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Stereoselective Synthesis of the Core Structures of Pyrrocidines and Wortmannines through the Excited-State Nazarov Reactions

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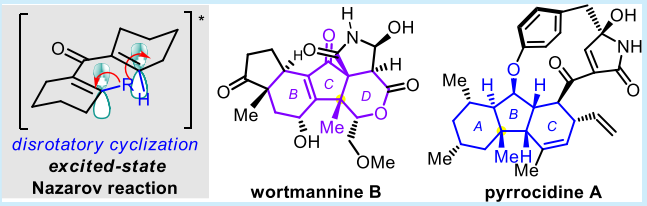
ABSTRACT: The reaction conditions and scope of the excited-state Nazarov reaction of dicyclicvinyl ketones were studied. The stereochemistry of this electrocyclization is consistent with the mechanism of the pericyclic reaction and Woodward–Hoffmann rule. UV-light-promoted excited-state Nazarov reactions gave hydrofluorenones bearing a *syn*–*cis* configuration via a disrotatory cyclization. The core tricyclic hydrofluorenones of pyrrocidines and wortmannines were constructed via the excited-state Nazarov reactions, which demonstrated their synthetic potential in complex natural product total synthesis.



Fluorenones, hydrofluorenones, and hydrofluorenols are comprised by a 6,5,6-fused tricyclic skeleton, which widely exists in polycyclic natural products.[1] The diverse stereochemistry and various substituted groups on the ring junctions result in their major structural differences and synthetic challenges (Figure 1A). For instance, the core *cis*-decahydro-9*H*-fluoren-9-one (**I**) was found in a small group of steroid wortmannines (Figure 1B).[2] Wortmannines A (**1**), B (**2**), and C (**3**) were isolated from the zeistic culture of *Talaromyces wortmannii* LGT-4 by Yang and co-workers in 2016.[3] Recently, structural analogues, such as wortmannines B1(**4**) and B3 (**5**), were discovered from the genus *Niesslia* (TTI-0426) by Gloer and co-workers.[4]

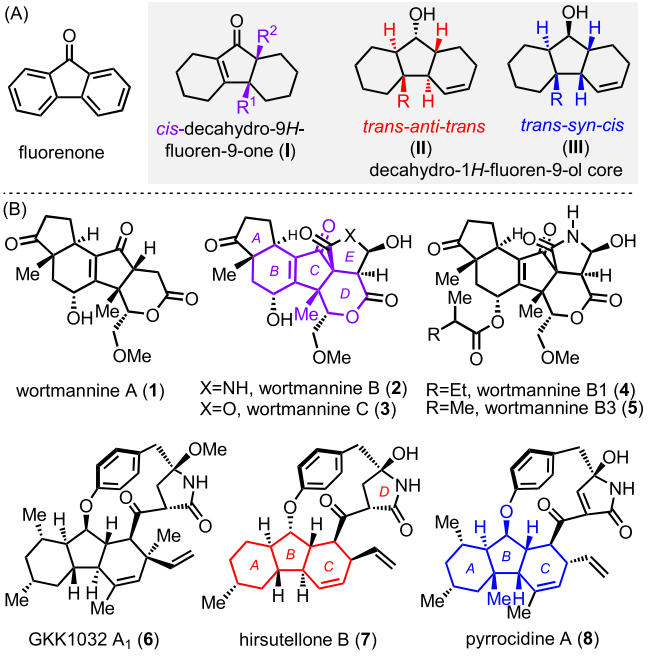


Figure 1. (A) Fluorenones and fluorenols. (B) Structures of polycyclic natural products bearing decahydro-1*H*-fluoren-9-ol cores and decahydro-9*H*-fluoren-9-one cores.

Moreover, the unprecedented *trans*–*anti*–*trans* decahydro-1*H*-fluoren-9-ol (**II**) (Figure 1A) comprises the core skeleton of a family of complex molecules, isolated from different fungal sources in the past decades.[5] GKK1032 A_1 (**6**) was among the first member that was isolated from *Penicillium sp.* GKK1032 in 2001.[6a,b] Hirsutellones A–E were discovered from the insect pathogenic fungus *Hirsutella nivea* BCC 2594 by Isaka and co-workers in 2005.[6c] The structure and configuration of hirsutellone B (**7**) were determined by X-ray crystallographic analysis. Specifically, the *trans*–*syn*–*cis* decahydro-1*H*-fluoren-9-ol (**III**) framework was also found in pyrrocidine A (**8**), which was isolated from the fungus *Cylindrocarpon* sp. *LL*-Cyan426 by He and co-workers in 2002.[6d,7]

Structural analyses of these natural molecules reveals that the stereoselective constructions of the 6,5,6-fused tricyclic cores (**I**, **II**, and **III**), containing up to five contiguous stereogenic centers including one all-carbon quaternary center, represent a great synthetic challenge. Considerable attention has been attracted by these complex natural polyketides from the synthetic community because of their challenging structures as well as potential biological activities. In 2009,

