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A Formal Synthesis of Crinipellin B Based on the Arene-Alkene *meta*-Photocycloaddition Reaction

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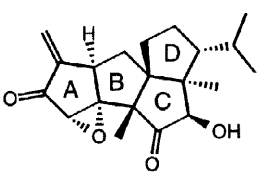
Abstract: Starting from triethyl phosphonopropionate and 3-nitro-2-methylbenzoic acid, a formal synthesis of crinipellin B was achieved. The strategy draws on the use of a novel version of the arene-alkene *meta*-photocycloaddition reaction that proceeds with the generation of 4 rings and 4 quaternary stereocenters in one synthetic operation.

New discoveries and inventions in chemistry and related fields are driven by the ability to make molecules in a simple, safe, and practical fashion. Despite the relatively long history of organic chemistry and noteworthy achievements, complex molecule synthesis remains a formidable challenge.[1,2] Efforts to address this challenge inexorably rely on the development of complexity increasing strategy level reactions and reaction cascades.[1-5] We describe herein a remarkable example of the former, in which an arene-alkene *meta*-photocycloaddition reaction[6-8] is employed to generate four rings and four quaternary centers in one step, leading in this case to a formal synthesis of the tetraquinane crinipellin B.



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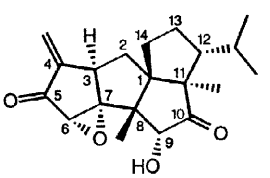

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Strain 7612 of the basidiomycetous fungus *Crinipellis stipitaria* produces the crinipellin antibiotics, which are active against gram-positive bacteria, yeasts, filamentous fungi, and Ehrlich carcinoma ascites cells.[9] In 1985, Steglich and co-workers identified two biologically active crinipellins: crinipellin A (**1**) and crinipellin B (**2**).[10] As the only currently known tetraquinane natural products, these molecules attracted the synthetic attention of the groups of Mehta,[11-13] Curran,[14-16] Crimmins,[17] Zhang,[18] and Piers.[19,20] The Piers group has reported the only total synthesis of a crinipellin, a noteworthy success based on a serial annelation strategy.

Our approach to the crinipellins started with the three-step preparation of 4-methyl-3-isopropyl-4-pentenal (**6**). The Wadsworth-Horner-Emmons reaction between triethyl 2-phosphonopropionate (**3**) and isobutyraldehyde produced ethyl 2,4-dimethyl-2-pentenoate (**4**) in 79% yield as a 30:70 mixture of *E/Z* isomers,[21,22,17] which upon lithium aluminum hydride reduction gave 2,4-dimethyl-2-pentenol (**5**).[23,17,21] Heating **5** at 200°C for 12 hours in a sealed Fisher-Porter bottle with *t*-butyl vinyl ether and catalytic

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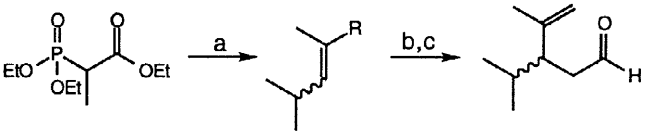
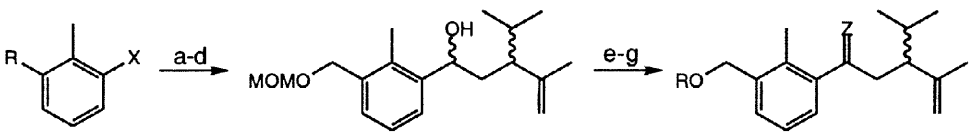
mercury(II)acetate generated the corresponding vinyl ether, which underwent Claisen rearrangement to give **6** in 69% overall yield.



