ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

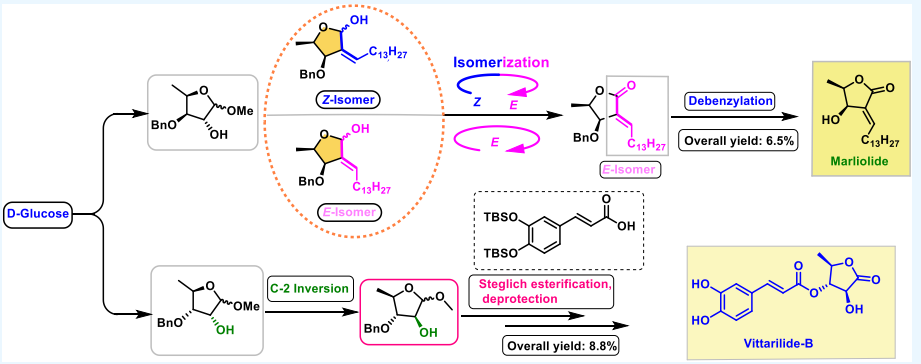
First Stereoselective Total Synthesis of Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one and Vittarilide-B: A Unified Strategy Utilizing a Chiral Pool Approach

Janardana Reddi Desireddi,* Mora Mallikarjuna Rao, Kiran Kumar Murahari, Shivanagababu Challa, Bhimcharan Maiti, and Ravinder Manchal*

Cite This: *ACS Omega* 2025, 10, 3199−3205

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: The first stereoselective total synthesis of the natural products Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (**1**) and Vittarilide-B (**1b**) has been accomplished using a carbohydrate-based approach starting from D-glucose. The synthesis of Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (**1**) was achieved in 13 steps with an overall yield of 6.5%, featuring key transformations such as reduction, Wittig olefination, TEMPO-mediated oxidation, isomerization, and debenzylation. Vittarilide-B (**1b**) was synthesized in 18 steps with an overall yield of 8.8%, involving crucial steps like inversion, radical-mediated lactonization, Steglich esterification, and deprotection. The synthesis of Marliolide (**1**) led to the discovery of a notable isomerization phenomenon, where the *Z*-isomer was converted to the *E*-isomer during the oxidation step using BAIB and TEMPO. Various reaction conditions were investigated for this isomerization process, with the TEMPO-mediated reaction consistently providing the best results. The synthesis of Vittarilide-B (**1b**) required the inversion of stereochemistry at the C-2 position of the common intermediate **6b**, followed by a sequence of steps to obtain the final product. The analytical data for both synthetic Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (**1**) and Vittarilide-B (**1b**) were consistent with the data reported for the natural compounds. This work demonstrates the efficiency of using readily available chiral pool materials like D-glucose in the stereoselective synthesis of complex natural products and provides a foundation for further exploration of their biological activities and potential therapeutic applications.

γ-Lactones, organic compounds found in various natural products, exhibit a wide range of biological activities, including antimicrobial, anticancer, anti-inflammatory, and antioxidant properties. These activities are crucial for drug discovery and development.[1−4] In this study, we focus on synthesizing compounds that include γ-lactones, given their frequent occurrence in nature. Various γ-butyrolactones have been discovered in *Litsea japonica*, each displaying unique biological activities, following the identification of Litsenolides.[5−7] Additionally, Chin *et al.* found that extracts from the bark of *Cinnamomum cambodianum* possess potent anti-inflammatory

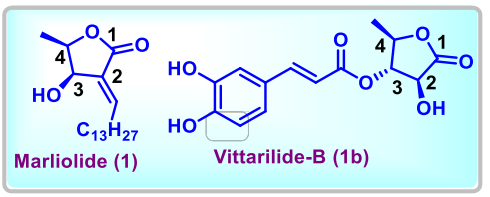
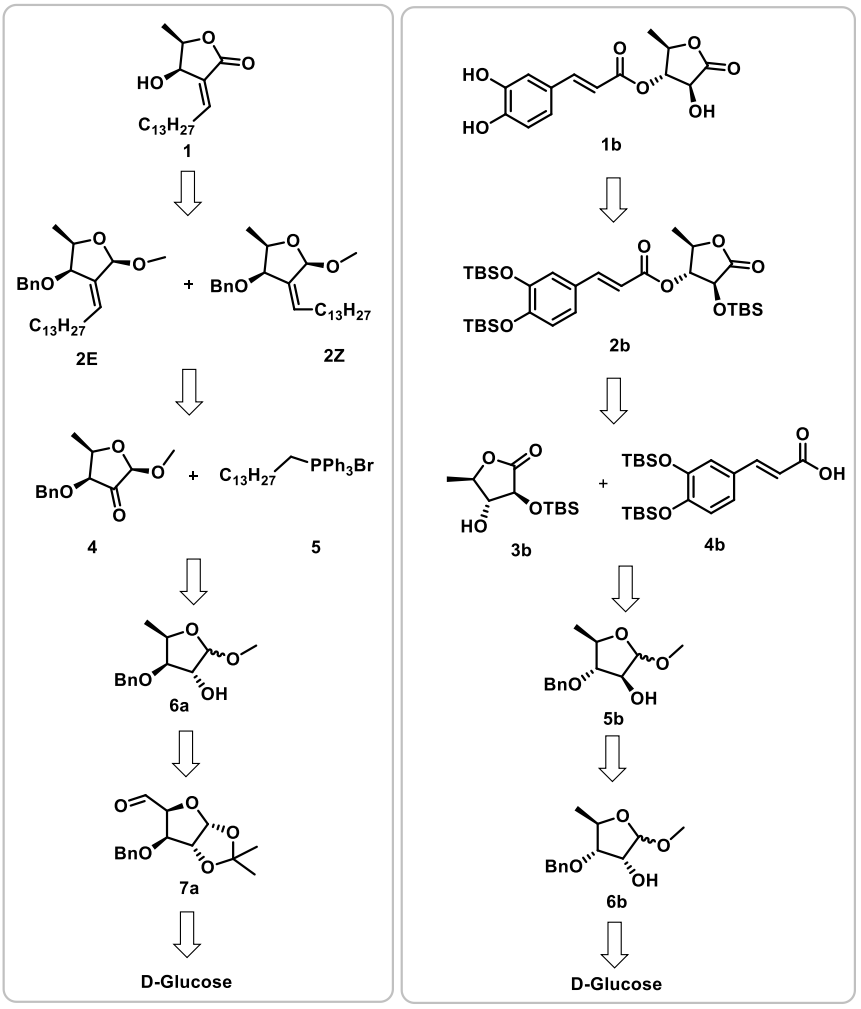


