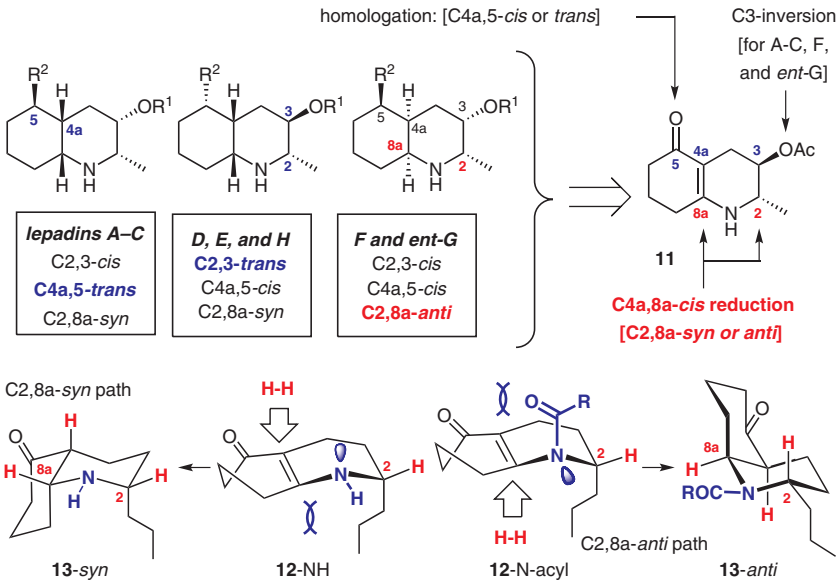
Scheme 4 Hydration of C3–4 olefin and the auxiliary removal

Based on the above analysis, we were able to quickly establish the C2,8a-*syn* pathway via the concise sequence shown in Scheme 6. The C2,8a-*syn* relative stereochemistry was confirmed via NOE experiments (see the box in Scheme 6) using alcohol **14**, which was attained from the hydrogenation of the C4a–8a olefin in 1-azadecalenone **11**. Intriguingly, the C5-ketone in **11** was also reduced under these conditions, and this was true even when not using Adam's catalyst and when the hydrogen pressure is <68.95 bar. Nevertheless, N-protection followed by Dess–Martin periodinane oxidation led to 1-azadecalone **16** that should be suitable for lepadins D, E, and H, and for A–C after inverting the C3 stereogenic center.

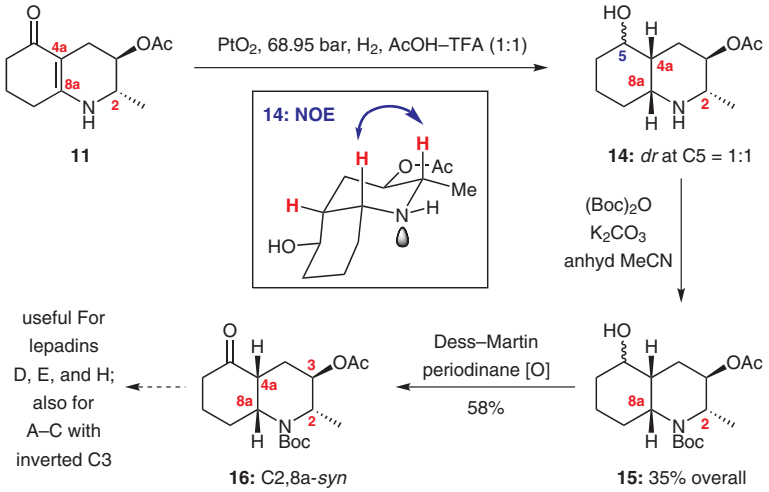
However, we encountered an immense number of problems in hydrogenations of the C4a–8a olefin in N-acylated substrates **19**–**21** (Scheme 8). After employing a variety of conditions, we were unable to isolate any of the desired respective products **22**–**24**. Instead, the major products that we were able to identify appeared to have the C5-ketone partially or completely reduced with the C4a–8a olefin being mostly untouched (see **25**–**27**). We were surprised by this outcome because the only difference between compounds **19**–**21** and **12**-N-acyl (see Scheme 5) is the additional oxygen substituent at C3. Given that N-acylated alcohol **21** with an unprotected C3-OH also failed, we believed that the cause is likely not the nature of the C3-OH protecting groups but its own stereochemical orientation. We proceeded to invert the C3-OH group, but only to find that that neither **9** nor **21** would undergo the Mitsunobu inversion employing standard conditions.

We then examined an alternative route for inverting the C3 stereocenter. As shown in Scheme 9, ketone **28** could be directly prepared from diol **8** under acidic conditions. However, with the chiral auxiliary intact, sodium borohydride reduction of ketone **28** gave alcohol **9** as an epimeric mixture at C3 that still favored β-C3-OH. Fortuitously,

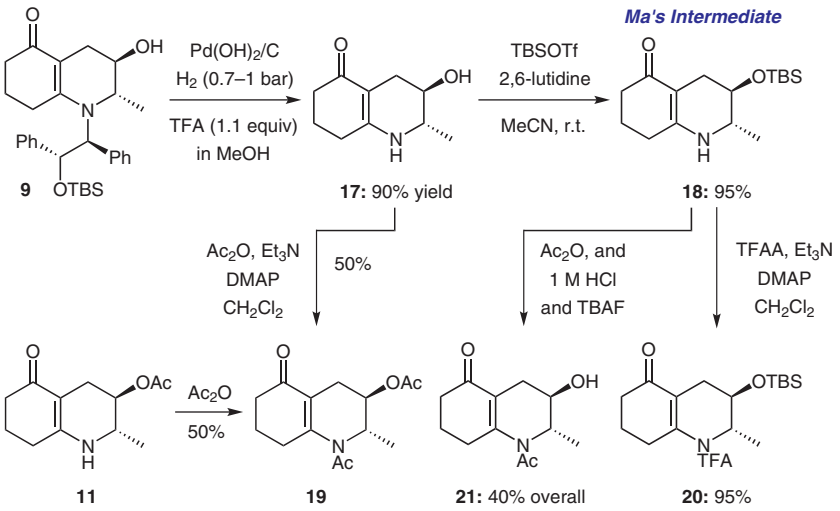
Downloaded by: Queen's University. Copyrighted material.