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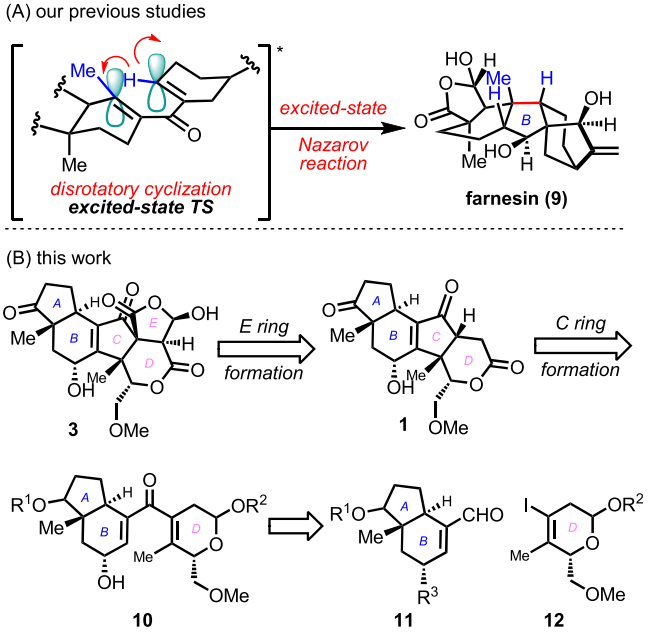
Nicolaou and co-workers disclosed an elegant strategy for the first total synthesis of hirsutellone B (**7**), and the decahydro-1*H*-fluoren-9-ol skeleton was built through a cascade epoxide opening Diels–Alder reaction.[8] Synthetic studies, reported by the groups of Uchiro,[9] Sorensen,[10] Liu,[11] Nay,[12] and others,[13] toward this family of natural molecules mainly relied on the intramolecular Diels–Alder reaction to build the required B–C rings, which was inspired by the biosynthetic pathway of these natural polyketides.[5] However, the total synthesis of wortmannines has not been disclosed to date.

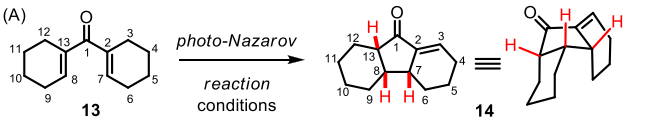
We envisioned that the core decahydro-1*H*-fluoren-9-ol and decahydro-9*H*-fluoren-9-one skeletons could be stereospecifically constructed by means of the Nazarov reaction[14,15] of dicyclicvinyl ketones, wherein the stereochemistry of the cyclization could be predicted and controlled by the adopted reaction conditions. These electrocyclizations were consistent with the mechanism of the pericyclic reaction and Woodward–Hoffmann rule.[16] UV-light-promoted excited-state Nazarov reactions give the hydrofluorenones bearing a *cis–syn* configuration via disrotatory cyclization,[17] while the acid-promoted ground-state Nazarov reactions of the same substrates produce the tricyclic products with a *trans–anti* configuration via conrotatory cyclization. In our previous studies,[18] we have applied the excited-state Nazarov reaction in the total synthesis of farnesin, a rearranged *ent*-kaurenoid (Scheme 1A).[18c] Herein, we report the detailed reaction

Scheme 1. Synthetic Plan



condition screening of the excited-state Nazarov reactions of dicyclicvinyl ketones and its applications in the formation of the tricyclic core of pyrrocidine A. As a further synthetic application, we planned to investigate the practicality of the photo-Nazarov reaction to build the basic skeleton of wortmannines using the substrate bearing the acid sensitive cyclic acetal group, such as dicyclicvinyl ketone **10** (Scheme 1B).[19] A convergent approach was planned to couple two fragments **11** (A–B ring) and **12** (D ring).

We started to optimize the reaction conditions of the photo-Nazarov reaction by using a simple dicyclicvinyl ketone **13** as a model substrate. The influence of the solvents was first investigated under the 254 nm UV light (entries 1–7, Figure 2A). Most solvents other than dioxane worked, including



entry	*hv* (λ/nm)	solvent [a]	additives	time (min)	conversion [b]	yield [b]
1	254	DCM	---	40	100%	25%
2	254	THF	---	50	100%	21%
3	254	CH_3CN	---	30	100%	19%
4	254	dioxane	---	50	100%	0
5	254	DCE	---	45	100%	36%
6	254	toluene	---	39	100%	13%
7	254	Et_2O	---	50	100%	8%
8	300	DCE	---	15	100%	45%
9	366	DCE	---	40	100%	52%
10	419	DCE	---	6 h	83%	10%
11	575	DCE	---	6 h	95%	17%
12[c]	366	DCE	AcOH	50	100%	93%
13[c]	366	DCE	LiCl	50	100%	79%
14[c]	366	DCE	$FeCl_3$	50	100%	37%
15[c]	366	DCE	$TiCl_4$	50	100%	41%
16[c]	366	DCE	$Sc(OTf)_3$	50	100%	51%