Figure 1. Structures of Marliolide (**1**) and Vittarilide-B (**1b**).

Received: November 30, 2024
Accepted: December 23, 2024
Published: January 11, 2025

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205

Scheme 1. Retrosynthetic Pathway of Marliolide (1) and Vittarilide-B (1b)



properties, primarily attributed to Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (**1**), sparking further research into its structural variants.[8]

Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (**1**), a natural product, which has been identified in the leaves of *Mollinedia marliae*, a plant known for its anti-inflammatory, antimicrobial, and antioxidant properties. This discovery adds to the growing list of bioactive compounds derived from the Mollinedia genus, underscoring their significance in natural product chemistry.[9,10] To date, only the racemic synthesis of Marliolide, has been accomplished, with most studies focusing on synthesizing its structural derivatives.[11−13] However, the synthesis of (4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (Marliolide) (**1**) has not yet been reported. This study presents the first asymmetric synthesis of Marliolide-(4*R*,5*R*,3*E*)-4-hydroxy-5-methyl-3-tetradecylidenedihydrofuran-2(3*H*)-one (**1**), an *α*, *β*-unsaturated *γ*-lactone with an exocyclic double bond side chain at C-2. This work is part of ongoing efforts to develop novel chemical entities derived from D-glucose.

In 2005, Wu *et al.* identified Vittarilide-B (**1b**), a component of the crude methanol extract of Vittaria anguste-elongata Hayata, which exhibited moderate cytotoxicity against lung, gastric, and nasopharyngeal carcinoma cell lines.[14,15] The study also reported the successful total synthesis and absolute stereochemical assignment of Vittarilide-B (**1b**), a promising target for synthesis due to its low natural abundance and significant biological activity. This study will be helpful in developing novel chemical entities derived from D-glucose and exploring their pharmacological potential and applications in medicine (see Figure 1).

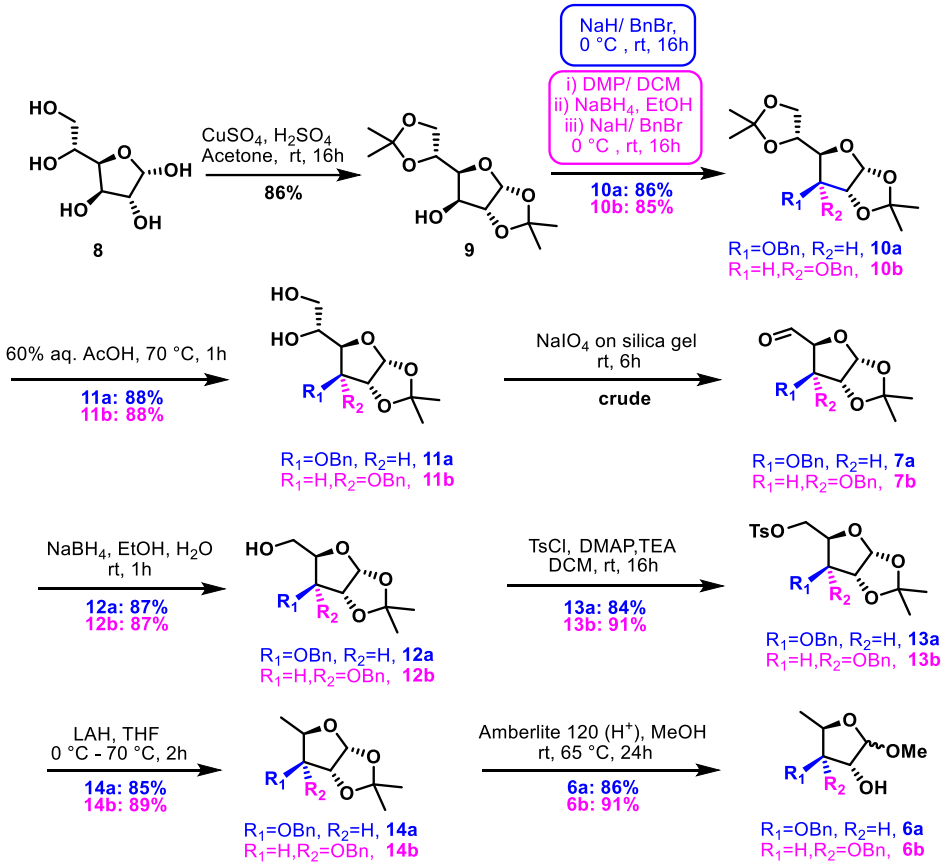
Our retrosynthetic plan, inspired by the structural features of the target compounds, led us to focus on obtaining D-glucose from commercially available sources. Both compounds were synthesized from D-glucose using the intermediates methyl glycosides **6a** and **6b**. These secondary alcohols, **6a** and **6b**, can be readily obtained from D-glucose following established procedures.[16−18] Marliolide (**1**), a trisubstituted olefin system, was produced via the Wittig olefination of ketone **4** with Wittig salt **5**. Ketone **4** was synthesized by oxidizing the ***β***-anomer of intermediate **6a**.

