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An Approach to the Core Skeleton of Lancifodilactone F

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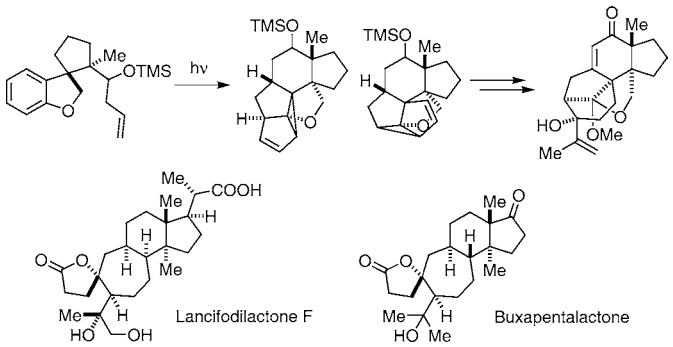
ABSTRACT



Two cycloaddition reactions were utilized for the construction of the 5,6,7-tricyclic skeleton of lancifodilactone F and buxapentalactone. A [2+2] ketene cycloaddition reaction was first used to set their adjacent all-carbon quaternary centers at the 5,6-ring junction. An arene–olefin *meta*-photocycloaddition reaction was then used to install the 6- and 7-membered rings concurrently.

Recently, a series of structurally intriguing triterpenoids was isolated from the Chinese herb *Schisandra*.[1−6] These natural products bear an usual 5,6,7- or 5,8,7-tricyclic skeleton. Among them, lancifodilactone F (**1**)[1c] particularly attracted our attention. Unlike other 5,6,7-tricyclic terpenoids[7] isolated from the same sources,[1a,2b,5,6] for example, micrandilactone C (**2**), it bears two all-carbon quaternary centers at the 5,6-ring junction (Figure 1). Its structure was proposed based on NMR experiments and X-ray analysis. It is interesting to note the structural resemblance of **1** and buxapentalactone (**3**),[8a] which was reported 16 years ago but received little attention. In contrast to **2**, **3**, and their biogenic precursor

(1) Isolation of lancifodilactones: (a) Li, R.-T.; Li, S.-H.; Zhao, Q.-S.; Lin, Z.-W.; Sun, H.-D.; Lu, Y.; Wang, C.; Zheng, Q.-T. *Tetrahedron Lett.* **2003**, *44*, 3531−3534. (b) Li, R.-T.; Xiang, W.; Li, S.-H.; Lin, Z.-W.; Sun, H.-D. *J. Nat. Prod.* **2004**, *67*, 94−97. (c) Xiao, W.-L.; Li, R.-T.; Li, S.-H.; Li, X.-L.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q.-T. *Org. Lett.* **2005**, *7*, 1263−1266; correction: *Org. Lett.* **2006**, *8*, 801. (d) Xiao, W.-L.; Zhu, H.-J.; Shen, Y.-H.; Li, R.-T.; Li, S.-H.; Sun, H.-D.; Zheng, Y.-T.; Wang, R.-R.; Lu, Y.; Wang, C.; Zheng, Q.-T. *Org. Lett.* **2005**, *7*, 2145−2148; correction: *Org. Lett.* **2006**, *8*, 801. (e) Xiao, W.-L.; Tian, R.-R.; Pu, J.-X.; Li, X.; Wu, L.; Lu, Y.; Li, S.-H.; Li, R.-T.; Zheng, Y.-T.; Zheng, Q.-T.; Sun, H.-D. *J. Nat. Prod.* **2006**, *69*, 277−279. (f) Xiao, W.-L.; Huang, S.-X.; Zhang, L.; Tian, R.-R.; Wu, L.; Li, X.-L.; Pu, J.-X.; Zheng, Y.-T.; Lu, Y.; Li, R.-T.; Zheng, Q.-T.; Sun, H.-D. *J. Nat. Prod.* **2006**, *69*, 650−653. Synthetic studies: (g) Fischer, D.; Theodorakis, E. A. *Eur. J. Org. Chem.* **2007**, 4193−4196. (h) Krishnan, K. S.; Smitha, M.; Suresh, E.; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 12345−12350.