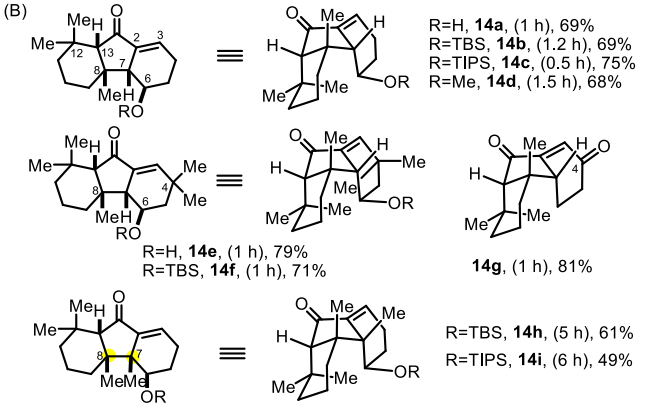


Figure 2. Reaction conditions of the photo-Nazarov reaction. Reaction scale (**13**, 0.1 mmol). (a) All the photoreactions were run in degassed anhydrous solvent. (b) Conversion, ratio, and yields were determined by ^1H NMR spectroscopic crude analysis using CH_2Br_2 as an internal standard, unless noted. (c) Additives (3.0 equiv).

dichloromethane, tetrahydrofuran, acetonitrile, 1,2-dichloroethane, toluene, and ether, among which 1,2-dichloroethane (DCE) was superior to the others, generating the desired product **14** in 36% yield (entry 5, Figure 2A). The newly generated double bond in the corresponding product **14** was located at the C2═C3 position, and its relative stereochemistry matched with the structure obtained in our previous work.[18c] We further optimized photolytic conditions by screening the light sources and additives using 1,2-dichloroethane as the solvent. UV light at λ_{max} = 366 nm gave a better reaction yield of 52% (entry 9, Figure 2A). While using UV light at 419 and 575 nm, a longer reaction time was needed, and it resulted in lower yields (entries 10 and 11, Figure 2A). Subsequently, acidic additives including Brønsted acids and Lewis acids were added during photolysis, such as AcOH, LiCl, $FeCl_3$, $TiCl_4$, and $Sc(OTf)_3$ (entries 12–16, Figure 2A). We were pleased to find that the addition of LiCl and AcOH

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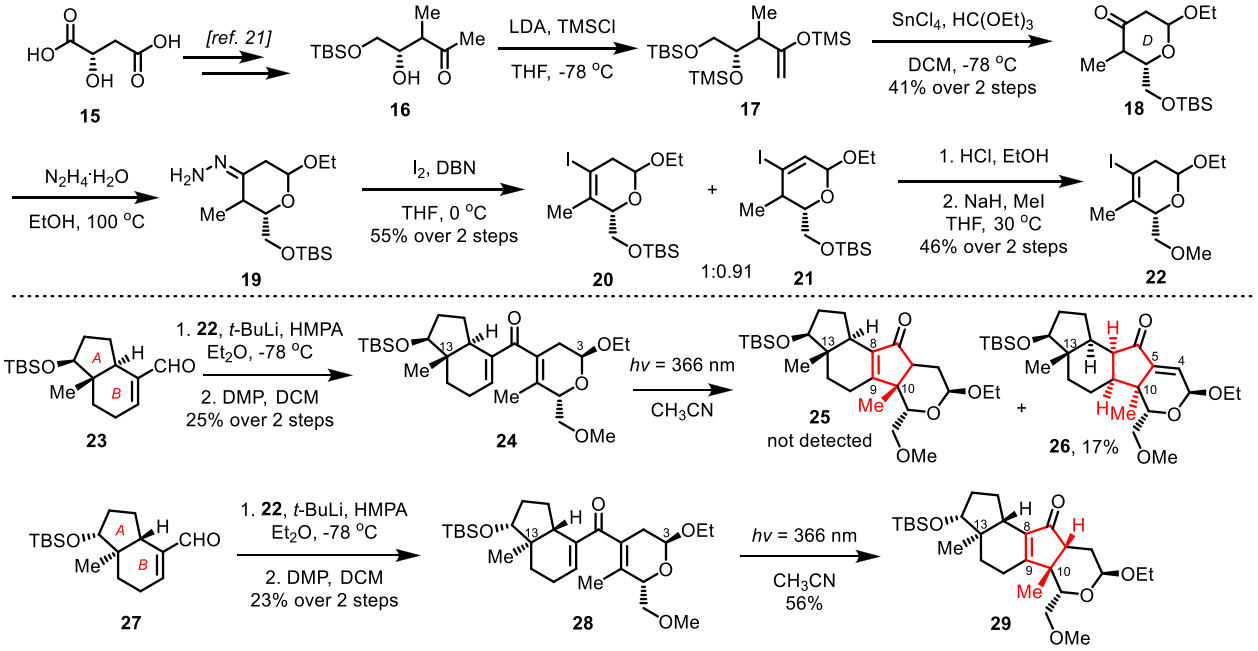
Scheme 2. Construction of the Core Structure of Wortmannines