According to our retrosynthetic analysis, Vittarilide-B (**1b**) can be synthesized through the esterification of secondary alcohol **3b** with di-TBS protected *trans*-caffoeyl moiety **4b**. The secondary alcohol **3b**, in turn, can be derived from the common intermediate **6b** by inverting the stereochemistry at the C-2 position and subsequent lactonization (Scheme 1).

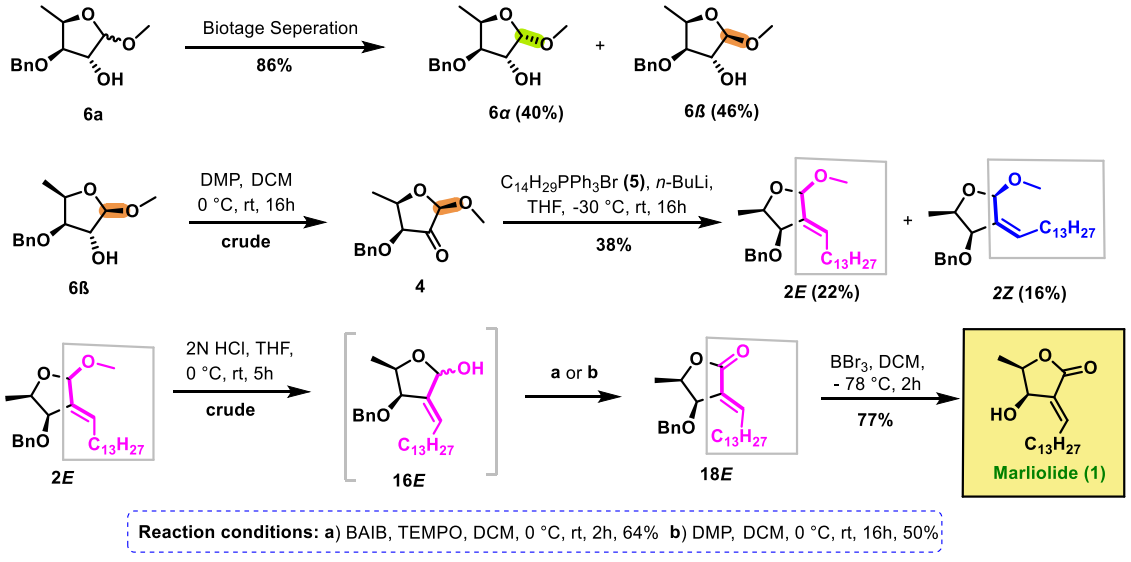
Marliolide (**1**), and Vittarilide-B (**1b**) were obtained in 86% yield from the chiral pool precursor D-glucose, which was first converted into diacetonide **9** using acetone and $CuSO_4$ in an acidic medium. In the synthesis of Vittarilide-B (**1b**), the

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205

Scheme 2. Synthesis of Marliolide (1) and Vittarilide-B (1b) Intermediates 6a and 6b



Scheme 3. Synthesis of Marliolide (1)



stereochemistry at the C-3 position was inverted by oxidation to a ketone using DMP, followed by reduction with $NaBH_4$, resulting in a 78% yield. However, in Marliolide (**1**), the stereochemistry remained unchanged. The secondary alcohol at the C-3 position was protected as a benzyl ether **10a** in 86% yield using BnBr and NaH as a base, while Vittarilide-B (**1b**) afforded **10b** in an 85% yield under similar conditions. The acetonide deprotection at the C-5 and C-6 positions of the benzyl ether was carried out using 60% AcOH, resulting in compounds **11a** and **11b**, with an 88% yield for both Marliolide (**1**) and Vittarilide-B (**1b**).

The resulting diol was oxidized using silica-supported sodium periodate to produce the corresponding aldehyde, which, upon reaction with sodium borohydride, yielded the corresponding primary alcohols **12a** and **12b** in 87% yield. The next step involved protecting of this primary alcohol by tosylation with TsCl and TEA, yielding **13a** in 84% yield for Marliolide (**1**) and **13b** in 91% yield for Vittarilide-B (**1b**). The