3 **4**: R=CO_2Et **5**: R=CH_2OH **6**

(a) NaH, DME, 0°C; isobutyraldehyde, rt, 79%; (b) LAH, ether, 0°C, 87%; (c) *t*-butylvinyl ether, $Hg(OAc)_2$, 200°C, 140 psi, 69%

The aromatic portion of the cycloaddition precursor was synthesized from 3-nitro-2-methylbenzoic acid (**7**).[24] In one step, **7** was hydrogenated to the corresponding amine, and subsequently iodinated by a Sandmeyer reaction to give 3-iodo-2-methyl benzoic acid (**8**) in 91% yield.[25] Borane-methyl sulfide reduction of the carboxylic acid in the presence of trimethyl borate gave benzylic alcohol **9** (83% yield),[24] which was then protected as the methoxymethyl ether to give aromatic iodide **10** in 97% yield.[26]



7: R=CO_2H, X=NO_2
8: R=CO_2H, X=I
9: R=CH_2OH, X=I
10: R=CH_2OMOM, X=I

11

12: R=MOM, Z=O
13: R=MOM, Z=H,H
14: R=H, Z=H,H

(a) H_2, 43 psi, 10% Pd/C, DMF; HCl, $NaNO_2$, DMF; KI, 91%; (b) $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, rt, 83%; (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C-rt, 97%; (d) *t*-BuLi, THF, -78°C; aldehyde **6**; (e) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 0-22°C, 78% for two steps; (f) H_2NNH_2, KOH, diethylene glycol, 118-122°C; 230-232°C; 92%; (g) 3M HCl, THF, reflux, 93%

Treatment of **10** with *t*-butyllithium at -78°C followed by addition of **6** gave a 1:2 ratio of diastereomeric alcohols **11**. The most effective method for deoxygenation of this mixture involved oxidizing the alcohols to ketone **12** with TPAP[27,28] followed by a modified Wolff-Kishner reduction[29] to give **13** in 72% yield from **10**. Cleavage of the MOM ether with 3 M HCl in refluxing THF gave benzylic alcohol **14** in 93% yield.[30]

The photocycloaddition of benzylic alcohol **14** (0.02 M in cyclohexane, low pressure mercury arc lamp) proceeded with the development of 4 contiguous quaternary centers to provide **15**, possessing the BCD ring system of the crinipellins, and its vinylcyclopropane isomer **16**. Separation of these adducts was accomplished by HPLC (silica column, 3% MTBE/hexanes) or flash chromatography with $AgNO_3$ impregnated silica gel (20% EtOAc/hexanes) and their structures were established by photochemical interconversion and by NOE, HMQC, and HMBC experiments on the linear adduct. Shorter irradiation times gave a preponderance of the linear adduct **16**. The vinylcyclopropane adducts are photolytically labile; irradiation of either the angular isomer **15** or the linear isomer **16** produces a mixture (1:1) of **15** and **16**. Prolonged irradiation of the isomers leads to decomposition.

Heating the mixture of adducts **15** and **16** in thiophenol[31,32] gave the ring opened products **17** and **18** (68% yield), which were easily separated by flash chromatography. This proved to be the preferred point to separate the linear and angular isomers rather than at the photochemical step.

Treatment of thioether **17** with trimethyloxonium tetrafluoroborate[33] produced allylic ether **19** (74% yield), presumably by sulfur methylation followed by S_N2' displacement of thioanisole by the hydroxyl group. Allylic ether **19** was then hydrogenated at 49 psi in EtOAc with 10% Pd/C to give ether **20**, which underwent

ruthenium tetraoxide oxidation[34,35] to afford lactone **21** in 72% yield. Methyllithium at -78°C proved to be an excellent nucleophile for addition to this lactone, providing hemiacetal **22** in 95% yield. A 1:1 mixture of acetates **23** and **24** resulted from Baeyer-Villiger oxidation of **22** using *m*CPBA. Hydroxyacetate **23** was separated from **24** and immediately oxidized with excess Dess-Martin periodinane[36-38] to give keto-acetate **25**. The remaining hydroxy acetate **24** spontaneously equilibrated to a 1:1 mixture of acetates **23** and **24** over a period of about 10 days, allowing for recycling the mixture through the purification process and a greater effective yield of **23**.

With keto-acetate **25** in hand, all that remained to correlate with **27**, a known precursor of crinipellin B,[19,20] was to exchange the acetate for a *t*-butyldimethylsilyl group. Toward this end, the acetate was removed by brief exposure to methanolic barium hydroxide[39] to give **26** in 80% yield. Protection of the C9 alcohol with TBS-triflate[19] gave **27** in 86% yield. This compound is spectroscopically identical to the one synthesized by Piers and Renaud;[19,20,40] therefore, this constitutes a formal synthesis of crinipellin B.