Scheme 5 Original designs for the stereodivergent approach

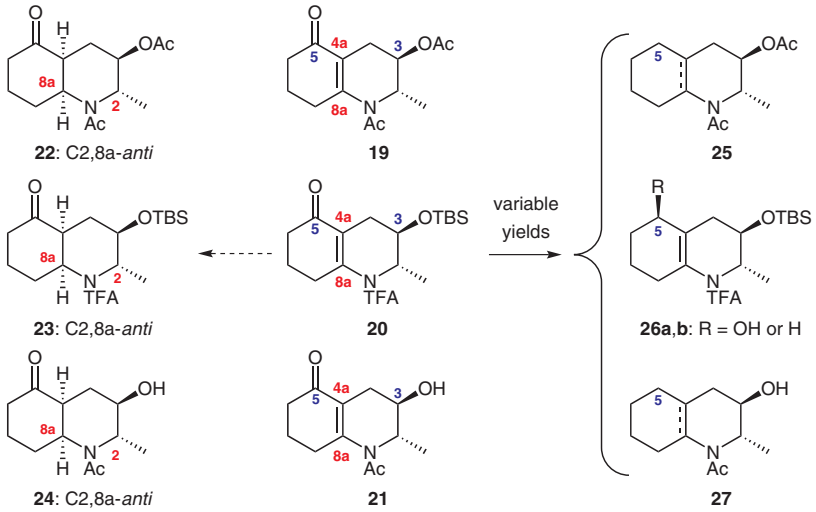


Scheme 6 A stereoselective pathway to C2,8a-*syn* stereochemistry



Scheme 7 Precursors for setting C2,8a-*anti* stereochemistry

Downloaded by: Queen's University. Copyrighted material.

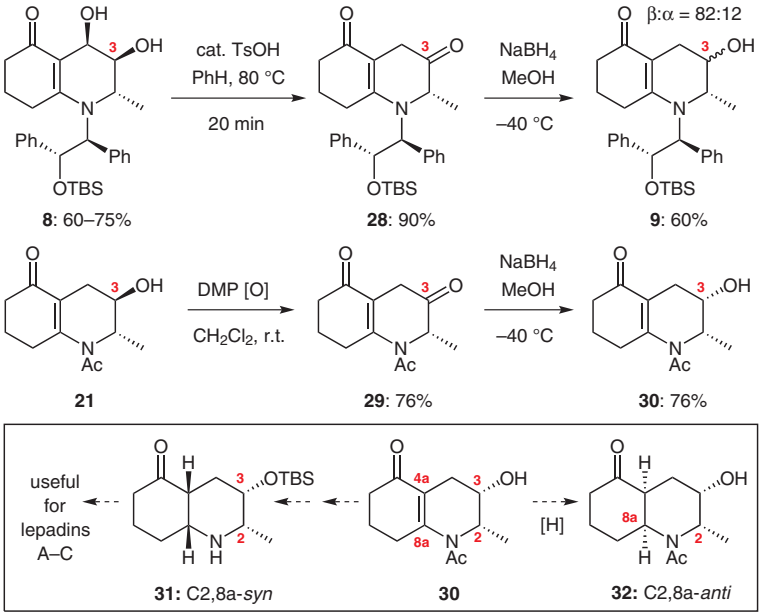


Scheme 8 Failed attempts in installing C2,8a-*anti* stereochemistry. *Reagents and conditions*: Examples attempted, H_2 (1 bar, 4.14 bar, or 68.95 bar), r.t., catalyst: Pd/C, $Pd(OH)_2$/C, or PtO_2, solvent: EtOH, MeOH or AcOH–TFA, additive: Na_2CO_3.

sodium borohydride reduction of ketone **29**, attained from Dess–Martin periodinane oxidation of N-acylated alcohol **21**, afforded alcohol **30** in a good overall yield with complete inversion at C3, thereby establishing a useful entry for inverting the C3 stereochemistry.

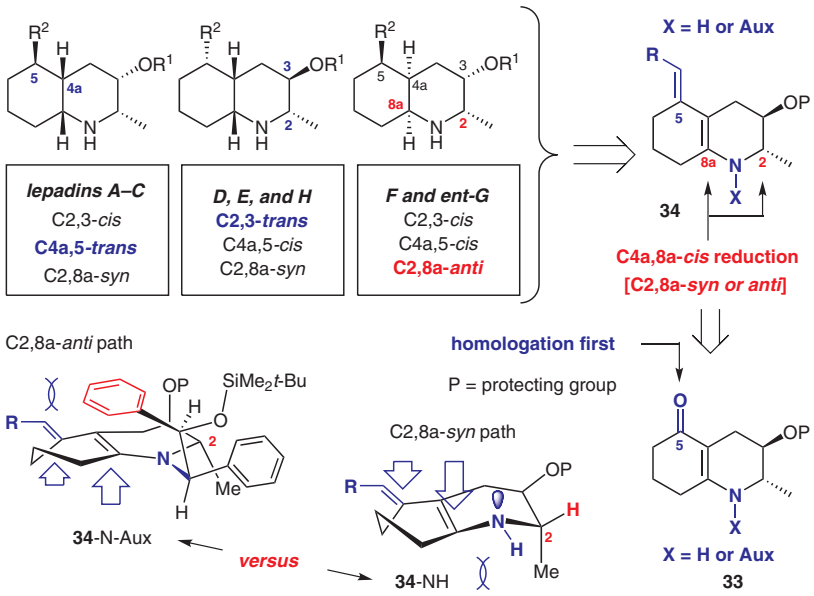
This inversion provides a clear entry to the C2,3-*cis* relative configuration. Therefore, given our ability to access the C2,8a-*syn* stereochemical manifold (see Scheme 6), alcohol **30** represents a suitable starting point for synthesizing lepadins A–C via possible intermediates such as **31** (Scheme 9). On the other hand, we remain unsuccessful in hydrogenating the C4a–8a olefin in **30** to achieve the desired C2,8a-*anti* manifold (see **32**) after employing a range of conditions including 5–15 mol% Crabtree's catalyst[20] in an attempt to carry out a Stork–Crabtree directed hydrogenation,[21] having been inspired by a related example reported by Padwa.[22]

These difficulties led us to the realization that we needed to revise our original plan. As shown in Scheme 10, we contemplated the possibility of first pursing the homologation of the C5 carbonyl at an early stage using intermediates such as **33**, and subsequently, deploy the homologated intermediate **34** as the key stereodivergent point. In this case, while the hydrogenation of **34**-NH (X = H) could again lead to the C2,8a-*syn* manifold, with the chiral auxiliary still intact as in **34**-N-Aux, we may achieve the C2,8a-*anti* manifold because the conformation analysis reveals that one of the two phenyl rings on the auxiliary is actually shielding the top π-face of the C4a–8a olefin. This new design allows us to take advantage of the chiral auxiliary for a threefold purpose instead of just one. It is now useful not just for controlling the stereochemical outcome of the key aza-[3+3] annulation at



Scheme 9 A useful protocol for inverting the C3 stereochemistry

Downloaded by: Queen's University. Copyrighted material.