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205

Scheme 4. Isomerization:*Z*-Isomer to *E*-Isomer

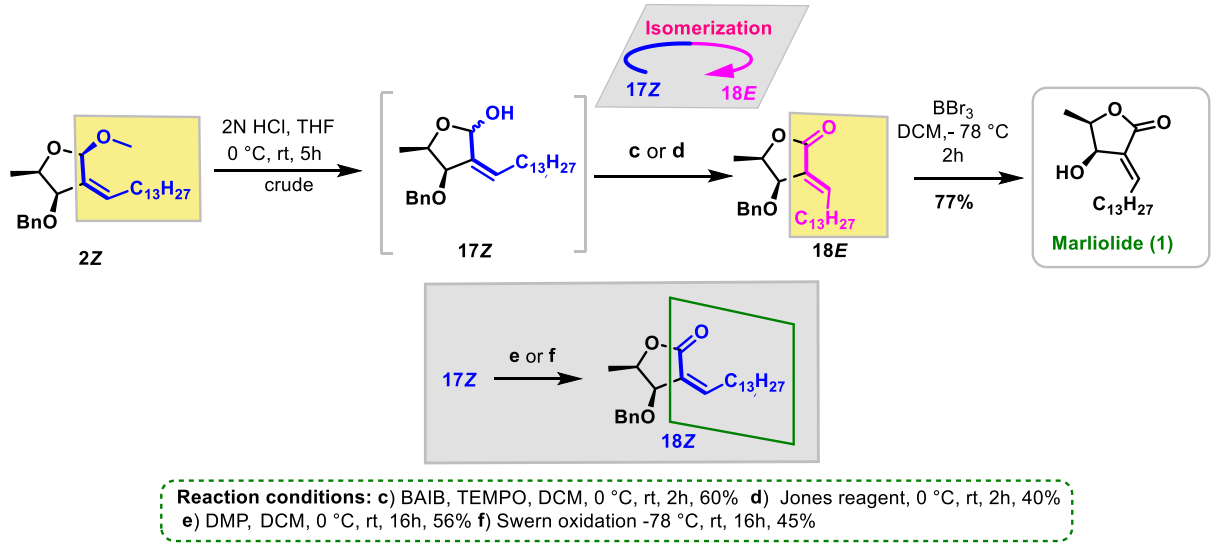


Table 1. Reaction Conditions for the Conversion of 17*Z* to 18*E* or 18*Z*

S.No	Reactant	Conditions	Product	Yield
1	17 *Z*	BAIB, TEMPO, DCM, 0 °C, rt, 2h	18*E*	60%
2		Jones reagent, 0 °C, rt, 2h		40%
3		DMP, DCM, 0 °C, rt, 16h	18*Z*	56%
4		Swern oxidation -78 °C, rt, 16h		45%

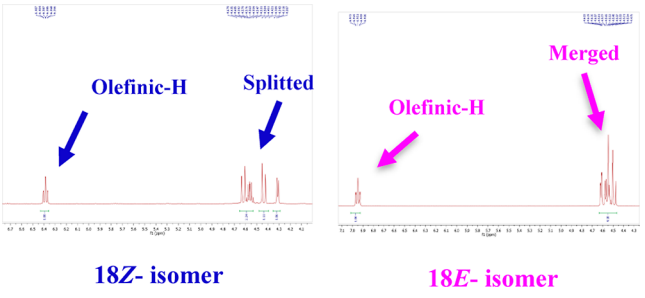


Figure 2. ^{1}H NMR spectral comparison of **18*Z*** and **18*E*** isomers.

tosylates were then treated with LAH in 1M THF at 70 °C, producing the deoxygenated methyl derivatives **14a** for Marliolide (**1**) in 85% yield and **14b** for Vittarilide-B (**1b**) in 89% yield. This deoxygenated derivative was then treated with Amberlite-IR-120 (H^+) to yield methyl glycoside anomers **6*α*** (40%) and **6*β*** (46%) in 86% yield for Marliolide (**1**) and 91% yield for Vittarilide-B (**1b**)[16−18] (Scheme 2).

The ***α***- and ***β***-anomers were separated for the synthesis of Marliolide (**1**), whereas for Vittarilide-B (**1b**), the synthesis proceeded with a mixture of anomers. The ***α***- and ***β***-anomers

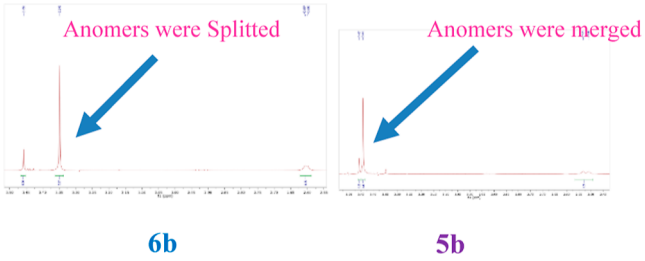


Figure 3. Inversion of **6b** to **5b** depicted in ^{1}H NMR spectra.