(2) Isolation of micrandilactones: (a) Li, R.-T.; Zhao, Q.-S.; Li, S.-H.; Han, Q.-B.; Sun, H.-D.; Lu, Y.; Zhang, L.-L.; Zheng, Q.-T. *Org. Lett.* **2003**, *5*, 1023−1026; correction: *Org. Lett.* **2006**, *8*, 801. (b) Li, R.-T.; Han, Q.-B.; Zheng, Y.-T.; Wang, R.-R.; Yang, L.-M.; Lu, Y.; Sang, S.-Q.; Zheng, Q.-T.; Zhao, Q.-S.; Sun, H.-D. *Chem. Commun.* **2005**, 2936. (c) Li, R.-T.; Xiao, W.-L.; Shen, Y.-H.; Zhao, Q.-S.; Sun, H.-D. *Chem.−Eur. J.* **2005**, *11*, 2989−2996; correction: *Chem.−Eur. J.* **2005**, *11*, 6763−6765. Synthetic studies: (d) Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 885−888. (e) Zhang, Y.-D.; Tang, Y.-F.; Luo, T.-P.; Shen, J.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2006**, *8*, 107−110.

(3) Isolation of hendridilactones: Li, R.; Shen, Y.; Xiang, W.; Sun, H.-D. *Eur. J. Org. Chem.* **2004**, 807−811.

(4) Isolation of sphenadilactones: Xiao, W.-L.; Pu, J.-X.; Chang, Y.; Li, X.-L.; Huang, S.-X.; Yang, L.-M.; Li, L.-M.; Lu, Y.; Zheng, Y.-T.; Li, R.-T.; Zheng, Q.-T.; Sun, H.-D. *Org. Lett.* **2006**, *8*, 1475−1478; correction: *Org. Lett.* **2006**, *8*, 4669.

(5) Isolation of rubriflordilactones: Xiao, W.-L.; Yang, L.-M.; Gong, N.-B.; Wu, L.; Wang, R.-R.; Pu, J.-X.; Li, X.-L.; Huang, S.-X.; Zheng, Y.-T.; Li, R.-T.; Lu, Y.; Zheng, Q.-T.; Sun, H.-D. *Org. Lett.* **2006**, *8*, 991−994.

(6) Isolation of wuweizidilactones: Huang, S.-X.; Yang, L.-B.; Xiao, W.-L.; Lei, C.; Liu, J.-P.; Lu, Y.; Weng, Z.-Y.; Li, L.-M.; Li, R.-T.; Yu, J.-L.; Zheng, Q.-T.; Sun, H.-D. *Chem.−Eur. J.* **2007**, *13*, 4816−4822.

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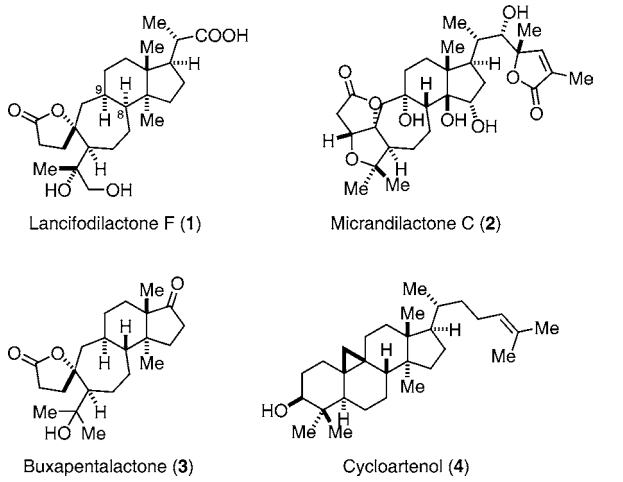


Figure 1. Structures of triterpenoids **1**−**4**.