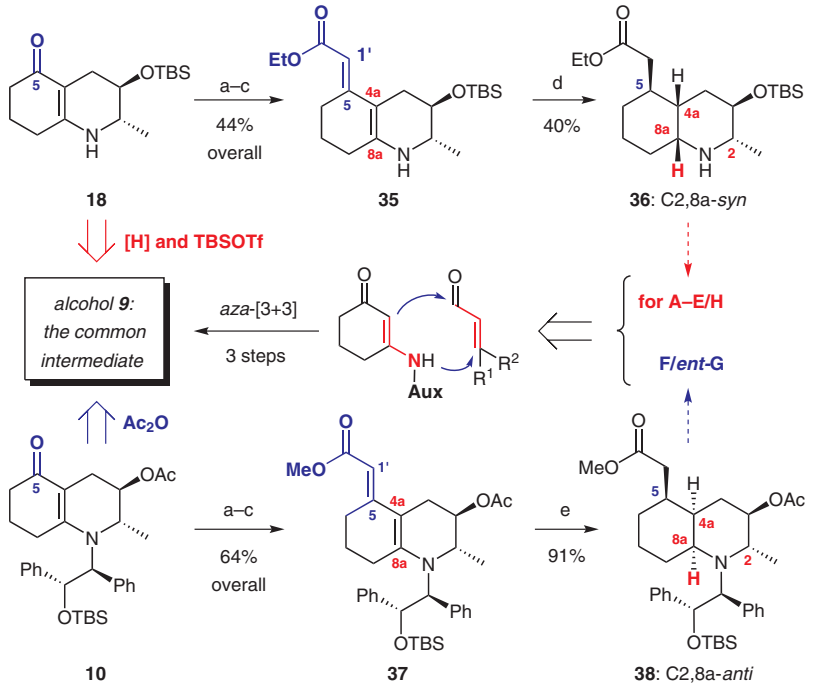


Scheme 10 New designs for the stereodivergent approach

C2, but also, that of the reduction at C4a and C8a and the side chain stereochemistry at C5.

The execution of this new plan is detailed in Scheme 11. Vinylogous amide **18** was homologated[23] employing Eschenmoser's episulfide contraction method,[24,25] while standard Wittig olefination was not successful.[26] It is noteworthy that homologations of vinylogous amides via Eschenmoser's episulfide contraction is much less common than using amides or lactams. The ensuing hydrogenation of ethyl dienoic ester **35** afforded ethyl ester **36**. Although only in modest yield, excellent stereochemical control at C4a, C8a, and C5 as predicted, thereby setting the C2,8a-*syn* relative manifold that was concisely assigned by NOE (Figure 1).

Most critically, while **36** can be useful for constructing lepadins A–E and H, methyl dienoic ester **37** was also prepared through homologation of vinylogous amide **10** (Scheme 11). The ensuing hydrogenation gave methyl ester **38** in 91% yield using Adam's catalyst with complete stereochemical control at C4a and C8a (at C5 7:1 ratio favoring **38**). This successful sequence finally afforded the much anticipated C2,8a-*anti* manifold, thereby complet-



Scheme 11 Execution of the new stereodivergent plan. *Reagents and conditions*: (a) Lawesson reagent, THF, r.t., 1 h; (b) $BrCH_2CO_2R$ (R = Me or Et), K_2CO_3, THF or acetone; (c) Ph_3P (2.0 equiv), Et_3N or DIPEA, MeCN, reflux, 3 h; (d) Pt/C, AcOH, H_2 (1.38 bar), r.t., 2 h; (e) PtO_2, H_2 (1.02 bar), MeOH, 30 min.

Downloaded by: Queen's University. Copyrighted material.

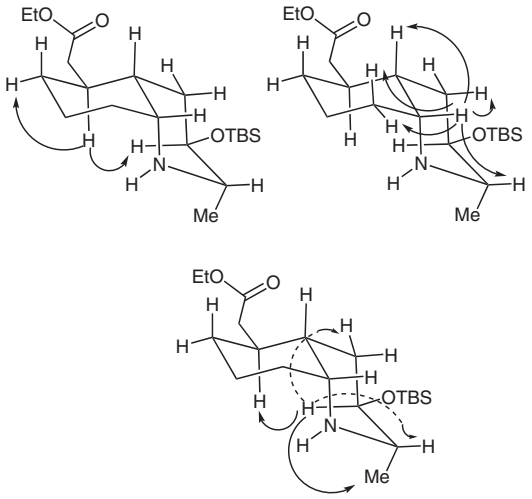


Figure 1 NOE experiments of ethyl ester **36**

ing the design of a stereodivergent approach for installing both C2,8a-*syn* and C2,8a-*anti* manifolds through a common intermediate **9**, and the threefold stereochemical control at C2, C4a, C8a, and C5 through the chiral auxiliary. We recently employed the methyl ester intermediate **38** and completed a total synthesis of (+)-lepadin F.[27]

We have described here details of our efforts in developing a stereodivergent approach to the lepadin family and achieving the concept of accessing both C2,8a-*syn* and C2,8a-*anti* relative stereochemical manifolds through a common intermediate. This work provides a solid foundation for us to construct all members of the lepadin family, which consists of three major subsets based on an array of interesting relative configurations. Our efforts further underline the synthetic prominence of aza-[3+3] annulation as a unified strategy in de novo syntheses of alkaloids.