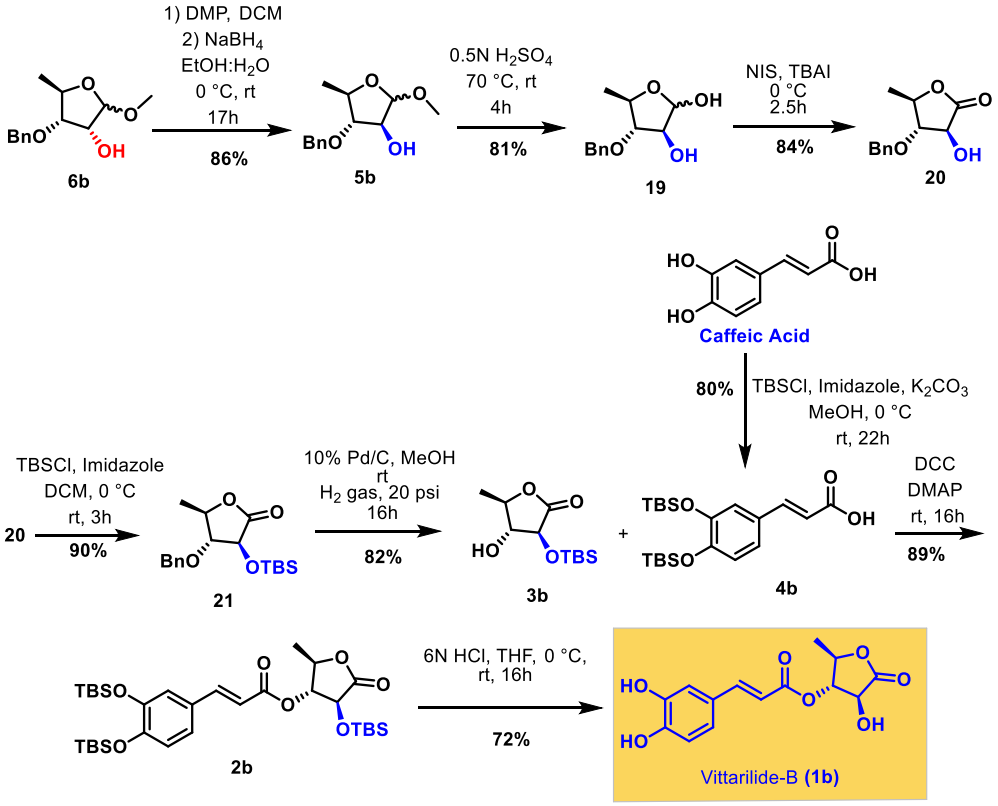
were structurally confirmed using various 2D NMR techniques, including COSY, NOE, HSQC, and NOESY. In the ^{1}H NMR spectrum, the **6*α***-anomer resonated at δ 4.94 (d, J = 4.8 Hz, 1H) ppm, while the **6*β***-anomeric proton appeared at δ 4.75 (d, J = 2.5 Hz, 1H) ppm. In the ^{13}C NMR spectra, the **6*α***-anomeric carbon resonated at δ 101.5 ppm, while the 6***β***-anomeric carbon resonated at δ 109.2 ppm. Consistently, in ^{1}H NMR, the ***α***-anomers appeared further downfield and had higher J values than the ***β***-anomers, while in ^{13}C NMR, the ***β***-anomers showed greater chemical shift values than the ***α***-anomers.

We continued with the ***β***-isomer for the rest of the synthesis, which was oxidized using Dess-Martin periodinane to give ketone **4** in quantitative yield. The keto compound **4** was treated with Wittig salt **5** [(tetradecyl)triphenylphosphonium bromide] in the presence of *n*-BuLi in THF, yielding a 38% mixture of **2*E*** (22%) and **2*Z*** (16%) isomers.[19] In the ^{1}H NMR spectrum, the ***E***-isomer shows a resonance at δ 5.87 ppm, slightly downfield compared to the ***Z***-isomer, which resonates at δ 5.78 ppm. The distinction between the ***E*** and ***Z*** isomers was further confirmed using 2D NMR techniques, specifically NOE and HSQC analysis.

Our next objective was to produce the lactol, which was subsequently oxidized to produce the lactone with the ***E*** isomer. The **2*E***-isomer was then treated with 2N HCl in THF to produce lactol **16*E*** in quantifiable yield. The lactol **16*E*** was then treated with BAIB and catalytic TEMPO in DCM, yielding lactone **18*E*** in 64% yield[20] and the same reaction performed in Dess-Martin periodinane in DCM yielded lactone in 50%. The characteristic lactone peak was observed

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205

Scheme 5. Synthesis of Vittarilide-B (1b)



in the ^{13}C NMR spectrum at δ 170.05 ppm. The final step involved deprotecting the benzyl group by treating lactone **18*E*** with BBr_3 in dichloromethane, yielding Marliolide (**1**) in 77%[21] (Scheme 3). The analytical results for synthetic Marliolide (**1**) were consistent with existing data for the natural compound.

"We investigated the synthesis of the lactone corresponding to the *Z*-isomer from the lactol intermediate and discovered a notable isomerization phenomenon. The **2*Z***-isomer was treated with 2N HCl in THF, resulting in Lactol **17*Z*** with quantitative yield. Lactol **17*Z*** was subsequently reacted with BAIB and TEMPO in dichloromethane (DCM), yielding lactone **18*E*** in 60% yield, rather than the anticipated *Z*-isomer **18*Z***. This reaction facilitated both oxidation and isomerization in a single step (Scheme 4). Various reagents were evaluated for the isomerization process, as summarized in Table 1. The TEMPO-mediated reaction consistently delivered the best results compared to the Jones reagent.[22] In contrast, Dess-Martin periodinane and Swern oxidation did not induce isomerization, and the stereochemistry at the **17*Z***-isomer remained unchanged.

The ^1H NMR spectrum of the **18*Z***-isomer exhibited the olefinic proton at δ 6.41−6.36 ppm (m, 1H), appearing upfield compared to the corresponding signal in the **18*E***-isomer, which resonated at δ 6.97−6.93 ppm (m, 1H). In the **18*Z***-isomer, the benzyl methylene protons and the C-3 and C-4 protons displayed splitting, whereas in the **18*E***-isomer these signals merged. The ^1H NMR spectra for both **18*Z*** and **18*E*** are shown in Figure 2.