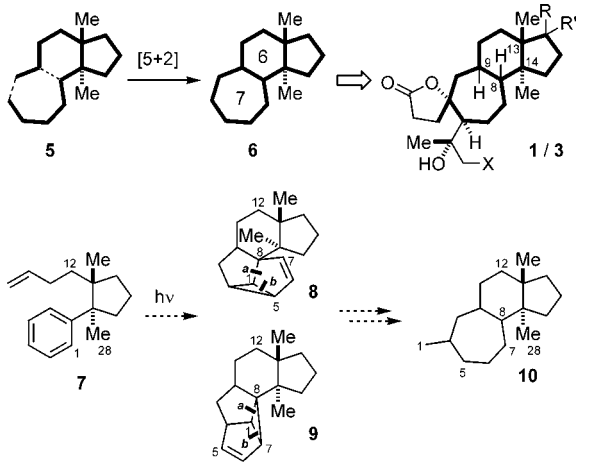


Figure 2. Synthetic strategy for the core Skeleton of **1** and **3**.

cycloartenol (**4**), the C-8 stereogenic center of **1** was proposed to be (*S*)-configured based on NMR analyses. However, this assignment is not supported by the crystallographic data.[9]

With the uncertainty of the structure of **1** in mind, we developed a flexible approach that allows not only a facile construction of its 5,6,7-tricyclic skeleton with the two adjacent quaternary centers but also access to either configuration at the C-8 and C-9 positions (Figure 2). We envisioned that the 6- and 7-membered rings could be formed concurrently with an intramolecular [5+2] cycloaddition reaction.[10] In addition, we expected that it would be easier to introduce the C-13 and C-14 adjacent quaternary centers during an early stage of the synthesis. We anticipated that photolysis of **7** would afford the cycloaddition adducts **8** and **9**. Selective cleavage of their ***a*** and ***b*** linkages would then reveal the lancifodilactone skeleton **10**. We have explored the arene−alkene *meta*-photocycloaddition reaction[11,12] for this [5+2] strategy owing to its high functional group compatibility and the accessibility of synthetic precursors.

The arene−olefin *meta*-photocycloaddition reaction was discovered more than four decades ago.[11] Its synthetic utility has been clearly demonstrated by Wender and co-workers.[13] Although the 4-atom-tethered intramolecular arene−olefin *meta*-photocycloaddition was shown to be problematic,[14] Wender and DeLong noted that restriction of the tether conformations improved the efficiency.[15] Recently, Russell and co-workers also found that a fused cyclohexane ring helped constrain the 4-carbon tether in favorable conformations and the photocycloaddition adducts were obtained in good yields despite as a 1:1 mixture of endo/exo isomers.[16] Interestingly, we did not observe similar beneficial effects

(7) Cyathane diterpenoids also bear a 5,6,7-tricylic core skeleton. For examples of their synthesis, see: (a) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644−7645. (b) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 2844−2845. (c) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334−5335. (d) Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514−13515. (e) Ward, D. E.; Shen, J. *Org. Lett.* **2007**, *9*, 2843−2846. (f) Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359−362. (g) Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407−1410. (h) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105−2108. (i) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553−3560. (j) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885−899.

(8) There has been no report of synthetic studies on buxapentalactone. For isolation of selected *Buxus* triterpenoids, see: (a) Atta-ur-Rahman, Habib, N.; Asif, S. E.; Safdar, A.; Zahida, I.; Choudhary, M. I.; Clardy, J. *Tetrahedron* **1992**, *48*, 3577−3584. (b) Bénéchie, M.; Khuong-Huu, F. *Tetrahedron* **1976**, *32*, 701−707. (c) Guilhem, J. *Tetrahedron Lett.* **1975**, *16*, 2937−2938.

(9) The crystallographic data of **1** published by Sun and co-workers (CCDC-254747) supports the (9*R*)-configuration instead. However, the anisotropic displacement parameters for most atoms are not acceptable, including 15 of them being non-positive definite. The published data do not contain suitable information for reinterpretation.

(10) Reviews: (a) Battiste, M. A.; Pelphrey, P. M.; Wright, D. *Chem.*−*Eur. J.* **2006**, *12*, 3438−3447. (b) Wender, P. A.; Gamber, G. G.; Williams, T. J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 263−299. (c) Wender, P. A.; Love, J. A. *Adv. Cycloaddit.* **1999**, *5*, 1−45. (d) Mascareñas, J. L. *Adv. Cycloaddit.* **1999**, *6*, 1−54.