In summary, the arene-alkene *meta*-photocycloaddition reaction is shown to provide rapid access to the triquinane core of the crinipellins, leading to a formal synthesis of crinipellin B. Two key findings led to the success of this strategy: the use of a 1,2,3-trisubstituted aryl component in the photocycloaddition step and the development of a new functionalization strategy for elaboration of the cycloadducts. A noteworthy feature of this cycloaddition process, which bodes well for its further utilization in complex molecule synthesis, is its capacity to produce multiple (4) quaternary centers, a rare result for any reaction type.

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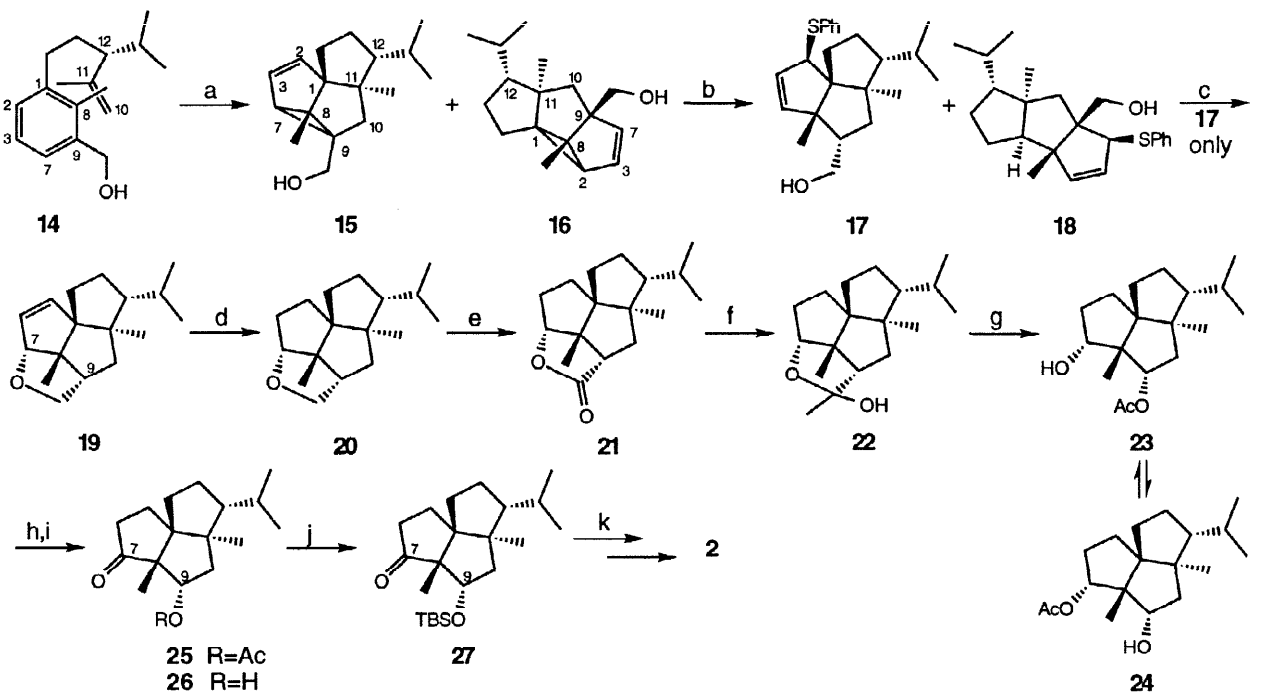

(a) hv, vycor filter, cyclohexane, 33% (59% SM and other adducts); (b) PhSH, 95-105°C, 68%; (c) Me_3OBF_4, CH_2Cl_2, reflux, 74%; (d) H_2 (49 psi), 10% Pd/C, EtOAc, 97%; (e) $RuCl_3$, $NaIO_4$, 2:2:3 $CCl_4/CH_3CN/H_2O$, rt, 72%; (f) MeLi, THF, -78°C, 95%; (g) *m*CPBA, $CHCl_3$, rt, 55% after 1 recycle; (h) Dess-Martin periodinane, CH_2Cl_2, rt, 87%; (i) $Ba(OH)_2$, MeOH, 0°C, 3hr; 80%; (j) TBSOTf, Et_3N, CH_2Cl_2, -78°C; 86% (k) 12 steps[19,20]

