Published in final edited form as:

Synthesis (Stuttg). 2009 September 1; 2009(17): 2905. doi:10.1055/s-0029-1216920.

A Stereodivergent Approach for Accessing Both C2,8a-Syn and C2,8a-Anti Relative Stereochemical Manifolds in the Lepadin Family via a TiCl₄-Promoted Aza-[3 + 3] Annulation

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

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

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 work paves a 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.

Keywords

TiCl₄-promoted aza-[3 + 3] annulation; vinylogous amides; iminium ions; a unified strategy in alkaloid synthesis; the lepadin alkaloids; stereodivergent approach; Eschenmoser's *epi*-sulfide contraction

Introduction

We^{1–3} have been embarking on the chemistry of an aza-[3 + 3] annulation strategy⁴ involving vinylogous amides and vinyl iminium ions⁵ for the past decade [Figure 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 our attention.

The lepadin family [Scheme 1], isolated from various sources such as tunicate *Clavelina lepadiformis*,^{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, anti-plasmodial, anti-trypanosomal properties, and anti-malarial properties.⁸ While all contain a *cis*-1-aza-decalin, 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 1. 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.

Results and Discussions

A unique advantage of developing a stereodivergent approach the lepadin family featuring the *aza*-[3 + 3] annulation product **1** can be seen in Scheme 2. That is, the annulation product **1** could be assembled rapidly from available chiral amino alcohol **2** and 1,3-cyclohexanedione in just 3 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 equiv TiCl₄ as a promoter at rt 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.: BF₃·OEt₂; SnCl₄; AlCl₃; TMSOTf; Cu(OTf)₂; MgBr₂·OEt₂; ZnCl₂] were not successful, the TiCl₄ 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-*aza*-decalenone **11**. As shown in Scheme 3, the sequence involved essentially a hydration equivalent at C3–4 olefin via dihydroxylation^{16,17} followed by reductive removal of the C4-OH group in the resulting diol **8** using either TES-H¹⁸ or alternatively H₂ 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-*aza*-decalenone **11**.

The significance of 1-*aza*-decalenone **11** is revealed in Scheme 4. While the original stereodivergent plan¹⁹ 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 C4a–8a olefin of **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-*n*-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-*n*-Pr to alleviate allylic-type strain, thereby shielding the top π -face of the olefin.^{2a}

Based on the above analysis, we were able to quickly establish the C2,8a-*syn* pathway via the concise sequence shown in Scheme 5. The C2,8a-*syn* relative stereochemistry was confirmed via nOe experiments [see the box] using alcohol **14**, which was attained from the hydrogenation of C4a–8a olefin in 1-*aza*-decalenone **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 H₂ pressure is <1000 *psi*. Nevertheless, N-protection followed by Dess-Martin periodinane oxidation led to 1-*aza*-decalone **16** that should be suitable for lepadins D, E and H, and for A–C after inverting the C3 stereogenic center.

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 6. 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 TFAA afforded trifluoroacetamide **20**, and finally, acylation using Ac₂O followed by desilylation gave *N*-acylated alcohol **21**.

However, we encountered an immense amount of problems in hydrogenations of C4a–8a olefin in *N*-acylated substrates **19–21** [Scheme 7]. 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 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 4] is the additional C3 oxygen substituent. Given that *N*-acylated alcohol **21** with an unprotected C3-OH also failed, we believed that the cause is likely not the nature of 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 8, ketone **28** could be directly prepared from diol **8** under acidic conditions. However, with the chiral auxiliary intact, NaBH₄ reduction of ketone **28** gave alcohol **9** as a C3-epimeric mixture that still favored β-C3-OH. Fortunately, NaBH₄ 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 5], alcohol **30** represents a suitable starting point for synthesizing lepadins A–C via possible intermediates such as **31** [Scheme 8]. On the other hand, we remain unsuccessful in hydrogenating C4-8a 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 catalyst²⁰ 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 9, we contemplated the possibility of first pursuing 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 C4a–8a olefin. This new design allows us to take advantage of the chiral auxiliary for a three-fold purpose instead of just one. It is now useful not just for controlling the stereochemical outcome of the key *aza*-[3 + 3] annulation at 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 10. Vinylogous amide **18** was homologated²³ employing Eschenmoser's *epi*-sulfide contraction method,^{24,25} while standard Wittig olefination was not successful.²⁶ It is noteworthy that homologations of vinylogous amides via Eschenmoser's *epi*-sulfide 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 2].