Vittarilide-B. In the synthesis of Vittarilide-B (**1b**), the secondary alcohol **6b** was oxidized to the corresponding ketone using Dess-Martin periodinane in dichloromethane. Subsequent reduction of the ketone with $NaBH_4$ in methanol afforded compound **5b** in 86% yield. The transformation was confirmed by TLC and ^1H NMR analysis. In **6b**, the methoxy protons of the anomers were well-separated, while in **5b**, they shifted closer together. The ^1H NMR spectra for both **6b** and **5b** are shown in Figure 3.

The Lactol **19** was obtained in 81% yield[27] by demethylating the methyl glycoside **5b** with 0.5N H_2SO_4 at 70 °C and was subsequently converted to lactone **20** in 84% yield using *N*-iodosuccinimide and tetrabutylammonium iodide.[23]

The alcohol **20** was protected with TBS using TBSCl and imidazole, resulting **21** in a 90% yield.[24] The benzyl ether was hydrogenated in the presence of 10% Pd/C in methanol, producing secondary alcohol **3b** in 82% yield.[25]

In the penultimate phase, we employed Steglich esterification to produce the tri-TBS derivative **2b** in 89% yield by treating alcohol **3b** with di-TBS protected caffeic acid[15a] **4b** using DCC and DMAP in DCM.[26] Vittarilide-B (**1b**) was obtained by deprotecting the TBS groups of **2b** under acidic conditions with 6N HCl in THF, resulting in a 72% yield (Scheme 5).[27] The analytical results for synthetic Vittarilide-B (**1b**) were consistent with the reported data for the natural compound.

CONCLUSION

In conclusion, we successfully accomplished the first stereoselective total synthesis of Marliolide (**1**) and Vittarilide-B (**1b**) using a carbohydrate-based approach. Both natural products were synthesized from D-glucose in 13 and 18 steps, respectively, with overall yields of 6.5% and 8.8%. The synthesis of Marliolide (**1**) involved several key transformations, including reduction, Wittig olefination, TEMPO-mediated oxidation, isomerization, and debenzylation. On the other hand, Vittarilide-B (**1b**) was synthesized through a

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205

sequence involving inversion, radical-mediated lactonization, Steglich esterification, and deprotection.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c10876.

Detailed experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Janardana Reddi Desireddi − *Medicinal Chemistry Division, Aragen Life Sciences Pvt Limited, Hyderabad 500076 Telangana, India; Department of Chemistry, Chaitanya (Deemed to be University), Hyderabad 500075 Telangana, India*; Email: janardanareddi@gmail.com

Ravinder Manchal − *Department of Chemistry, Chaitanya (Deemed to be University), Hyderabad 500075 Telangana, India*; Email: ravinder@chaitanya.edu.in

Authors

Mora Mallikarjuna Rao − *Process Research and Development Department, Sai Lifesciences Limited, Hyderabad 500078 Telangana, India*

Kiran Kumar Murahari − *Medicinal Chemistry Division, Aragen Life Sciences Pvt Limited, Hyderabad 500076 Telangana, India*

Shivanagababu Challa − *Department of Chemistry, Georgia State University, Atlanta, Georgia 30302, United States*

Bhimcharan Maiti − *Medicinal Chemistry Division, Aragen Life Sciences Pvt Limited, Hyderabad 500076 Telangana, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c10876

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank Aragen Life Sciences Private Limited (previously known as GVK Biosciences Private Limited) for their ongoing support and for providing the facilities needed to complete this research. The analytical department's assistance with all spectroscopic analyses is much appreciated. Dr Somesh sharma (EVP & Head, Discovery Services, Aragen Life Sciences Private Limited) provided invaluable assistance and inspiration. We sincerely acknowledge Dr. Rajashekar Reddy Nimmareddy, Aragen Life Sciences Private Limited, for his invaluable support and insightful contributions to this work. We are also grateful to the management of Chaitanya (deemed to be a university) for their unwavering support.

■ REFERENCES

(1) Schmidt, T. J.; Brun, R.; Willuhn, G.; Khalid, S. A. Sesquiterpene Lactones: Diversity, Biological Activity, and Therapeutic Potential. *J. Nat. Prod.* **2002**, *65*, 1551−1560.

(2) Chadwick, M.; Trewin, H.; Gawthrop, F.; Wagstaff, C. Bioactive Sesquiterpene Lactones from Plants. *Phytochemistry* **2013**, *92*, 123−150.

(3) Hu, Y.; Sun, W.; Wang, M. Marine-Derived γ-Lactones and δ-Lactones: Isolation, Biological Activity, and Synthesis. *Nat. Prod. Rep.* **2016**, *33*, 655−708.

(4) Wang, Y.; Xu, Y.; Liu, L.; Dong, Z. Bioactive γ-Lactones from Marine Sponges. *Mar. Drugs* **2017**, *15*, 302.

(5) Takeda, K. I.; Sakurawi, K.; Ishii, H. Components of the Lauraceae family−I: New lactonic compounds from Litsea japonica. *Tetrahedron* **1972**, *28*, 3757−3766.

(6) Niwa, M.; Iguchi, M.; Yamamura, S. The isolation and structure of obtusilactone. *Tetrahedron Lett.* **1975**, *16*, 1539−1542.