All reactions were performed in flame-dried glassware under a nitrogen or argon atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Fluka), except where noted. Chromatographic separations were performed using Bodman 60 Å silica gel. ^{1}H and ^{13}C NMR spectra were obtained on Varian VI-400 and VI-500 spectrometers using $CDCl_3$ as solvent. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were collected on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain. Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or were performed at University of Wisconsin Mass Spectrometry Laboratories. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported. X-ray analyses were performed at the X-ray facility in University of Minnesota.

Literature references to known compounds: **1**, **8**: see ref. 16; **3**, **12**, **13**: see ref. 2a; **5**, **7**: see ref. 3f; **9**, **10**, **17**, **20**, **26a**, **26b**, **37**, **38**: see ref. 27.

(2*S*,3*R*)-3-Acetoxy-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (11)

To a soln of **10** (446.0 mg, 0.836 mmol) in MeOH (8 mL) was added TFA (71.0 μL, 0.919 mmol) and $Pd(OH)_2$/C (117.0 mg). The mixture was pressurized with H_2 (4.14 bar) for 24 h. When the reaction was completed (TLC analysis), the reaction was filtered through Celite and concentrated in vacuo. Purification by column chromatography (50% to 90% EtOAc–hexane) provided pure **11** (183.0 mg, 97%); R_f = 0.25 (10% MeOH–EtOAc).

IR (neat): 3254 (br w), 2936 (m), 1734 (s), 1676 (s), 1524 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.8 Hz, 3 H), 1.94–1.20 (m, 2 H), 2.05 (s, 3 H), 2.42–2.51 (m, 5 H), 2.63 (dd, *J* = 4.4, 16.4 Hz, 1 H), 3.52 (quint, *J* = 6.4 Hz, 1 H), 4.88 (dd, *J* = 5.6, 10.0 Hz, 1 H), 6.33 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 21.3, 21.4, 22.8, 28.9, 34.7, 50.3, 69.5, 101.5, 161.5, 170.4, 192.7.

MS (APCI): *m*/*z* (%) = 224.2 (100).

(2*S*,3*R*,4a*R*,8a*R*)-3-Acetoxy-1-(*tert*-butoxycarbonyl)-2-methyloctahydroquinolin-5(1*H*)-one (16)

To soln of **11** (50.0 mg, 0.224 mmol) in MeOH (4 mL) was added PtO_2 (50 mg). The mixture was placed in a high-pressure hydrogenation apparatus (steel bomb) at 68.95 bar for 24 h. When the reaction was completed (TLC analysis), the mixture was filtered through Celite and concentrated in vacuo to give the alcohol intermediate **14** (21.0 mg, 41%).

To a soln of **14** (21.0 mg, 0.092 mmol) in anhyd MeCN (4 mL) was added sequentially $(Boc)_2O$ (36.0 mg, 0.166 mmol) and K_2CO_3 (1.40 mg, 0.0090 mmol) and the mixture was heated to gentle reflux under N_2 for 24 h. After this time H_2O was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with an equal volume of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give **15** (25.9 mg, 85%) as a colorless oil.

To a soln of **15** prepared above (7.0 mg, 0.021 mmol) in CH_2Cl_2 (4 mL) was added Dess–Martin reagent (0.025 mmol) at r.t. The resultant mixture was stirred for 1.5 h and then the mixture was partitioned with H_2O and separated; the resulting aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a colorless oil which was purified by flash column chromatography (silica gel) to yield pure **16** (4.00 mg, 58%); R_f = 0.67 (100% EtOAc).

IR (neat): 3456 (br w), 2972 (m), 1735 (m), 1686 (s), 1457 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 7.2 Hz, 3 H), 1.47 (s, 9 H), 1.53–1.58 (m, 1 H), 1.79 (dt, *J* = 3.6, 14.0 Hz, 1 H), 1.78–1.85 (m, 1 H), 1.91–2.02 (m, 2 H), 2.01 (dd, *J* = 2.4, 14.0 Hz, 1 H), 2.08 (s, 3 H), 2.28 (dd, *J* = 6.0, 13.2 Hz, 1 H), 2.33–2.38 (m, 1 H), 2.94 (dt, *J* = 4.8, 13.6 Hz, 1 H), 4.24 (q, *J* = 6.8 Hz, 1 H), 4.30–4.44 (br m, 1 H), 4.90 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 21.5, 22.0, 23.6, 26.9, 28.6, 38.2, 45.7, 69.6, 80.4, 158.0, 170.4, 212.0.

MS (ESI): *m*/*z* (%) = 348.2 (100, $[M + Na]^+$).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{27}NO_5Na$: 348.1782; found: 348.1785.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (18)

To a soln of **17** (393.0 mg, 2.17 mmol) in anhyd MeCN (60 mL) was added 2,6-lutidine (0.76 mL, 6.50 mmol). The soln was cooled to 0 °C and TBSOTf (1.50 mL, 6.50 mmol) was added dropwise via syringe. The soln was stirred at r.t. for 12 h, then diluted with CH_2Cl_2 and quenched with H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined or-

Downloaded by: Queen's University. Copyrighted material.

ganic layers were washed with equal volumes of sat. aq $NaHCO_3$ and sat. aq NaCl, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue via flash column chromatography (silica gel, gradient 50% to 100% EtOAc–hexanes) gave pure **18** (640.0 mg, 100%); mp 205–206 °C; R_f = 0.46 (10% MeOH–EtOAc).

IR (thin film): 3268 (br s), 2933 (s), 2857 (s), 1571 (w), 1516 (m), 1459 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.09 (s, 3 H), 0.88 (s, 9 H), 1.21 (d, *J* = 6.0 Hz, 3 H), 1.87–1.96 (m, 2 H), 2.11 (dd, *J* = 9.0, 16 Hz, 1 H), 2.26–2.32 (m, 4 H), 2.73 (dd, *J* = 5.0, 15.5 Hz, 1 H), 3.13 (quint, *J* = 6.5, 7.0 Hz, 1 H), 3.48 (ddd, *J* = 5.5, 9.5, 13.5 Hz, 1 H), 4.45 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, –3.8, 18.2, 19.1, 21.9, 26.0, 29.1, 36.4, 53.6, 70.8, 103.8, 158.1, 194.8.