Most critically, while **36** can be useful for constructing lepadins A–E and H, methyl dienolic ester **37** was also prepared through homologation of vinylogous amide **10** [Scheme 10]. The ensuing hydrogenation gave methyl ester **38** in 91% yield using Adam's catalyst with complete stereochemical control at C4a, C8a, and C5. This successful sequence finally afforded the much anticipated C2,8a-*anti* manifold, thereby completing the design of a stereodivergent approach for installing both C2,8a-*syn* and C2,8a-*anti* manifolds through a common intermediate **9**, and the three-fold 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

Conclusions

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.

Experimental Section

Synthesis of 1-Aza-Decalene 11

To a solution acetate **10** (446.0 mg, 0.836 mmol) in MeOH (8 mL) were added TFA (71.0 μ L, 0.919 mmol) and Pd(OH)₂/C (117.0 mg). The mixture was pressurized to 60 *psi* of H₂ for 24 h. When the reaction was completed as indicated by TLC analysis, the reaction was filtered through Celite™ and concentrated *in vacuo*. Purification by column chromatography (eluent 50% to 90% EtOAc in Hexane) provided the pure 1-*aza*-decalene **11** (183.0 mg, 97% yield).

1-Aza-Decalene (11)

R_f = 0.25 [10% MeOH in EtOAc].

IR (neat): 3254 (brw), 2936 (m), 1734 (s), 1676 (s), 1524 cm⁻¹ (s).

¹H NMR (400 MHz, CDCl₃): δ = 1.21 (d, 3H, *J* = 6.8 Hz), 1.94–1.20 (m, 2H), 2.05 (s, 3H), 2.42–2.51 (m, 5H), 2.63 (dd, *J* = 4.4, 16.4 Hz, 1H), 3.52 (quint, *J* = 6.4 Hz, 1H) 4.88 (dd, *J* = 5.6, 10.0 Hz, 1H), 6.33 (brs, 1H).

¹³C NMR (100 MHz, CDCl₃): 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* (% relative intensity) 224.2 (100).

Synthesis of 1-Aza-Decalone 16

To solution of **11** (50.0 mg, 0.224 mmol) in MeOH (4 mL) was added PtO₂ (50mg). The mixture was placed in a high-pressure hydrogenation apparatus [steel bomb] at 1000 *psi* for 24 h. When the reaction was completed as indicated via TLC analysis, the reaction mixture was filtered through Celite™ and concentrated *in vacuo* to give the alcohol intermediate **14** (21.0 mg, 41%).

To a solution of compound **14** (21.0 mg, 0.092 mmol) in anhyd CH₃CN (4 mL) were sequentially added (Boc)₂O (36.0 mg, 0.166 mmol) and K₂CO₃ (1.40 mg, 0.0090 mmol) and the reaction mixture was heated to gentle reflux under N₂ for 24 h. After which, H₂O was added to quench the reaction, and the organic layer was separated with the aqueous layer being extracted with equal volume of CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give **15** (25.9 mg, 85% yield) as colorless oil.

To a solution of compound **15** prepared above (7.0 mg, 0.021 mmol) in CH₂Cl₂ (4 mL) was added Dess-Martin reagent (0.025 mmol) at rt. After the resultant mixture was stirred for 1.5 h, the reaction mixture was partitioned with H₂O and was separated, and the resulting aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to give a colorless oil which was purified via silica gel flash column chromatography to yield the pure 1-*aza*-decalone **16** (4.00 mg, 58% yield).

1-Aza-Decalone (16)

R_f = 0.67 [100% EtOAc].

IR (neat): 3456 (brw), 2972 (m), 1735 (m), 1686 (s), 1457 cm⁻¹ (m).

¹H NMR (400 MHz, CDCl₃): δ = 1.27 (d, *J* = 7.2 Hz, 3H), 1.47 (s, 9H), 1.53 – 1.58 (m, 1H), 1.79 (dt, *J* = 3.6, 14.0 Hz, 1H), 1.78 – 1.85 (m, 1H), 1.91 – 2.02 (m, 2H), 2.01 (dd, *J* = 2.4, 14.0 Hz, 1H), 2.08 (s, 3H), 2.28 (dd, *J* = 6.0, 13.2 Hz, 1H), 2.33 – 2.38 (m, 1H), 2.94 (dt, *J* = 4.8, 13.6 Hz, 1H), 4.24 (q, *J* = 6.8 Hz, 1H), 4.30 – 4.44 (brm, 1H), 4.90 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): 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* (% relative intensity) 348.2 (100), (M+Na)⁺.