dramatically improved the reaction yields. When 3.0 equiv of AcOH was added, the photoreaction occurred smoothly to give **14** in 93% yield. We reasoned that an interaction between LiCl or AcOH and the enone group of **13**, through a weak coordination or hydrogen bonding, stabilized the photolytic intermediates and accelerated the electrocyclization (for the discussion of the reaction mechanism, see Schemes S1−S3 in the Supporting Information). These results were consistent with that of photolysis of 2-furyl vinyl ketones observed by Coombs and co-workers.[20]

We then explored the scope of the photo-Nazarov reaction to examine its generality for the construction of hydrofluorenones (Figure 2B). Photolysis of dicyclicvinyl ketones bearing a hydroxyl group at C-6, methyl group at C-8, and *gem*-dimethyl group at C-4 and C-12 generated the desired cyclized products **14a**−**14f** with four contiguous stereogenic centers in moderate yields (68−79%) under the optimal conditions. These structures feature a *syn*−*cis* tricyclic framework, which was confirmed by the X-ray diffraction analysis in our previous work,[18c] and it also matched with the required A−B−C ring of pyrrocidine A (**8**). Photoinduced electrocyclization of a substrate with a carbonyl group at the C-4 position afforded a conjugated enone product **14g** in 81% yield. Notably, substrates bearing two methyl groups at C-7 and C-8 positions also worked and generated the cyclized products **14h** and **14i** with contiguous all-carbon quaternary centers at the bridgehead. The reaction time increased with increasing the steric hindrance of the substituted groups on enones and protective groups on the hydroxyl group at C-6. These results highlight the capability and synthetic potential of the photo-Nazarov cyclizations of dicyclicvinyl ketones to build the challenging hydrofluorenone architectures.

To construct the basic skeleton of wortmannines, we selected the known *β*-hydroxyl-ketone **16**, generated from *L*-(−)-malic acid **15**, as the starting material to prepare the D ring (Scheme 2).[21] Substrate **16** was converted to the silyl enol ether **17** under basic conditions, which was treated by Lewis acid $SnCl_4$ in the presence of triethyl orthoformate at −78 °C to yield cyclic acetal **18**.[22] Reaction of the ketone on **18** with hydrazine afforded hydrazone **19**, which was immediately exposed to iodine in the presence of 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) to produce tetra- and trisubstituted vinyl iodide **20** and **21** as an inseparable mixture.[23] After two steps of deprotection and methylation, the methyl ether **22** was obtained in 46% over two steps. The bicyclic compound **23** bearing the unsaturated aldehyde was prepared according to a known procedure[24] and coupled with vinyl iodide **22** through a nucleophilic addition reaction followed by the DMP oxidation. In order to facilitate the following transformations and structure determination, we isolated one diastereomer of dicyclicvinyl ketone **24** bearing a *β*-OEt group at C-3 to investigate the photoreaction.

We then turned our attention to study the photo-Nazarov reaction of **24** to construct the tetracyclic core of wortmannines with the all-carbon quaternary center at C-10. We found that the dicyclicvinyl ketone **24**, bearing the sensitive acetal motif, was unstable under the optimized reaction conditions. Most of the starting material decomposed when DCE was used as a solvent for the photolysis. After several trials, we found that the photoreaction occurred to furnish the cyclized product **26** in low yield (17%) when the anhydrous and degassed acetonitrile was used. However, the configuration of the all-carbon quaternary center at C-10 in **26** was opposite to that of the corresponding natural products. Furthermore, the newly formed C4═C5 double bond was located on the D ring. We speculated that the stereochemistry of this photo-electrocyclization was controlled by the rigid *trans*-fused A−B ring. Then, we prepared bicycle **27**, the enantiomer of **23**, which was converted to dicyclicvinyl ketone **28**, to verify this hypothesis. Under similar photoreaction condition, photolysis of **28** generated the cyclized product **29** in 56% yield. The relative configuration of two quaternary centers at C-10 and C-13 was still opposite which matched with the results obtained from substrate **24**. Interestingly, the enone group of **29** was consistent with the natural product wortmannine **A** (**1**).

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In summary, we investigated the photoinduced Nazarov reaction of dicyclicvinyl ketones to assemble the *syn*−*cis*-fused tricyclic hydrofluorenones. Three stereogenic centers, including contiguous all-carbon quaternary centers, could be stereospecifically formed through this photo-electrocyclization. As synthetic applications, the core structures of pyrrocidine A and wortmannines were constructed. These studies gave us hints to better understand the reactivity and stereoselectivity of the photo-Nazarov reaction, which will guide the synthetic design for the total synthesis of structurally related natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00643.