MS (ESI): *m*/*z* (%) = = 318.2 (92, $[M + Na]^+$), 296.2 (100, $[M]^+$), 284.2 (11).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{29}NO_2SiNa$: 318.1865; found: 318.1855.

(2*S*,3*R*)-1-Acetyl-3-(*tert*-butyldimethylsiloxy)-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one

To a soln of **18** (106.0 mg, 0.359 mmol) in anhyd CH_2Cl_2 (3 mL) was added 2,6-lutidine (1.38 mL, 1.18 mmol) and DMAP (8.80 mg, 0.72 mmol). Ac_2O (5 mL, 46.7 mmol) was then added dropwise via syringe. The resulting soln was stirred at 40 °C for 40 h and then diluted with CH_2Cl_2 (10 mL) and quenched with sat. aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with an equal volume of CH_2Cl_2. The combined organic layers were washed with an equal volume of sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo.

The above crude product was dissolved in THF (7 mL) and aq 1.0 M HCl soln (1.17 mL) was added. The acidification was allowed to run for 6 h before it was diluted with CH_2Cl_2 (10 mL) and quenched with sat. aq $NaHCO_3$. This process was monitored via TLC analysis, and more HCl was added if not complete. The organic layer was separated and the aqueous layer was extracted with an equal volume CH_2Cl_2. The combined organic layers were washed with an equal volume of sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography gave the corresponding N-acylated silyl ether intermediate (82.7 mg, 68%) and also some N-acylated alcohol **21** (7.80 mg, 4%) that was already desilylated; R_f = 0.80 (10%, EtOAc–hexane).

^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 0.75 H), 0.02 (s, 0.75 H), 0.04 (s, 2.25 H), 0.05 (s, 2.25 H), 0.82 (s, 9 H), 1.04 (d, *J* = 6.5 Hz, 3 H), 1.58–1.70 (m, 0.33 H), 1.83–1.92 (m, 0.67 H), 2.03–2.09 (m, 1 H), 2.23 (s, 3 H), 2.25–2.31 (m, 1.5 H), 2.34–2.39 (m, 1.5 H), 2.22–2.48 (m, 2 H), 3.20–3.29 (m, 1 H), 3.93–3.96 (m, 1 H), 4.05 (ddd, *J* = 3.0, 6.5, 13.5 Hz, 0.8 H), 4.14 (ddd, *J* = 3.0, 6.5, 13.5 Hz, 0.8 H); Non-integer counts of protons are due to rotameric issue.

MS (APCI): *m*/*z* (%) = 338.2 (100, $[M + H]^+$).

(2*S*,3*R*)-1-Acetyl-3-hydroxy-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (21)

To a soln of the above silyl ether (39.4 mg, 0.12 mmol) in anhyd THF (3 mL) at 0 °C was added dropwise 1.0 M TBAF in THF (0.12 mL). The resulting mixture was stirred for 5 h and then poured into H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with sat. aq NaCl (45 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue by flash column chromatography (silica gel, gradient 10% to 30% EtOAc–hexanes) gave **21** (12.8 mg, 49%) as a colorless oil and also some recovered silyl ether (3.60 mg, 9%); R_f = 0.25 (10% MeOH–EtOAc).

IR (neat): 3286 (br m), 2937 (m), 173s (m), 1651 (s), 1604 (s), 1525 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.0 Hz, 3 H), 1.80–1.92 (m, 1 H), 2.01–2.09 (m, 1 H), 2.29 (s, 3 H), 2.32–2.47 (m, 5 H), 3.20–3.30 (m, 1 H), 4.00 (br s, 1 H), 4.12 (ddd, *J* = 4.4, 6.8, 10.4 Hz, 1 H).

MS (APCI): *m*/*z* (%) = = 224.1 (100, $[M + H]^+$).

(2*S*,3*S*)-1-Acetyl-3-hydroxy-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (30)

To a soln of alcohol **21** (19.0 mg, 0.085 mmol) and $NaHCO_3$ (28.6 mg, 0.48 mmol) in CH_2Cl_2 (1.5 mL) was added self-made Dess–Martin periodinane (36.0 mg, 0.085 mmol). The soln was stirred at r.t. for ~35 min. When the reaction was completed (TLC analysis; 10% MeOH–EtOAc or LCMS), it was quenched with a few drops of *i*-PrOH. The mixture was filtered through Celite and concentrated under reduced pressure. Purification of the crude residue via flash column chromatography (silica gel, gradient 0% to 10% MeOH–EtOAc) afforded ketone **29** (14.2 mg, 76%) as a colorless oil, which was immediately used for the following step.

To a soln of ketone **29** prepared above (11.4 mg, 0.052 mmol) in anhyd MeOH (1.2 mL) under N_2 at –41 °C was added $NaBH_4$ (2.00 mg, 0.052 mmol). The soln was stirred at same temperature for 1 h (TLC monitoring). The mixture was quenched with aq 0.5 M HCl soln (0.5 mL) and diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. aq NaCl, dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude residue via flash column chromatography (silica gel, gradient 0% to 5% MeOH–EtOAc) gave pure **30** (8.80 mg, 76%) as a colorless oil; R_f = 0.45 (10% MeOH–EtOAc).

IR (neat): 3371 (br m), 2934 (m), 1644 (s), 1602 (s), 1375 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 1.81–1.92 (m, 1 H), 1.96–2.09 (m, 2 H), 2.29 (s, 3 H), 2.35–2.47 (m, 3 H), 2.80 (ddd, *J* = 2.4, 6.4, 17.6 Hz, 1 H), 3.23 (m, 1 H), 3.98 (br m, 1 H), 4.18 (qd, *J* = 4.4, 6.8 Hz, 1 H).

MS (APCI): *m*/*z* (%) = 224.2 (100, $[M + H]^+$).

Ethyl [(2*S*,3*R*,*E*)-3-(*tert*-Butyldimethylsiloxy)-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-ylidene]acetate (35)

Lawesson's reagent (39.0 mg, 0.097 mmol) was added to a soln of **18** (57.0 mg, 0.19 mmol) in THF (5 mL), and the resulting mixture was stirred at r.t. for 1 h. The solvent was removed in vacuo and then column chromatography (silica gel) gave the desired thio-vinylogous amide intermediate (52.0 mg, 87%) as a yellow oil.