HRMS (ESI): *m/z* calcd for C₁₇H₂₇NO₅Na⁺: 348.1782; found 348.1785.

Synthesis of Silyl Ether 18

To a solution of **17** (393.0 mg, 2.17 mmol) in dry CH₃CN (60 mL) were added 2,6-lutidine (0.76 mL, 6.50 mmol). After which, the solution was cooled to 0 °C and TBSOTf (1.50 mL, 6.50 mmol) was added dropwise via syringe. Solution was stirred for 12 h at rt, then diluted with CH₂Cl₂ and quenched with water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with equal volumes of sat aq NaHCO₃ solution, sat aq NaCl, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 50% to 100% EtOAc in Hexanes) gave the pure silyl ether **18** (640.0 mg, 100 % yield).

Silyl Ether (18)

R_f = 0.46 [10% MeOH in EtOAc]; mp 205–206 °C;

IR (thin film): 3268 (brs), 2933 (s), 2857 (s), 1571 (w), 1516 (m), 1459 cm⁻¹ (s).

¹H NMR (500 MHz, CDCl₃): δ = 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.87–1.96 (m, 2H), 2.11 (dd, *J* = 9.0, 16 Hz, 1H), 2.26–2.32 (m, 4H), 2.73 (dd, *J* = 5.0, 15.5 Hz, 1H), 3.13 (quint, *J* = 6.5, 7.0 Hz, 1H), 3.48 (ddd, *J* = 5.5, 9.5, 13.5 Hz, 1H), 4.45 (brs, 1H).

¹³C NMR (125 MHz, CDCl₃): 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 (% relative intensity) = 318.2 (92) ($M + Na$)⁺, 296.2 (100) M^+ , 284.2 (11).

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

Synthesis of *N*-Acylated Alcohol 21

To a solution of **18** (106.0 mg, 0.359 mmol) in anhyd CH_2Cl_2 (3 mL) were added 2,6-lutidine (1.38 mL, 1.18 mmol), and DMAP (8.80 mg, 0.72 mmol). Acetic anhydride (5 mL, 46.7 mmol) was then added dropwise via syringe. The resulting solution was stirred for 40 h at 40 °C. After which, it was 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 equal volume of CH_2Cl_2 . The combined organic layers were washed with equal volume of sat aq $NaHCO_3$, dried over Na_2SO_4 , and concentrated *in vacuo*.

The above crude product was dissolved in 7 mL THF and aq HCl solution (1.0 *M*, 1.17 mL) was added. The acidification was allowed to run for 6 h before being diluted it 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 equal volume CH_2Cl_2 . The combined organic layers were washed with equal volume of sat aq $NaHCO_3$, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by column chromatography gave the corresponding *N*-acylated silyl ether intermediate (82.7 mg, 68% yield) and also some *N*-acylated alcohol **21** (7.80 mg, 4% yield) that was already desilylated.

N-Acylated Silyl Ether

R_f = 0.80 [10%, EtOAc in hexane].

1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 0.75H), 0.02 (s, 0.75H), 0.04 (s, 2.25H), 0.05 (s, 2.25H), 0.82 (s, 9H), 1.04 (d, J = 6.5 Hz, 3H), 1.58–1.70 (m, 0.33H), 1.83–1.92 (m, 0.67H), 2.03–2.09 (m, 1H), 2.23 (s, 3H), 2.25–2.31 (m, 1.5H), 2.34–2.39 (m, 1.5H), 2.22–2.48 (m, 2H), 3.20–3.29 (m, 1H), 3.93–3.96 (m, 1H), 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 (% relative intensity) 338.2 (100) ($M+H$)⁺.

To a solution of the above silyl ether (39.4 mg, 0.12 mmol) in anhyd THF (3 mL) at 0 °C was added dropwise TBAF (1.0 *M* in THF, 0.12 mL). The resulting reaction mixture was stirred for 5 h before it was poured into water and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with sat aq NaCl (45 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 10% to 30% of EtOAc in hexanes) gave *N*-acylated alcohol **21** (12.8 mg, 49% yield) as colorless oil and also some recovered silyl ether (3.60 mg, 9% yield).

N-Acylated Alcohol (21)

R_f = 0.25 [10% MeOH in EtOAc].