General experimental procedures; characterization data; ^{1}H NMR, ^{13}C NMR, and Noesy spectra of new compounds; and X-ray data (PDF)

FAIR data, including the primary NMR FID files, for compounds **13a**, **13b**, **13c**, **13d**, **13e**, **13f**, **13g**, **13h**, **13i**, **14a**, **14b**, **14c**, **14d**, **14e**, **14f**, **14g**, **14h**, **14i**, **18**, **20**, **21**, **22**, **23**, **24**, **26**, **28**, and **29** (ZIP)

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Author Contributions

[§]D.X. and Y.Q. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Shi, Y.; Gao, S. Recent advances of synthesis of fluorenone and fluorene *containing* natural products. *Tetrahedron* **2016**, *72*, 1717−1735.

(2) For the isolation of wortmannin, see: (a) Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Norris, G. L. F. Wortmannin, an antibiotic produced by *Penicillium* wortmanni. *Trans. Br. Mycol. Soc.* **1957**, *40*, 365−368. For the total synthesis of wortmannin, see: (b) Sato, S.; Nakada, M.; Shibasaki, M. The First Chemical Synthesis of Wortmannin by Starting from Hydrocortisone. *Tetrahedron Lett.* **1996**, *37*, 6141−6144. (c) Mizutani, T.; Honzawa, S.; Tosaki, S.; Shibasaki, M. Total Synthesis of (±)-Wortmannin. *Angew. Chem., Int. Ed.* **2002**, *41*, 4680−4682. (d) Shigehisa, H.; Mizutani, T.; Tosaki, S.; Ohshima, T.; Shibasaki, M. Formal Total Synthesis of (+)-Wortmannin using Catalytic Asymmetric Intramolecular Aldol Condensation Reaction. *Tetrahedron* **2005**, *61*, 5057−5065. (e) Guo, Y.; Quan, T.; Lu, Y.; Luo, T. Enantioselective Total Synthesis of (+)-Wortmannin. *J. Am. Chem. Soc.* **2017**, *139*, 6815−6818. (f) Xue, D.; He, H.; Gao, S. Strategies for the Total Synthesis of the Furanosteroids: wortmannin and viridin. *Chem. Lett.* **2021**, *50*, 497−502.

(3) Fu, G.; Yang, Z.; Zhou, S.; Li, X.; Yu, H.; Yao, X.; Fang, J.; Shu, Z.; Xue, H.; Wang, Y. Wortmannines A−C, three novel wortmannin derivatives with an unusual five-membered B ring from the endophytic fungus *Talaromyces wortmannii* LGT-4. *Tetrahedron Lett.* **2016**, *57*, 4608−4611.

(4) Dischler, N. M.; Xu, L.; Li, Y.; Nichols, C. B.; Alspaugh, J. A.; Bills, G. F.; Gloer, J. B. Wortmannin and Wortmannine Analogues from an Undescribed *Niesslia* sp. *J. Nat. Prod.* **2019**, *82*, 532−538.

(5) Li, X.; Ear, A.; Nay, B. Hirsutellones and beyond: figuring out the biological and synthetic logics toward chemical complexity in fungal PKS-NRPS compounds. *Nat. Prod. Rep.* **2013**, *30*, 765−782.

(6) (a) Koizumi, F.; Hasegawa, K.; Ando, K.; Ogawa, T.; Hara, A. *Jpn. Kokai Tokkyo Koho* 2001, JP 2001147574 A2 200109. (b) Hasegawa, A.; Koizumi, F.; Takahashi, Y.; Ando, K.; Ogawa, T.; Hara, M.; Yoshida, M. 43rd Tennen Yuki Kagobutu Touronnkai Koen Yoshishu: Osaka, 2001; pp 467−472. (c) Isaka, M.; Rugseree, N.; Maithip, P.; Kongsaeree, P.; Prabpai, S.; Thebtaranonth, Y. Hirsutellones A−E, antimycobacterial alkaloids from the insect pathogenic fungus *Hirsutella nivea* BCC 2594. *Tetrahedron* **2005**, *61*, 5577−5583. (d) He, H.; Yang, H. Y.; Bigelis, R.; Solum, E. H.; Greenstein, M.; Carter, G. Pyrrocidines A and B, new antibiotics produced by a filamentous fungus. *Tetrahedron Lett.* **2002**, *43*, 1633−1636.

(7) Uesugi, S.; Fujisawa, N.; Yoshida, J.; Watanabe, M.; Dan, S.; Yamori, T.; Shiono, Y.; Kimura, K. Pyrrocidine A, a metabolite of endophytic fungi, has a potent apoptosis-inducing activity against HL60 cells through caspase activation *via* the Michael addition. *J. Antibiot.* **2016**, *69*, 133−140.