(11) (a) Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 2066−2067. (b) Bryce-Smith, D.; Gilbert, A.; Orger, B. H. *Chem. Commun.* **1966**, 512−514.

(12) Reviews: (a) Wender, P. A.; Siggel, L.; Nuss, J. M., In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 645−673. (b) Keukeleire, D. D.; He, S. L. *Chem. Rev.* **1993**, *93*, 359−380. (c) Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615−669. (d) Hoffmann, N. *Synthesis* **2004**, 481−495. (e) Mattay, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 663−665.

(13) (a) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688−690. (b) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445−4450. (c) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, *23*, 3983−3986.

(14) (a) Gilbert, A. *Pure Appl. Chem.* **1980**, *52*, 2669−2682. (b) Gilbert, A.; Taylor, G. N. *J. Chem. Soc., Chem. Commun.* **1979**, 229−230. (c) Gilbert, A.; Taylor, G. N. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1761−1768. (d) Ellis-Davies, G. C. R.; Gilbert, A.; Heath, P.; Lane, J. C.; Warrington, J. V.; Westover, D. L. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1833−1841. There is one exception reported by De Keukeleire and He. Irradiation of a 3-(benzyloxymethyl)cyclopentene derivative at 254 nm in cyclohexane-ethyl acetate (5:1) gave the *meta*-photocycloaddition product in 42% yield: (e) De Keukeleire, D.; He, S.-L. *J. Chem. Soc., Chem. Commun.* **1992**, 419−420.

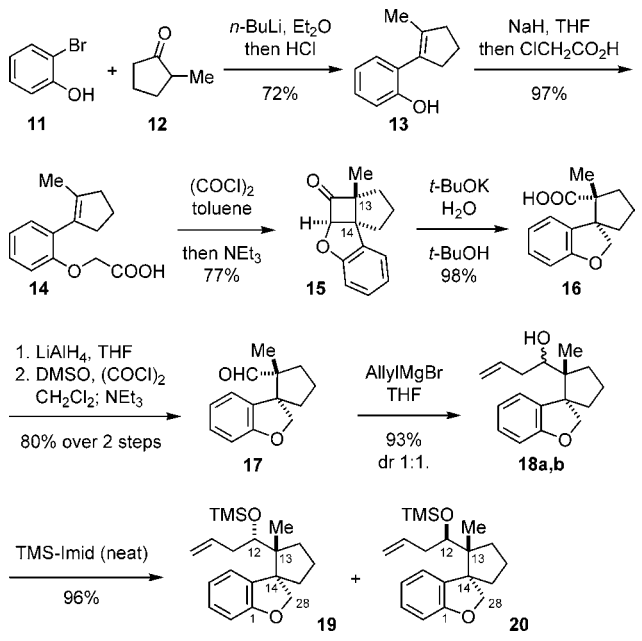
(15) Wender and DeLong have found that photolysis of an oxygen-bridged arene−olefin system with Hanovia medium-pressure mercury lamp through Vycor glass in cyclohexane for 2 h provided the desired *meta*-photocycloaddition products in 68% yield at 60% conversion based on recovered starting material. Prolong irradiation led to product decomposition. DeLong, M. Ph.D. Thesis, Stanford University, 1992.

in the systems that bear a fused cyclopentane ring and the C-13,14 adjacent quaternary centers. Photolysis of a series of derivatives of **7** resulted only in decomposition under various conditions.

To overcome the difficulties encountered in the photolysis of **7**, we introduced a trimethylsiloxyl group to the C-12 position of the tether and a phenol group to the C-1 position of the arene (**19** and **20**). We anticipated that the C-12 siloxyl group and cyclopentane ring would act cooperatively to constrain the tether conformations. By connecting to the adjacent C-28 methyl group, the C-1 phenol group would control both the regioselectivity and endo/exo selectivity of the photocycloaddition. The C-1 phenol group would further assist the cleavage of the ***a*** and ***b*** linkages selectively after photolysis.