IR (neat): 3286 (brm), 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, 3H), 1.80–1.92 (m, 1H), 2.01–2.09 (m, 1H), 2.32–2.47 (m, 5H), 3.20–3.30 (m, 1H), 4.00 (brs, 1H), 4.12 (ddd, J = 4.4, 6.8, 10.4 Hz, 1H).

MS (APCI): m/z (% relative intensity) = 224.1(100) ($M+H$)⁺.

Synthesis of Alcohol 30

To a solution of the above alcohol **21** (19.0 mg, 0.085 mmol) and NaHCO₃ (28.6 mg, 0.48 mmol) in CH₂Cl₂ (1.5 mL) was added self-made Dess-Martin periodinane (36.0 mg, 0.085 mmol). The reaction solution was then stirred at rt for about 35 min. When the reaction was completed as indicated by TLC analysis (10% MeOH/EtOAc) or LCMS, the reaction was quenched with a few drops of isopropyl alcohol. The reaction was filtered through Celite™ and concentrated under reduced pressure. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% to 10% MeOH in EtOAc) afforded ketone **29** (14.2 mg, 76% yield) as colorless oil. Ketone **29** was immediately used for the following step.

To a solution of ketone **29** prepared above (11.4 mg, 0.052 mmol) in anhyd MeOH (1.2 mL) under N₂ at -41 °C was added NaBH₄ (2.00 mg, 0.052 mmol). The reaction solution was stirred at same temperature for 1 h and was monitored using TLC analysis. After which, the reaction mixture was quenched with aq HCl solution (0.5 M, 0.5 mL) and diluted with CH₂Cl₂. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with sat aq NaCl, dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% to 5% MeOH in EtOAc) gave the pure alcohol **30** (8.80 mg, 76% yield) as colorless oil.

Alcohol (30)

R_f = 0.45 [10% MeOH in EtOAc].

IR (neat): 3371 (brm), 2934 (m), 1644 (s), 1602 (s), 1375 cm⁻¹ (s).

¹H NMR (400 MHz, CDCl₃): δ = 1.12 (d, *J* = 6.8 Hz, 3H), 1.81–1.92 (m, 1H), 1.96–2.09 (m, 2H), 2.29 (s, 3 H), 2.35–2.47 (m, 3H), 2.80 (ddd, *J* = 2.4, 6.4, 17.6 Hz, 1H), 3.23 (m, 1H), 3.98 (brm, 1H), 4.18 (qd, *J* = 4.4, 6.8 Hz, 1H).

MS (APCI): *m/z* (% relative intensity) 224.2 (100) (M+H)⁺.

Synthesis of Ethyl Dienoic Ester 35

Lawesson's reagent (39.0 mg, 0.097 mmol) was added to a solution of **18** (57.0 mg, 0.19 mmol) in THF (5 mL), and the resulting mixture was stirred at rt for 1 h. After removal of the solvent *in vacuo*, the desired thio-vinylogous amide intermediate (52.0 mg, 87% yield) was isolated by silica gel column chromatography as yellow oil.

To a solution of thio-vinylogous amide (32.9 mg, 0.11 mmol) in acetone (5 mL) were successively added K₂CO₃ (29.2 mg, 0.21 mmol) and ethyl α-bromo acetate (0.013 mL, 0.12 mmol). The resulting reaction mixture was stirred at rt for 1 h, and after which, solids were filtered. After solvent removal *in vacuo*, a thiirane intermediate (42.2 mg, 100% yield) was obtained as yellow oil by silica gel column chromatography.

A mixture of this thiirane (42.2 mg, 0.11 mmol), PPh₃ (36.0 mg, 0.14 mmol), and diisopropylethylamine (7.00 μL, 0.041 mmol) in CH₃CN (5 mL) was heated in a sealed tube at 90 °C for 24 h. After evaporating excess solvent *in vacuo*, the crude residue was subjected to silica gel flash column chromatography (gradient eluent: 0% to 2% MeOH in EtOAc) to give desired ethyl diennoic ester **35** (19.7 mg, 51% yield) as light yellow oil.

Ethyl Diennoic Ester (35)

R_f = 0.60 [10% MeOH in EtOAc]; [α]_D²³ = -179.6 (*c* 0.40, CHCl₃).