(7) (a) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. Tumor inhibitors. 69. Structure-cytotoxicity relations among the sesquiterpene lactones. *J. Med. Chem.* **1971**, *14*, 1147−1152. (b) Rosowsky, A.; Papathanasopoulos, N.; Lazarus, H.; Foley, G. E.; Modest, E. J. Cysteine scavengers. 2. Synthetic. alpha-methylenebutyrolactones as potential tumor inhibitors. *J. Med. Chem.* **1974**, *17*, 672−676. (c) Grieco, P. A.; Noguez, J. A.; Masaki, Y.; Hiroi, K.; Nishizawa, M.; Rosowsky, A.; Oppenheim, S.; Lazarus, H. Synthesis of mono-and bifunctional. alpha. methylene lactone systems as potential tumor inhibitors. *J. Med. Chem.* **1977**, *20*, 71−76. (d) Fujita, E.; Nagao, Y. Tumor inhibitors having potential for interaction with mercapto enzymes and/or coenzymes: A review. *Bioorg.Chem.* **1977**, *6*, 287−309. (e) Cassady, J. M.; Byrn, S. R.; Stamos, I. K.; Evans, S. M.; McKenzie, A. Potential antitumor agents. Synthesis, reactivity, and cytotoxicity of. alpha. -methylene carbonyl compounds. *J. Med. Chem.* **1978**, *21*, 815−819.

(8) (a) Chae, H. S.; Khiev, P.; Lee, H. K.; Oh, S. R.; Chin, Y. W. Anti-allergic effect of a chloroform-soluble extract of Cinnamomum cambodianum in bone marrow-derived mast cells. *Immunopharmacol. Immunotoxicol.* **2012**, *34*, 639−644. (b) Pel, P.; Kim, Y.; Chin, Y. W. Chemical Constituents with Anti-allergic Activity from the Barks of Cinnamomum cambodianum Collected in Cambodia. *Bull. Korean Chem. Soc.* **2015**, *36*, 384−387.

(9) Claros, B. M.; da Silva, A. J.; Vasconcellos, M. L.; de Brito, A. P. P.; Leitão, G. G. Chemical Constituents of Two Mollinedia Species. *Phytochemistry* **2000**, *55*, 859−862.

(10) Zhao, Y.; Guo, Y. W.; Zhang, W. Rotundifolides A and B, Two New Enol-Derived Butenolactones from the Bark of Litsea rotundifolia var. oblongifolia. *Helv. Chim. Acta* **2005**, *88*, 349−353.

(11) Mailar, K.; Choi, W. J. The First Asymmetric Synthesis of Marliolide from Readily Accessible Carbohydrate as a Chiral Template. *Carbohydr. Res.* **2016**, *432*, 31−35.

(12) (a) Wood, W. W.; Watson, G. M. The Total Synthesis of Litsenolides C1 and C2. *J. Chem. Soc., Chem. Commun.* **1986**, 1599−1600. (b) Wood, W. W.; Watson, G. M. The Total Synthesis of (−)-Litsenolides C-1 and C-2. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2681−2688.

(13) (a) Rollinson, S. W.; Amos, R. A.; Katzenellenbogen, J. A. Total synthesis of Lauraceae lactones: obtusilactones, litsenolides, and mahubanolides. *J. Am. Chem. Soc.* **1981**, *103*, 4114−4125. (b) Takahata, H.; Uchida, Y.; Momose, T. New Synthesis of All Four Isomers of 3-Hydroxy-4-methyl-. gamma-butyrolactone by Stereoselective Intramolecular Lactonization. Application to Asymmetric Synthesis of Biologically Active Compounds. *J. Org. Chem.* **1994**, *59*, 7201−7208. (c) Adam, W.; Renze, J.; Wirth, T. Stereoelectronic control of the diastereoselectivity in the photooxygenation (Schenck ene reaction) of an electron-poor allylic alcohol and its ethers. *J. Org. Chem.* **1998**, *63*, 226−227. (d) Chen, M. J.; Lo, C. Y.; Chin, C. C.; Liu, R. S. Total synthesis of (+)-blastmycinone, (−)-litsenolide C1, and related natural trisubstituted lactones via alkynyltungsten compounds. *J. Org. Chem.* **2000**, *65*, 6362−6367. (e) Harcken, C.; Brückner, R. Stereopure 1, 3-butadiene-2-carboxylates and their conversion into non-racemic α-alkylidenebutyrolactone natural products by asymmetric dihydroxylation. *Tetrahedron Lett.* **2001**, *42*, 3967−3971. (f) Tamura, S.; Tonokawa, M.; Murakami, N. Stereo-controlled synthesis of analogs of peumusolide

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205

A, NES non-antagonistic inhibitor for nuclear export of MEK. *Tetrahedron Lett.* **2010**, *51*, 3134−3137. (g) Lee, S. I.; Jang, J. H.; Hwang, G. S.; Ryu, D. H. Asymmetric Synthesis of α-Alkylidene-β-hydroxy-γ-butyrolactones via Enantioselective Tandem Michael−Aldol Reaction. *J. Org. Chem.* **2013**, *78*, 770−775.

(14) Wu, P. L.; Hsu, Y. L.; Zao, C. W.; Damu, A. G.; Wu, T. S. Constituents of Vittaria anguste-elongata and Their Biological Activities. *J. Nat. Prod.* **2005**, *68*, 1180−1184.