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REFERENCES

1. Wender, P. A.; Miller, B. L. Toward the Ideal Synthesis: Connectivity Analysis and Multi-Bond Forming Processes. In *Organic Synthesis: Theory and Applications;* Hudlicky, T. Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2; pp. 27-66.
2. Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765-769.
3. Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.
4. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136.
5. Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103-13159.
6. Wender, P. A.; Dore, T. M. Intra- and Intermolecular Cycloadditions of Benzene Derivatives. In *Handbook of Organic Photochemistry and Photobiology;* Horspool, W. M.; Song, P. Eds.; CRC Press: Boca Raton, FL, 1995; pp. 280-290.
7. Wender, P. A.; Siggel, L.; Nuss, J. M. [3+2] and [5+2] Arene-Alkene Photocycloadditions. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon: Elmsford, NY, 1991; Vol. 5; pp. 645-673.
8. Cornelisse, J. *Chem. Rev* **1993**, *93*, 615-669.
9. Kupka, J.; Anke, T.; Oberwinkler, F.; Schramm, G.; Steglich, W. *J. Antibiot.* **1979**, *32*, 130-135.
10. Anke, T.; Heim, J.; Knoch, F.; Mocek, U.; Steffan, B.; Steglich, W. *Angew. Chem.* **1985**, *97*, 714-716.
11. Mehta, G.; Rao, K. S.; Reddy, M. S. *Tetrahedron Lett.* **1988**, *29*, 5025-5028.
12. Mehta, G.; Rao, K. S.; Reddy, M. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 693-700.
13. Mehta, G.; Barone, R.; Azario, P.; Barberis, F.; Arbelot, M.; Chanon, M. *Tetrahedron* **1992**, *48*, 8953-8962.
14. Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272-9284.
15. Curran, D. P.; Sisko, J.; Yeske, P. E.; Liu, H. *Pure Appl. Chem.* **1993**, *65*, 1153-1159.
16. Curran, D. P.; Sisko, J.; Balog, A.; Sonoda, N.; Nagahara, K.; Ryu, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1591-1593.
17. Stark, T. L. *Studies Directed Toward the Total Synthesis of Crinipellin A*, Univ. of North Carolina, 1992.
18. Zhang, C.; Wu, S. F.; Guo, X. C. *Chin. Chem. Lett.* **1994**, *5*, 561-562.
19. Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11-13.
20. Piers, E.; Renaud, J.; Rettig, S., J. *Synthesis* **1998**, 590-602.
21. Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 4225-4236.
22. McGreer, D. E.; Chiu, N. W. K. *Can. J. Chem.* **1968**, *46*, 2225-2232.
23. Bushby, R. J.; Mann, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2497-2503.
24. Cardin, C. J.; Convery, M. A.; Kavanagh, P. V.; Lambert, M. T. B.; McKenna, B.; McMurry, T. B. H. *J. Chem. Research (M)* **1992**, 3026-3038.
25. DeGraw, J. I.; Brown, V. H.; Colwell, W. T. *J. Med. Chem.* **1974**, *17*, 762-764.
26. Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275-1276.
27. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1989**, 1625-1627.
28. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13-19.
29. Huang-Minlon. *J. Am. Chem. Soc.* **1949**, *71*, 3301-3303.
30. Meyers, A. I.; Durandetta, J. L.; Munavu, R. *J. Org. Chem.* **1975**, *40*, 2025-29.
31. Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1983**, *24*, 5325-5328.
32. Baralotto, C.; Chanon, M.; Julliard, M. *J. Org. Chem.* **1996**, *61*, 3576-3577.
33. Kearney, P. C.; Mizoue, L. S.; Kumpf, R. A.; Forman, J. E.; McCurdy, A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1993**, *115*, 9907-9919.
34. Smith, A. B.; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308-1320.
35. Carlson, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
36. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.
37. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
38. Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549-7552.
39. Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897-7898.
40. Piers, E. University of British Columbia, personal communication, 1997.