To a soln of thio-vinylogous amide (32.9 mg, 0.11 mmol) in acetone (5 mL) was added successively K_2CO_3 (29.2 mg, 0.21 mmol) and ethyl α-bromoacetate (0.013 mL, 0.12 mmol). The resulting mixture was stirred at r.t. for 1 h, and after which, solids were filtered. After solvent removal in vacuo, column chromatography (silica gel) gave the thiirane intermediate (42.2 mg, 100%) as a yellow oil.

A mixture of this thiirane (42.2 mg, 0.11 mmol), Ph_3P (36.0 mg, 0.14 mmol), and DIPEA (7.00 μL, 0.041 mmol) in MeCN (5 mL) was heated in a sealed tube at 90 °C for 24 h. The excess solvent was evaporated in vacuo and the crude residue was subjected to flash column chromatography (silica gel, gradient 0% to 2% MeOH–EtOAc) to give **35** (19.7 mg, 51%) as a light yellow oil; R_f = 0.60 (10% MeOH–EtOAc).

$[\alpha]_D^{23}$ –179.6 (*c* 0.40, $CHCl_3$).

IR (neat): 3363 (br w), 2929 (m), 2857 (m), 1736 (m), 1560 (m), 1503 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.59–

Downloaded by: Queen's University. Copyrighted material.

1.72 (m, 1 H), 1.75–1.87 (m, 1 H), 2.04–2.20 (m, 3 H), 2.44 (dd, *J* = 5.6, 15.2 Hz, 1 H), 2.71 (m, 1 H), 3.08 (qd, *J* = 6.4, 7.2 Hz, 1 H), 3.34 (dt, *J* = 5.6, 17.6 Hz, 1 H), 3.55 (dt, *J* = 5.6, 8.8 Hz, 1 H), 3.70 (br s, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 5.23 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, –3.8, 14.7, 18.1, 18.8, 21.8, 25.9, 27.0, 29.1, 32.8, 52.9, 58.8, 71.6, 100.2, 101.1, 148.2, 158.0, 168.5.

MS (APCI): *m*/*z* (%) = 366.2 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{36}NO_3Si$: 366.2459; found: 366.2459.

Ethyl [(2*S*,3*R*,4a*S*,8a*R*)-3-(*tert*-Butyldimethylsiloxy)-2-methyldecahydroquinolin-5-yl]acetate (36)

To a soln of **35** (4.60 mg, 0.013 mmol) in anhyd AcOH (2 mL) was added 10% Pt/C (12.3 mg). The mixture was placed in a Lab-Crest pressure reaction vessel at 1.38 bar H_2 pressure for 2 h. When the reaction was complete (LCMS analysis), the mixture was filtered through Celite and concentrated in vacuo. Purification of the crude residue by flash column chromatography (silica gel, gradient 0% to 2% MeOH–EtOAc) afforded **36** (1.80 mg, 40%) as a light yellow oil; R_f = 0.40 (5% MeOH–EtOAc).

IR (neat): 3395 (br w), 2929 (s), 2858 (m), 1733 (s), 1462 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.89 (s, 9 H), 0.96–1.05 (m, 1 H), 1.12 (d, *J* = 6.5 Hz, 3 H), 1.26 (t, *J* = 7.0 Hz, 3 H), 1.33–1.48 (m, 3 H), 1.48–1.67 (m, 3 H), 1.77 (br d, *J* = 12.5 Hz, 1 H), 1.97–2.05 (m, 2 H), 2.17–2.28 (m, 1 H), 2.50–2.58 (m, 2 H), 2.97 (br m, 1 H), 3.28–3.33 (m, 1 H), 4.10–4.18 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.5, –4.0, 14.4, 18.2, 20.8, 26.0, 31.8, 32.4, 33.0, 36.9, 39.4, 42.1, 55.5, 60.0, 60.3, 71.0, 77.4, 173.5.

MS (APCI): *m*/*z* (%) = 370.2 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{40}NO_3Si$: 370.2772; found: 370.2767.

Methyl {(2*S*,3*R*,*E*)-3-Acetoxy-1-[(1*S*,2*R*)-2-(*tert*-Butyldimethylsiloxy)-1,2-diphenylethyl]-2-methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-ylidene}acetate (37)

R_f = 0.30 (20% EtOAc–hexanes).

$[\alpha]_D^{23}$ +499.4 (*c* 0.16, $CHCl_3$).

IR (neat): 2933 (m), 2887 (m), 2859 (m), 1739 (m), 1699 (m), 1544 (s), 1433 (m), 839 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.42 (s, 3 H), 0.06 (s, 3 H), 0.18 (d, *J* = 6.8 Hz, 3 H), 0.65 (s, 9 H), 1.00–1.11 (m, 1 H), 1.38–1.50 (m, 2 H), 1.86–1.98 (m, 1 H), 2.16–2.30 (m, 4 H), 2.37 (dd, *J* = 6.0, 18.0 Hz, 1 H), 2.47–2.58 (m, 1 H), 3.02 (dt, *J* = 4.8, 15.6 Hz, 1 H), 3.61 (s, 3 H), 3.79 (br q, *J* = 6.4 Hz, 1 H), 4.96–5.00 (m, 1 H), 5.00 (d, *J* = 8.8 Hz, 1 H), 5.07 (d, *J* = 8.8 Hz, 1 H), 5.14 (s, 1 H), 7.23–7.36 (m, 8 H), 7.56–7.60 (dd, *J* = 2.0, 9.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.9, –3.6, 16.9, 18.0, 21.8, 21.9, 25.7, 25.8, 26.4, 27.7, 50.4, 51.4, 68.2, 70.7, 74.0, 99.7, 100.0, 127.6, 127.7, 128.0, 128.1, 128.2, 131.0, 137.8, 143.9, 148.9, 158.7, 168.8, 170.5

MS (APCI): *m*/*z* (%) = 590.4 (100, M + H]$^+$), 558.3 (10).

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{48}NO_5Si$: 590.3296; found: 590.3305.

Methyl {(2*S*,3*R*,4a*R*,8a*S*)-3-Acetoxy-1-[(1*S*,2*R*)-2-(*tert*-Butyldimethylsiloxy)-1,2-diphenylethyl]-2-methyldecahydroquinolin-5-yl}acetate (38)

R_f = 0.35 (20% EtOAc–hexanes).