(8) (a) Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. Total Synthesis of Hirsutellone B. *Angew. Chem., Int. Ed.* **2009**, *48*, 6870−6874. (b) Nicolaou, K. C.; Sun, Y.-P.; Sarlah, D.; Zhan, W.; Wu, T. R. Bioinspired Synthesis of Hirsutellones A, B, and C. *Org. Lett.* **2011**, *13*, 5708−5710.

(9) (a) Uchiro, H.; Kato, R.; Arai, Y.; Hasegawa, M.; Kobayakawa, Y. Total Synthesis of Hirsutellone B via Ullmann-Type Direct 13-

Membered Macrocyclization. *Org. Lett.* **2011**, *13*, 6268−6271. (b) Uchiro, H.; Kato, R.; Sakuma, Y.; Takagi, Y.; Arai, Y.; Hasegawa, M. Synthetic studies of GKK1032s: the asymmetric synthesis of the decahydrofluorene skeleton via a novel cyclization of silyl enol ether and sequential retro Diels−Alder and intramolecular Diels−Alder reactions. *Tetrahedron Lett.* **2011**, *52*, 6242−6245.

(10) (a) Tilley, S. D.; Reber, K. P.; Sorensen, E. J. A Rapid, Asymmetric Synthesis of the Decahydrofluorene Core of the Hirsutellones. *Org. Lett.* **2009**, *11*, 701−703. (b) Reber, K. P.; Tilley, S. D.; Carson, C. A.; Sorensen, E. J. Toward a Synthesis of Hirsutellone B by the Concept of Double Cyclization. *J. Org. Chem.* **2013**, *78*, 9584−9607.

(11) (a) Huang, M.; Song, L.; Liu, B. Construction of the Cyclophane Core of the Hirsutellones via a RCM Strategy. *Org. Lett.* **2010**, *12*, 2504−2507. (b) Huang, M.; Huang, C.; Liu, B. Studies toward the total synthesis of the hirsutellones. *Tetrahedron Lett.* **2009**, *50*, 2797−2800. (c) Song, L.; Huang, C.; Huang, M.; Liu, B. Toward the synthesis of hirsutellone B via an intramolecular Diels−Alder/ketene-trapping strategy. *Tetrahedron* **2015**, *71*, 3603−3608.

(12) Li, X.; Ear, A.; Roger, L.; Riache, N.; Deville, A.; Nay, B. Bio-Inspired Formal Synthesis of Hirsutellones A−C Featuring an Electrophilic Cyclization Triggered by Remote Lewis Acid-Activation. *Chem. - Eur. J.* **2013**, *19*, 16389−16393.

(13) (a) Arai, N.; Ui, H.; Omura, S.; Kuwajima, I. Studies toward the Total Synthesis of GKK1032A$_2$, a Structurally Unique Antitumor Compound: Stereoselective Construction of the Tricarbocyclic System. *Synlett* **2005**, 1691−1694. (b) Asano, M.; Inoue, M.; Katoh, T. Enantioselective Synthesis of the Tricyclic Core of GKK1032, Novel Antibiotic Anti-Tumor Agents, by Employing an Intramolecular Diels-Alder Cycloaddition Strategy. *Synlett* **2005**, *2005*, 1539−1542. (c) Asano, M.; Inoue, M.; Watanabe, K.; Abe, H.; Katoh, T. Synthetic Studies toward GKK1032s, Novel Antibiotic Antitumor Agents: Enantioselective Synthesis of the Fully Elaborated Tricyclic Core via an Intramolecular Diels−Alder Cycloaddition. *J. Org. Chem.* **2006**, *71*, 6942−6951. (d) Halvorsen, G. T.; Roush, W. R. Stereoselective synthesis of the decahydrofluorene core of the hirsutellones. *Tetrahedron Lett.* **2011**, *52*, 2072−2075. (e) Tanaka, R.; Ohishi, K.; Takanashi, N.; Nagano, T.; Suizu, H.; Suzuki, T.; Kobayashi, S. Synthetic Study of Pyrrocidines: First Entry to the Decahydrofluorene Core of Pyrrocidines. *Org. Lett.* **2012**, *14*, 4886−4889.