We utilized an intramolecular [2+2] ketene cycloaddition reaction to install the C-13,14 adjacent all-carbon quaternary centers of **19** and **20** and secure their relative stereochemistry. The synthesis of **19** and **20** started with addition of the dianion derived from **11** to ketone **12** to provide **13** after dehydration (Scheme 1). Alkylation of **13** with chloroacetic

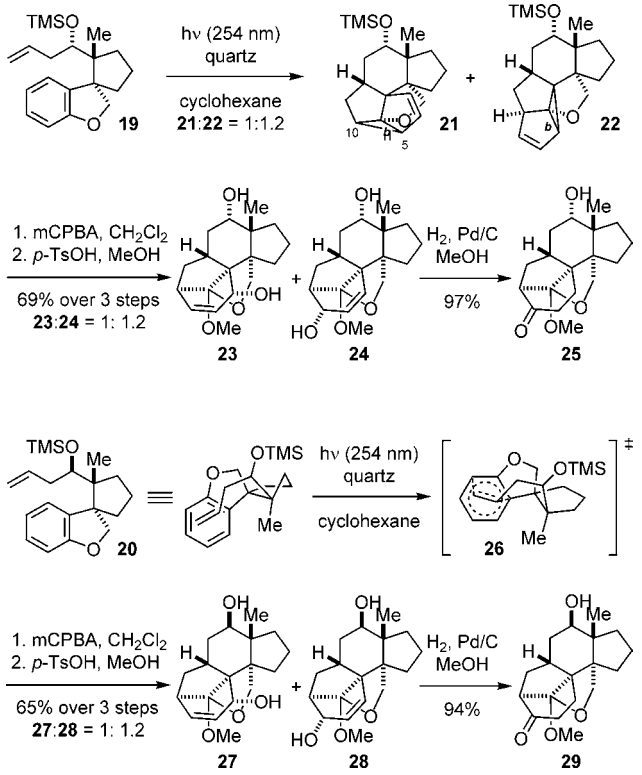
Scheme 1. Establishing the Stereochemistry of the C-13,14 Adjecant All-Carbon Quaternary Centers



acid afforded the ketene precursor **14**. Treating **14** with oxalyl chloride followed by triethylamine initiated the [2+2] ketene cycloaddition reaction to give **15** as the only diastereomer. A Haller−Bauer reaction[17] then opened the cyclobutane ring of **15**. The resulting acid **16** was converted to aldehyde **17**. Allylation of **17** gave a 1:1 diastereomeric mixture of alcohols **18**, which were separated and silylated to give **19** and **20**.

We examined the photolysis of **19** and **20** under various conditions. We found that the arene−olefin *meta*-photocycloaddition reaction proceeded smoothly by irradiating in dilute cyclohexane at 254 nm through a quartz filter. For example, photolysis of **19** gave exclusively the exo cycloaddition products **21** and **22** in 89% isolated yield (Scheme 2). As chromatographic separation of **21** and **22** was difficult,

Scheme 2. Establishing the 5,6,7-Tricyclic Skeleton of **1** and **3**



and **21** degraded upon exposure to silica gel, the photolysis products were usually not purified and were used directly for the subsequent reactions.

The ***b*** linkage of **21** and **22** could be cleaved easily by acid hydrolysis after epoxidation to afford allylic alcohols **23** and **24**. Attempts to cleave the ***b*** linkage of **21** and **22** under reductive or Lewis/Brønsted acidic conditions were less efficient and resulted in a complex mixture of products, presumably due to the overlap of the C-10−C-5 bond with the olefin π orbital in **21**. Upon treating with catalytic amounts of palladium on carbon under 1 atm atmosphere of hydrogen, alcohol **24** underwent allylic isomerization to give ketone **25**. The structures of **23** and **25** were confirmed by X-ray analysis.

Likewise, **20** could be converted to **27**, **28**, and **29**. In fact, separation of the two diastereomers of **18** was not necessary. Silylation, photolysis, and cyclopropane ring cleavage could all be carried out with comparable overall yields using the mixtures of isomers. It is interesting to note that the configuration of the siloxyl group does not affect the stereochemical outcomes of these photocycloaddition reactions. We were surprised to find that, in contrast to the

(16) Boyd, J. W.; Greaves, N.; Kettle, J.; Russell, A. T.; Steed, J. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 944−946.
(17) Review: Mehta, G.; Venkateswaranb, R. V. *Tetrahedron* **2000**, *56*, 1399−1422.

chairlike conformation in Russell's system,[16] the olefin tether of **19** and **20** adopted the boat-like conformations (**26**) in the photocycloaddition reaction to give the exo products exclusively.