$[\alpha]_D^{23}$ +27.5 (*c* 0.16, $CHCl_3$).

IR (neat): 3063 (w), 3028 (m), 2855 (m), 1732 (s), 834 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.42 (s, 3 H), –0.12–0.00 (m, 1 H), –0.07 (s, 3 H), 0.56 (s, 9 H), 0.82–0.94 (m, 1 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.00 (qt, *J* = 3.5, 12.5 Hz, 1 H), 1.18–1.32 (m, 3 H), 1.38 (dtt, *J* = 2.5, 12.5 Hz, 1 H), 1.53 (dtt, *J* = 5.0, 12.0 Hz, 1 H), 1.71 (m, 1 H), 1.93 (s, 3 H), 2.03–2.12 (m, 2 H), 2.15 (dd, *J* = 5.0, 12.5 Hz, 1 H), 2.87 (dq, *J* = 6.5, 9.5 Hz, 1 H), 2.94 (dt, *J* = 3.5, 12.0 Hz, 1 H), 3.51 (ddd, *J* = 5.5, 10.0, 10.5 Hz, 1 H), 3.70 (s, 3 H), 4.28 (d, *J* = 9.5 Hz, 1 H), 5.11 (d, *J* = 9.0 Hz, 1 H), 7.18–7.32 (m, 10 H).

^{1}H NMR (500 MHz, C_6D_6): δ = –0.25 (s, 3 H), –0.02 (s, 3 H), 0.08–0.14 (m, 1 H), 0.67 (qd, *J* = 4.0, 13.0 Hz, 1 H), 0.76 (s, 9 H), 0.89–0.97 (m, 1 H), 0.99 (d, *J* = 6.0 Hz, 1 H), 1.16–1.24 (m, 3 H), 1.27 (dq, *J* = 3.0, 13.0 Hz, 1 H), 1.63 (s, 3 H), 1.69 (dt, *J* = 5.0, 12.5 Hz, 1 H), 1.85–1.94 (m, 1 H), 1.90 (dd, *J* = 8.0, 15.0 Hz, 1 H), 1.98 (dd, *J* = 7.0, 15.0 Hz, 1 H), 2.14–2.23 (m, 1 H), 2.92–3.02 (m, 2 H), 3.43 (s, 3 H), 3.80 (ddd, *J* = 5.5, 9.0, 10.5 Hz, 1 H), 4.43 (d, *J* = 9.0 Hz, 1 H), 5.25 (d, *J* = 9.0 Hz, 1 H), 7.10–7.18 (m, 2 H), 7.22 (t, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.36 (d, *J* = 7.0 Hz, 2 H), 7.45 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.0, –4.0, 16.4, 17.9, 19.7, 21.4, 24.9, 25.1, 25.7, 26.5, 37.8, 38.4, 38.5, 51.1, 51.6, 56.1, 65.8, 75.1, 76.8, 126.6, 127.6, 127.7, 128.0, 128.1, 128.9, 141.8, 144.6, 170.3, 173.7.

MS (APCI): *m*/*z* (%) = 594.4 (95, [M + H]$^+$), 534.3 (100).

HRMS (MALDI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{52}NO_5Si$: 594.3609; found: 594.3586.

Acknowledgment

Authors thank NIH [NS38049] for funding.

References

(1) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23. (c) Coverdale, H. A.; Hsung, R. P. *ChemTracts* **2003**, *16*, 238.

(2) For leading references, see: (a) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-L.; Gerasyuto, A. I.; Brennessel, W. W. *J. Am. Chem. Soc.* **2002**, *124*, 10435. (b) Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem. Int. Ed.* **2001**, *40*, 1516.

(3) For our general work on developing the aza-[3+3]-annulation method, see: (a) Ghosh, S. K.; Buchanan, G. S.; Long, Q. A.; Wei, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *63*, 883. (b) Sydorenko, N.; Hsung, R. P.; Vera, E. L. *Org. Lett.* **2006**, *8*, 2611. (c) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. W. *J. Org. Chem.* **2005**, *70*, 4248. (d) Sydorenko, N.; Hsung, R. P.; Darwish, O. S.; Hahn, J. M.; Liu, J. *J. Org. Chem.* **2004**, *69*, 6732. (e) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J.; Mulder, J. A. *Org. Lett.* **2000**, *2*, 1161. (f) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.

(4) For recent studies in this area, see: (a) Guo, H.; Qihai, X. u. Q.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318. (b) Alladoum, J.; Toum, V.; Hebbe, S.; Kadouri-Puchot, C.; Dechoux, L. *Tetrahedron Lett.* **2009**, *50*, 617. (c) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4012. (d) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504. (e) Mancey, N. C.; Butlin, R. J.; Harrity, J. P. A. *Synlett*

Downloaded by: Queen's University. Copyrighted material.

2008, 2647. (f) Zhong, W.; Lin, F.; Chen, R.; Su, W. *Synthesis* **2008**, 2561. (g) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357. (h) Schmidt, A.; Gütlein, J.-P.; Mkrrchyan, S.; Görls, H.; Langer, P. *Synlett* **2007**, 1305. (i) Pattenden, L. C.; Wybrow, R. A. J.; Smith, S. A.; Harrity, J. P. A. *Org. Lett.* **2006**, *8*, 3089. (j) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330. (k) Halliday, J. I.; Chebib, M.; Turner, P.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 3399. (l) Katsuyama, I.; Funabiki, K.; Matsui, M.; Muramatsu, H.; Shibata, K. *Heterocycles* **2006**, *68*, 2087. (m) Bose, D. S.; Kumar, R. K. *Heterocycles* **2006**, *68*, 549. (n) Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2005**, *7*, 2993. (o) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207.

(5) For leading reviews on the chemistry of iminium ions, see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (c) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (e) Scholz, U.; Winterfeldt, E. *Nat. Prod. Rep.* **2000**, *17*, 349.

(6) For some reviews see: (a) Gademann, K.; Lawrence, A. K. *Synthesis* **2008**, 331. (b) Stockman, R. A.; Sinclair, A. *Nat. Prod. Rep.* **2007**, *24*, 298. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (d) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862.