(14) (a) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1941**, 211−224. For reviews of the Nazarov reaction, see: (b) Habermas, K. L.; Denmark, S. E. T.; Jones, K. The Nazarov Cyclization. *Org. React. (N.Y.)* **1994**, *45*, 1−158. (c) Santelli-Rouvier, C.; Santelli, M. The Nazarov Cyclisation. *Synthesis* **1983**, *1983*, 429−442. (d) Denmark, S. E., Trost, B. M., Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. *5*, p 751. (e) Frontier, A. J.; Collison, C. The Nazarov cyclization in organic synthesis. Recent advances. *Tetrahedron* **2005**, *61*, 7577−7606. (f) Pellissier, H. Recent developments in the Nazarov process. *Tetrahedron* **2005**, *61*, 6479−6517. (g) Tius, M. A. Some New Nazarov Chemistry. *Eur. J. Org. Chem.* **2005**, *2005*, 2193−2206. (h) Nakanishi, N.; West, F. G. *Curr. Opin. Drug Discovery Dev.* **2009**, *12* (6), 732−751. (i) Shimada, N.; Stewart, C.; Tius, M. A. Asymmetric Nazarov cyclizations. *Tetrahedron* **2011**, *67*, 5851−5870. (j) Vaidya, T.; Eisenberg, R.; Frontier, A. J. Catalytic Nazarov Cyclization: The State of the Art. *ChemCatChem* **2011**, *3*, 1531−1548. (k) Di Grandi, M. J. Nazarov-like cyclization reactions. *Org. Biomol. Chem.* **2014**, *12*, 5331−5345. (l) Wenz, D. R.; Read de Alaniz, J. The Nazarov Cyclization: A Valuable Method to Synthesize Fully Substituted Carbon Stereocenters. *Eur. J. Org. Chem.* **2015**, *2015*, 23−37. (m) Vinogradov, M. G.; Turova, O. V.; Zlotin, S. G. Nazarov reaction: current trends and recent advances in the synthesis of natural compounds and their analogs. *Org. Biomol. Chem.* **2017**, *15*, 8245−8269.

(15) For examples using Nazarov reactions in natural product syntheses, see: (a) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. Synthesis of Taiwaniaquinoids via Nazarov Triflation. *J. Am. Chem. Soc.* **2006**, *128*, 11022−11023. (b) He, W.; Huang, J.; Sun, X.; Frontier, A. J. Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization. *J. Am. Chem. Soc.* **2007**, *129*, 498−499. (c) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. Polarizing the Nazarov Cyclization: The Impact of Dienone Substitution Pattern on Reactivity and Selectivity. *J. Am. Chem. Soc.* **2008**, *130*, 1003−1011. (d) Malona, J. A.; Cariou, K.; Frontier, A. J. Nazarov Cyclization Initiated by Peracid Oxidation: The Total Synthesis of (±)-Rocaglamide. *J. Am. Chem. Soc.* **2009**, *131*, 7560−7561. (e) He, W.; Huang, J.; Sun, X.; Frontier, A. J. Total Synthesis of (±)-Merrilactone A. *J. Am. Chem. Soc.* **2008**, *130*, 300−308. (f) Li, W.-D. Z.; Duo, W.-G.; Zhuang, C.-H. Concise Total Synthesis of (±)-Cephalotaxine via a Transannulation Strategy: Development of a Facile Reductive oxy-Nazarov Cyclization. *Org. Lett.* **2011**, *13*, 3538−3541. (g) Zhong, J.; Chen, K.; Qiu, Y.; He, H.; Gao, S. A Unified Strategy to Construct the Tetracyclic Ring of Calyciphylline A Alkaloids: Total Synthesis of Himalensine A. *Org. Lett.* **2019**, *21*, 3741−3745.

(16) (a) Woodward, R. B.; Hoffmann, R. *The conservation of orbital symmetry*; Academic Press: New York, 1970. (b) Woodward, R. B.; Hoffmann, R. The Conservation of Orbital Symmetry. The Conservation of Orbital Symmetry. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781−853. (c) Woodward, R. B. *Chem. Soc. Special Publications (Aromaticity)* **1967**, *21*, 237−239.

(17) (a) Smith, A. B., III; Agosta, W. C. Photochemical reactions of 1-cyclopentenyl and 1-cyclohexenyl ketones. Photochemical reactions of 1-cyclopentenyl and 1-cyclohexenyl ketones. *J. Am. Chem. Soc.* **1973**, *95*, 1961−1968. (b) Crandall, J. K.; Haseltine, R. P. The photochemistry of 2,7-cyclooctadienone. The photochemistry of 2,7-cyclooctadienone. *J. Am. Chem. Soc.* **1968**, *90*, 6251−6253. (c) Leitich, J.; Heise, I.; Werner, S.; Krürger, C.; Schaffner, K. The photo-Nazarov cyclization of 1-cyclohexenyl phenyl ketone revisited. Observation of intermediates. The photo-Nazarov cyclization of 1-cyclohexenyl phenyl ketone revisited. Observation of intermediates. *J. Photochem. Photobiol., A* **1991**, *57*, 127−151. (d) Leitich, J.; Heise, I.; Rust, J.; Schaffner, K. The Photo-Nazarov Cyclization of 1-Cyclohexenyl-(phenyl)methanone Revisited − Trapping of the 2-Oxyallyl Intermediates by Olefins. *Eur. J. Org. Chem.* **2001**, *2001*, 2719−2726. (e) Cai, S.; Xiao, Z.; Shi, Y.; Gao, S. The Photo-Nazarov Reaction: Scope and Application. *Chem. - Eur. J.* **2014**, *20*, 8677−8681.