(15) (a) Nimmareddy, R. R.; Gandham, H.; Challa, S.; Desireddi, J. R.; Modugu, N. R.; Leleti, K. R. Concise Stereoselective Synthesis of Vittarilide-A. *Tetrahedron* **2024**, *159*, 134013. (b) Yadav, J. S.; Chinnam, V. V.; Krishna, B. B. M.; Rao, K. L. S.; Das, S. Stereoselective Synthesis of Vittarilide-A. *Tetrahedron Lett.* **2015**, *56*, 1661−1663. (c) Takahashi, M.; Murata, Y.; Hakamata, Y.; Suzuki, K.; Sengoku, T.; Yoda, H. First Total Synthesis and Absolute Stereochemical Assignment of Vittarilide-A, an Antioxidant Extractive Component Isolated from *Vittaria anguste*-elongata Hayata. *Tetrahedron* **2012**, *68*, 7997−8002.

(16) (a) Desireddi, J. R.; Rao, M. M.; Murahari, K. K.; Nimmareddy, R. R.; Mothe, T.; Lingala, A. K.; Maiti, B.; Manchal, R. Study of the β-oxygen effect in the Barton−McCombie reaction for the total synthesis of (4R,5R)-4-hydroxy-γ-decalactone (Japanese orange fly lactone): a carbohydrate based approach. *RSC Adv.* **2022**, *12*, 25520−25527. (b) Desireddi, J. R.; Rao, M. M.; Murahari, K. K.; Nimmareddy, R. R.; Mothe, T.; Lingala, A. K.; Maiti, B.; Manchal, R. Stereo Selective Total Synthesis of 4-(S)-Hydroxy-5-(R)-octyldihydrofuran-2-one: Harvestmen Lactone. *ChemistrySelect* **2022**, *7*, No. e202201317.

(17) Srihari, P.; Kumaraswamy, B.; Bhunia, D. C.; Yadav, J. First stereoselective total synthesis of stagonolide G. *Tetrahedron Lett.* **2010**, *51*, 2903−2905.

(18) Gurjar, M. K.; Srinivas, N. R. A novel synthesis of methyl 2-O-methyl-α, β-l-fucofuranoside. *Carbohydr. Res.* **1990**, *205*, 398−401.

(19) (a) Nacro, K.; Lee, J.; Barchi Jr, J. J.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. Conformationally constrained analogues of diacylglycerol (DAG). Part 19: Asymmetric syntheses of (3R)-and (3S)-3-hydroxy-4, 4-disubstituted heptono-1, 4-lactones as protein kinase C (PK-C) ligands with increased hydrophilicity. *Tetrahedron* **2002**, *58*, 5335−5345. (b) Grélaud, S.; Lusseau, J.; Landais, Y. Acyl Radical Addition to Activated Olefins: A Stereocontrolled Route to Polysubstituted Tetrahydrofurans and Lactones, and Application to the Total Synthesis of (+)-No. 2106 A. *Eur. J. Org Chem.* **2017**, *10*, 1323−1330. (c) Wood, W. W.; Watson, G. M. The total synthesis of (−)-litsenolides C-1 and C-2. *J. Chem. Soc., Perkin Trans.* **1987**, *1*, 2681−2688.

(20) (a) Man, Y.; Zhou, C.; Fu, S.; Liu, B. Synthetic Study Aiming at the Tricyclic Core of 12-epi-JBIR-23/24. *Org. Lett.* **2021**, *23*, 3151−3156. (b) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. A versatile and highly selective hypervalent iodine (III)/2, 2, 6, 6-tetramethyl-1-piperidinyloxyl-mediated oxidation of alcohols to carbonyl compounds. *J. Org. Chem.* **1997**, *62*, 6974−6977. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. L.; Fong, K. C.; Choi, H. S. Total synthesis of the CP-molecules (CP-263,114 and CP-225,917, phomoidrides B and A). 2. Model studies for the construction of key structural elements and first-generation strategy. *J. Am. Chem. Soc.* **2002**, *124*, 2190−2201.

(21) Reference 19a.

(22) Kaden, F.; Nowotni, S.; Höfner, F.; Lorenz, M.; Barthel, A.; Jäger, A.; Metz, P. Asymmetric Total Synthesis of (−)-Dehydrocostus Lactone by Domino Metathesis. *Eur. J. Org Chem.* **2021**, *25*, 3579−3586.

(23) Sugimura, H.; Sato, S.; Tokudome, K.; Yamada, T. Stereoselective formation of tetrahydrofuran rings via [3+ 2] annulation: Total synthesis of plakortone L. *Org. Lett.* **2014**, *16*, 3384−3387.

(24) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. Total synthesis of the microtubule stabilizing antitumor agent laulimalide and some nonnatural analogues: the power of Sharpless' asymmetric epoxidation. *J. Org. Chem.* **2003**, *68*, 3026−3042.

(25) Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T. C.; Dong, H.; Tong, W. P.; Danishefsky, S. J. Complex target-oriented total synthesis in the drug discovery process: The discovery of a highly promising family of second generation epothilones. *J. Am. Chem. Soc.* **2003**, *125*, 2899−2901.

(26) Neises, B.; Steglich, W. Simple method for the esterification of carboxylic acids. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.

(27) (a) Yadav, J. S.; Chinnam, V. V.; Krishna, B. B. M.; Rao, K. L. S.; Das, S. Stereoselective synthesis of vittarilide-A. *Tetrahedron Lett.* **2015**, *56*, 1661−1663. (b) Yadav, J. S.; Mandal, S. S. Stereoselective Total Synthesis of (−)-Isocladospolide B and Cladospolide B and C. *Synlett* **2011**, *19*, 2803−2806.

https://doi.org/10.1021/acsomega.4c10876
ACS Omega 2025, 10, 3199−3205