(7) For synthesis of perhydrohistrionicotoxin, see: (a) McLaughlin, M. J.; Hsung, R. P.; Cole, K. C.; Hahn, J. M.; Wang, J. *Org. Lett.* **2002**, *4*, 2017. For synthesis of tangutorine, see: (b) Luo, S.; Zificsak, C. Z.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709. For synthesis of deplancheine, see: (c) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Org. Biomol. Chem.* **2005**, *3*, 2140. For synthesis of cylindricine C, see: (d) Swidorski, J. J.; Wang, J.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 777. (e) Wang, J.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P.; Coverdale, H. A.; Kuyava, J. M.; Liu, J. *Heterocycles* **2006**, *70*, 423. For synthesis of aza-phenylene alkaloid family, see: (f) Gerasyuto, A. I.; Hsung, R. P. *Org. Lett.* **2006**, *8*, 4899. (g) Gerasyuto, A. I.; Hsung, R. P. *J. Org. Chem.* **2007**, *72*, 2476. For synthesis of lasubine II, see: (h) Zhang, Y.; Long, Q. A.; Gerasyuto, A. I.; Hsung, R. P. *Synlett* **2009**, 237.

(8) For isolation of (–)-lepadin A, see: (a) Steffan, B. *Tetrahedron* **1991**, *47*, 8729. For isolation of (–)-B and (–)-C, see: (b) Kubanek, J.; Williams, D. E.; de Silva, E. D.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189. For isolation of (+)-D, (–)-E, and (–)-F, see: (c) Wright, A. D.; Goclik, E.; König, G. M.; Kaminsky, R. *J. Med. Chem.* **2002**, *45*, 3067. For isolation of (+)-F, (+)-G, and (+)-H, see: (d) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2002**, *65*, 454.

(9) For the first total synthesis of a lepadin family member, (–)-lepadin B, see: (a) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H. *Tetrahedron* **1999**, *55*, 10673. (b) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182. Also see: (c) Toyooka, N.; Nemoto, H. *Trends Heterocycl. Chem.* **2002**, *8*, 145. (d) Toyooka, N. *Yakugaku Zasshi* **2001**, *121*, 467.

(10) For total synthesis of (–)-lepadin B, see: Ozawa, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 2955.

(11) For total syntheses of (–)-lepadin A and (–)-lepadin C, see: Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338.

(12) For a formal synthesis of (±)-lepadin B: Kalaï, C.; Tate, E.; Zard, S. Z. *Chem. Commun.* **2002**, 1430.

(13) For an elegant stereodivergent total synthesis of lepadins A–E, and H, see: (a) Pu, X.; Ma, D. *J. Org. Chem.* **2006**, *71*, 6562. (b) Pu, X.; Ma, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4222.

(14) For total syntheses of (–)-lepadin F and (–)-lepadin G, see: Niethe, A.; Fischer, D.; Blechert, S. *J. Org. Chem.* **2008**, *73*, 3088.

(15) For other studies, see: (a) Mena, M.; Valls, N.; Borreg, M.; Bonjoch, J. *Tetrahedron* **2006**, *62*, 9166. (b) Mena, M.; Bonjoch, J.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930. (c) Mena, M.; Bonjoch, J. *Tetrahedron* **2005**, *61*, 8264. (d) Barbe, G.; Charette, A. B. *Abstracts of Papers, 232nd National Meeting of the American Chemical Society, San Francisco, CA, Sept 10–14, 2006*; American Chemical Society: Washington DC, **2006**, ORGN-747.

(16) Zehnder, L. R.; Wei, L.-L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *3*, 2141.

(17) This particular dihydroxylation was very difficult and required a stoichiometric amount of OsO_4, and Scheme 4 reveals our best conditions. Other conditions examined were: (i) 5–60 mol% OsO_4 with NMO, or with $K_2Fe(CN)_6$, or with *t*-BuOOH; bases were K_2CO_3, $MeSO_2NH_2$, or DABCO; (ii) cat. to 1.1 equiv of $K_2OsO_4{\cdot}2\,H_2O$ with $K_2Fe(CN)_6$; bases were K_2CO_3, or TMEDA, or pyridine; (iii) MCPBA or MMPP or AcOOH; (iv) NBS, DMSO; (v) DMDO or Ozone; (vi) $KMnO_4$ in H_2O–EtOH or with TEBACl in CH_2Cl_2; (vii) 9-BBN or $BH_3{\cdot}SMe_2$ and then H_2O_2, MeOH; (viii) $RuCl_3$, $NaIO_4$; (ix) $Hg(OAc)_2$, $NaBH_4$, NaOH; (x) O_2, *hν*, rose Bengal. However, none of these conditions led to any synthetically useful outcome.

(18) For related reductions, see: (a) Cole, K. P.; Hsung, R. P.; Yang, X.-F. *Tetrahedron Lett.* **2002**, *43*, 3341. (b) Hsung, R. P.; Cole, K. P.; Zehnder, L. R.; Wang, J.; Wei, L.-L.; Yang, X.-F.; Coverdale, H. A. *Tetrahedron* **2003**, *59*, 311.

(19) For our very first communication of this stereodivergent plan, see: Slafer, B.; Hsung, R. P.; Sklenicka, H. M. *Abstracts of Papers, 227th National Meeting of the American Chemical Society, Anaheim, CA, Mar 28 to Apr 1, 2004*; American Chemical Society: Washington DC, **2004**, ORGN-396.

(20) (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331.

(21) For the first application of directed hydrogenations employing Crabtree's catalyst, see: (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. For a leading application, also see: (b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.

(22) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.

(23) Vinylogous amide **18** is again the same as Ma's mid-stage intermediate. However, in their beautiful studies en route to lepadins A–E and H, hydrogenation of the C4a–8a olefin took place prior to homologation of the C5 carbonyl group via Wittig-type olefinations (see ref. 13).

(24) (a) Shiosaki, K. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 865. (b) Roth, M.; Dubs, P.; Götchi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710.

(25) Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 3715.

(26) Wittig olefination employing $Ph_3P{=}CHCHO$ in toluene did not lead to any desired homologation product.

(27) Li, G.; Hsung, R. P.; Slafer, B. W.; Sagamanova, I. K. *Org. Lett.* **2008**, *10*, 4991.

Downloaded by: Queen's University. Copyrighted material.