(18) (a) Gao, S.; Wang, Q.; Chen, C. Synthesis and Structure Revision of Nakiterpiosin. *J. Am. Chem. Soc.* **2009**, *131*, 1410−1412. (b) Shi, Y.; Yang, B.; Cai, S.; Gao, S. Total Synthesis of Gracilamine. *Angew. Chem., Int. Ed.* **2014**, *53*, 9539−9543. (c) Que, Y.; Shao, H.; He, H.; Gao, S. Total Synthesis of Farnesin through an Excited-State Nazarov Reaction. *Angew. Chem., Int. Ed.* **2020**, *59*, 7444−7449.

(19) (a) Shoppee, C. W.; Lack, R. E. Intramolecular electrocyclic reactions. Part I. Structure of 'bromohydroxyphorone': 3-bromo-5-hydroxy-4,4,5,5-tetramethylcyclopent-2-enone. *J. Chem. Soc. C* **1969**, *0*, 1346−1349. (b) Shoppes, C. W.; Cooke, B. J. A. Intramolecular electrocyclic reactions. Part II. Reactions of 1,5-di-phenylpenta-1,4-dien-3-one. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2271−2276. (c) Shoppee, C. W.; Cooke, B. J. A. Electrocyclic reactions. Part III. Some reactions of 2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one ($\alpha\alpha'$-dimethyldibenzylideneacetone). *J. Chem. Soc., Perkin Trans. 1* **1973**, 1026−1032.

(20) Ashley, W. L.; Timpy, E. L.; Coombs, T. C. Flow Photo-Nazarov Reactions of 2-Furyl Vinyl Ketones: Cyclizing a Class of Traditionally Unreactive Heteroaromatic Enones. *J. Org. Chem.* **2018**, *83*, 2516−2529.

(21) (a) Fuwa, H.; Matsukida, S.; Miyoshi, T.; Kawashima, Y.; Saito, T.; Sasaki, M. Progress toward the Total Synthesis of Goniodomin A: Stereocontrolled, Convergent Synthesis of the C12−C36 Fragment. *J. Org. Chem.* **2016**, *81*, 2213−2227. (b) Szpilman, A. M.; Cereghetti, D. M.; Manthorpe, J. M.; Wurtz, N. R.; Carreira, E. M. Synthesis and Biophysical Studies on 35-Deoxy Amphotericin B Methyl Ester. *Chem. - Eur. J.* **2009**, *15*, 7117−7128.

https://doi.org/10.1021/acs.orglett.1c00643
Org. Lett. 2021, 23, 2736−2741

(22) (a) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y. B.; Albizati, K. F. Chemistry of aldolate dianions. Effects of.beta.-heteroatom substituents on ketone enolization. *J. Am. Chem. Soc.* **1990**, *112*, 6965−6978. (b) Perron-Sierra, F.; Promo, M. A.; Martin, V. A.; Albizati, K. F. Chemistry of dioxenium cations. Synthetic and mechanistic studies on the stereocontrolled formation of tetrahydropyrans from homoallylic alcohols and ortho esters. *J. Org. Chem.* **1991**, *56*, 6188−6199. (c) Li, K.; Ou, J.; Gao, S. Total Synthesis of Camptothecin and Related Natural Products by a Flexible Strategy. *Angew. Chem., Int. Ed.* **2016**, *55*, 14778−14783.

(23) (a) McNeely, S. A.; Davis, R. D.; Kropp, P. J. Photochemistry of Alkyl Halides. 10. Vinyl Halides and Vinylidene Dihalides. *J. Am. Chem. Soc.* **1983**, *105*, 6907−6915. (b) Jarho, E. M.; Venäläinen, J. I.; Poutiainen, S.; Leskinen, H.; Vepsäläinen, J.; Christiaans, J. A. M.; Forsberg, M. M.; Männistö, P. T.; Wallén, E. A. A. 2(*S*)-(Cycloalk-1-enecarbonyl)-1-(4-phenyl-butanoyl)pyrrolidines and 2(*S*)-(aroyl)-1-(4-phenylbutanoyl)pyrrolidines as prolyl oligopeptidase inhibitors. *Bioorg. Med. Chem.* **2007**, *15*, 2024−2031.

(24) (a) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. A Hypervalent Iodine-Induced Double Annulation Enables a Concise Synthesis of the Pentacyclic Core Structure of the Cortistatins. *Org. Lett.* **2009**, *11*, 5394−5397. (b) Hu, Y.; Bai, M.; Yang, Y.; Tian, J.; Zhou, Q. Rapid Access to Tetracyclic Core of Wortmannin via an Intramolecular Reductive Olefin Coupling Strategy. *Org. Lett.* **2020**, *22*, 6308−6312.

https://doi.org/10.1021/acs.orglett.1c00643
Org. Lett. 2021, 23, 2736−2741