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

^1H NMR (400 MHz, CDCl_3) δ 0.09 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.20 (d, J = 6.0 Hz, 3H), 1.28 (t, 3H, J = 7.2 Hz), 1.59–1.72 (m, 1H), 1.75–1.87 (m, 1H), 2.04–2.20 (m, 3H), 2.44 (dd, J = 5.6, 15.2 Hz, 1H), 2.71 (m, 1H), 3.08 (qd, J = 6.4, 7.2 Hz, 1H), 3.34 (dt, J = 5.6, 17.6 Hz, 1H), 3.55 (dt, J = 5.6, 8.8 Hz, 1H), 3.70 (brs, 1H), 4.13 (q, J = 7.2 Hz, 2H), 5.23 (s, 1H).

^{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 (% relative intensity) 366.2 (100) ($\text{M}+\text{H}$) $^+$.

HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{36}\text{NO}_3\text{Si}^+$: 366.2459; found 366.2459.

Synthesis of Ethyl Ester 36

To a solution of ethyl dienoic ester **35** (4.60 mg, 0.013 mmol) in anhyd AcOH (2 mL) was added Pt/C (12.3 mg, 10% Pt/C). The mixture was placed in a Lab-Crest[®] pressure reaction vessel at 20 *psi* H_2 pressure for 2 h. When the reaction was completed as evident with LCMS analysis, the reaction mixture was filtered through Celite[™] and concentrated *in vacuo*.

Purification of the crude residue via silica gel flash column chromatography (gradient eluent: 0% to 2% MeOH in EtOAc) afforded the desired ethyl ester **36** (1.80 mg, 40% yield) as a light yellow oil.

Ethyl Ester (36)

R_f = 0.40 [5% MeOH in EtOAc].

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

^1H NMR (500 MHz, CDCl_3): δ = 0.60 (s, 3H), 0.70 (s, 3H), 0.89 (s, 9H), 0.96–1.05 (m, 1H), 1.12 (d, J = 6.5, 1H), 1.26 (t, J = 7.0 Hz, 3H), 1.33–1.48 (m, 3H), 1.48–1.67 (m, 3H), 1.77 (brd, J = 12.5 Hz, 1H), 1.97–2.05 (m, 2H), 2.17–2.28 (m, 1H), 2.50–2.58 (m, 2H), 2.97 (brs, 1H), 3.28–3.33 (m, 1H), 4.10–4.18 (m, 2H).

^{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 (%relative intensity) 370.2 (100) ($\text{M}+\text{H}$) $^+$.

HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{40}\text{NO}_3\text{Si}^+$: 370.2772; found 370.2767.

Methyl Dienoic Ester 37

R_f = 0.30 [20% EtOAc in Hexanes]; $[\alpha]_D^{23}$ = + 499.4 (*c* 0.16, CHCl_3).

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

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

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

MS (APCI): m/z (% relative intensity) 590.4 (100) ($\text{M}+\text{H}$) $^+$, 558.3 (10).

HRMS (MALDI): m/z calcd for $\text{C}_{35}\text{H}_{48}\text{NO}_5\text{Si}^+$: 590.3296; found 590.3305.

Methyl Ester (38)

$R_f = 0.35$ [20% EtOAc in 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).

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

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

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

MS (APCI): m/z (% relative intensity) 594.4 (95) ($\text{M}+\text{H}$) $^+$, 534.3 (100).

HRMS (MALDI): m/z calcd for $\text{C}_{35}\text{H}_{52}\text{NO}_5\text{Si}^+$: 594.3609; found 594.3586.

Acknowledgments

Authors thank NIH [NS38049] for funding.

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Figure 1.
An Aza-[3 + 3] Annulation Strategy.

Figure 2.
nOe Experiments of Ethyl Ester **36**.

Scheme 1.
A Stereodivergent Approach to the Lepadin Family.

Scheme 2.
 A *de novo* TiCl₄-Promoted Aza-[3 + 3] Annulation.

Scheme 3.
Hydration of C3–4 Olefin and the Auxiliary Removal.

Scheme 4.
Original Designs for the Stereodivergent Approach.

Scheme 5.
A Stereoselective Pathway to C2,8a-*Syn* Stereochemistry.

Scheme 6.
Precursors for Setting C2,8a-Anti Stereochemistry.

Scheme 7.
Failed Attempts in Installing C2,8a-Anti Stereochemistry.

Scheme 8.

A Useful Protocol for Inverting the C3 Stereochemistry.

Scheme 9.
New Designs for the Stereodivergent Approach.

Scheme 10.
Execution of the New Stereodivergent Plan.