The siloxyl group of **19** and **20** is crucial for the successful implementation of this arene−olefin *meta*-photocycloaddition reaction. Photolysis of **18** and **30** under various conditions resulted in complex mixtures of products. Moving the siloxyl group from the homoallylic to allylic position also led only to decomposition. Conformational analysis indicates that the siloxyl group helps lock the olefin tether in productive conformations (Figure 3). In particular, the olefin group of

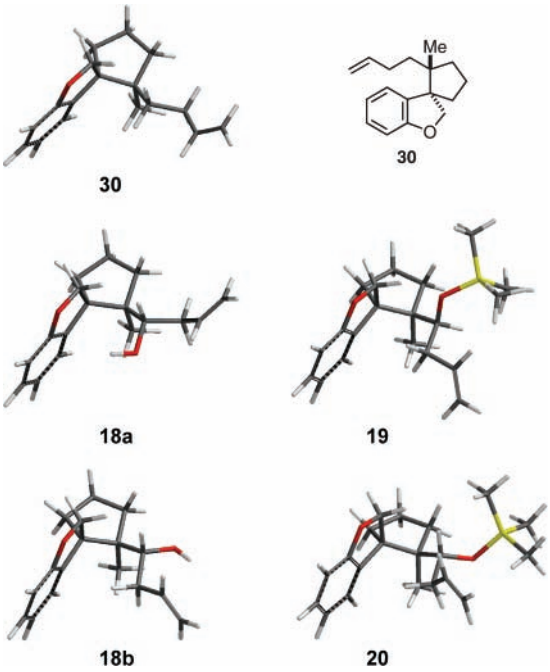
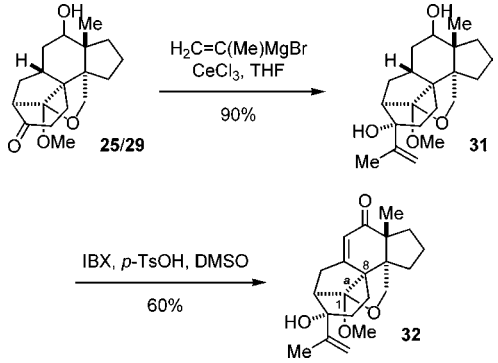


Figure 3. Conformational analysis of **18**−**20** and **30** (equilibrium geometry by MMFF/PM3).

18a resides away from arene, and the free hydroxyl group is buried between the olefin and arene. Silylation helps orient the olefin group toward the arene. The photocycloaddition is now the favorable reaction pathway, and decomposition is suppressed.

After successfully constructing the 5,6,7-tricyclic skeleton of **1** and **3**, we turned our attention to adjusting the C-9 configuration. We intended to use the enone chemistry to manipulate the C-8 and C-9 configurations. Ketones **25** and **29** reacted smoothly with isopropenyl Grignard in the presence of cerium(III) chloride to give tertiary alcohol **31** (Scheme 3). Oxidation of **31** with excess IBX[18] afforded

Scheme 3. Manipulating the C-9 Stereogenic Center



enone **32**. The C-9 stereocenter is now removed and the C-1−C-8 bond is activated for cleavage.

In summary, we have utilized two cycloaddition reactions to construct the 5,6,7-tricyclic skeleton of lancifodilactone F (**1**) and buxapentalactone (**3**). First, a [2+2] ketene cycloaddition reaction was used to set the C-13,14 adjacent all-carbon quaternary centers. Next, an arene−olefin *meta*-photocycloaddition reaction was used to construct the 6- and 7-membered rings concurrently. Although the relative stereochemistry of **1** is still open to discussion, our strategy allows flexible installation of both C-8 and C-9 stereocenters in either configuration. Implementation of this strategy to a more elaborated system for the synthesis of **1** and **3** is underway.

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Supporting Information Available: Detailed experimental procedures, tabulated spectroscopic data, and crystallographic data for **23**, **25**, **29**, and **31a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.