ORGANIC LETTERS

2006
Vol. 8, No. 13
2791−2794

# Studies toward Soraphen A: An Aldol–Metathesis Avenue to the Macrocyclic Framework

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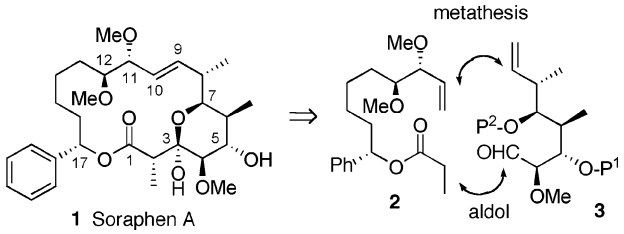
**Received April 11, 2006**

## ABSTRACT




**We describe a convergent approach to soraphen A, 1, that involves coupling of two fragments by an aldol condensation–olefin metathesis sequence. This route permits rapid access to congeners of 1.**

The threat that fungal pathogens pose to human and plant health has a sizable economic impact in terms of lost productivity and health care costs, as well as diminished crop yields and lower profitability.[1] As a consequence, the identification of new antifungal agents, both for human and for agrochemical use, remains an active field of research.[2] Especially relevant in that connection are substances that express antifungal activity by novel mechanisms.[3]

Unique among compounds that target alternative biochemical pathways vital to the fungal cell is soraphen A, **1** (Figure 1),[4] the namesake and the most potent representative of a class of over 30 natural products[5] that block fatty acid biosynthesis by inhibiting acetyl coenzyme A carboxylase.[6] Such a mode of action may also be relevant to the treatment of obesity and diabetes.[7] The noteworthy bioactivity of soraphens has induced us to launch research aimed at defining a rapid avenue to **1**[8] and its congeners.[9]

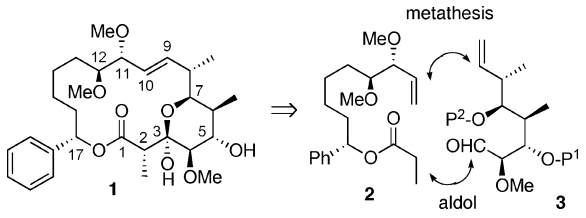



**Figure 1.** Structure and retrosynthesis of soraphen A.

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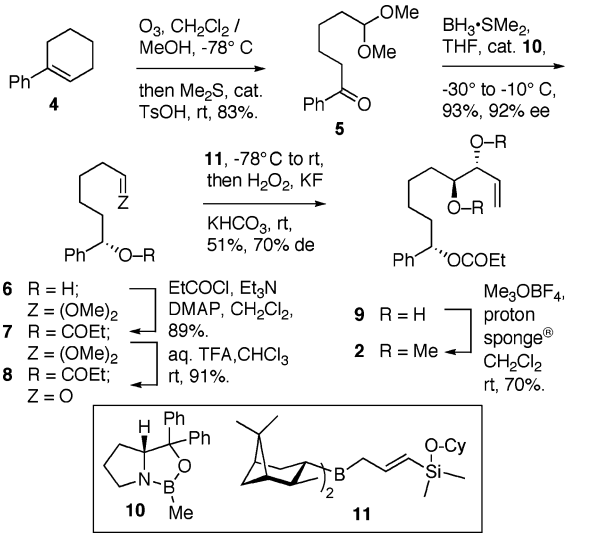
(1) Cf. *Chemistry of Crop Protection*; Voss, G., Ramos, G., Eds.; Wiley-VCH: Weinheim, Germany, 2003.
(2) Cf. (a) Russell, P. E. *J. Agric. Sci.* **2005**, *143*, 11. (b) Odds, F. C.; Brown, A. J. P.; Gow, N. A. R. *Trends Microbiol.* **2003**, *11*, 272.
(3) Lyr, H. *Modern Selective Fungicides: Properties, Applications, Mechanisms of Action*, 2nd ed.; Gustav Fischer Verlag: Villengang, Germany, 1995.

10.1021/ol060882s CCC: $33.50 
**Published on Web 06/01/2006**

Our approach to **1** deviates from the pioneering work of Giese,[8a] in that it focuses on the union of **2** and **3** through an aldol condensation−olefin metathesis sequence as an avenue to the macrocycle (Figure 1). The configuration of the C-2 methyl group in soraphen corresponds to the thermodynamically favored one. Ring-chain tautomerism of the pyran unit in **1** forms a transient $\beta$-ketoester that undergoes facile epimerization at C-2. Thus, the correct C-2 epimer will ultimately result regardless of the initial configuration at this center.[8] The assembly of segments **2** and **3** relies on modern asymmetric methodology, rather than on educts from the "chiral pool". This shortens the synthesis to a significant extent.

As outlined in Scheme 1, a Corey−Shibata asymmetric carbonyl reduction[10] and a Brown allylboration[11] are the key steps in the synthesis of **2**. Ozonolysis of commercially available **4** and reductive workup in the presence of TsOH[12] gave **5**, reduction of which to **6** proceeded with 92% ee.[13a,b] Release of the dimethylacetal (TFA in moist $CHCl_3$)[14] set the stage for allylboration of aldehyde **8** with reagent **11**,[15] followed by Tamao[16] oxidation of the intermediate allylsilane

**Scheme 1.** Synthesis of Fragment **2**




(not isolated). Compound **9** was obtained in 51% yield and 70% de.[13c] O-Methylation furnished the desired **2**.

The methylation step often produced a mixture of **2** and the two monomethylated derivatives of **9**. Rather than forcing the reaction to completion by adding more Meerwein salt and Proton Sponge,[17] we found it expedient to work up the reaction and resubmit the mixture of monomethylated products to methylation under identical conditions. Whatever the reasons for such a behavior, conversion of **9** to **2** was thus effected in a satisfactory 70% overall yield. The diastereoisomers produced during the allylboration reaction were separated at this stage.

The synthesis of a convenient form of **3** started with a stereochemically matched[18] Evans aldol condensation[19] of aldehyde **19**[20] with **12**, followed by O-protection to give **14** (Scheme 2). Difficulties were encountered during attempts to produce aldehyde **15** through release of the terminal TBS group and oxidation of the emerging primary alcohol. This was due to the proclivity of the latter to lactonize with concomitant expulsion of the Evans oxazolidinone. Among various remedies that were examined for such ills,[21] direct oxidation of **14**[22] (5 equiv of PCC, 3 days) emerged as the best solution, providing **15** in 82% yield.


(4) Bedorf, N.; Schmburg, D.; Gerth, B.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1993**, 1017.

(5) (a) Reichenbach, H.; Höfle, G.; Augustiniak, H.; Bedorf, N.; Forche, E.; Gerth, K.; Irshik, H.; Jansen, R.; Kunze, B.; Sasse, F.; Steinmetz, H.; Trowitzch-Kienast, W. EP282455 A2, 1988 (Ciba-Geigy AG). (b) Review: Vincent, G. Dissertation, Université Claude Bernard Lyon 1, 2005.

(6) Wan, H.; Sjolinder, M.; Schairer, H. U.; Leclerque, A. *J. Microbiol. Methods* **2004**, *57*, 33. (b) Shen, Y.; Volrath, S. L.; Weatherly, S. C.; Elich, T. C.; Tong, L. *Mol. Cell* **2004**, *16*, 881.

(7) Gubler, M.; Mizrahi, J. WO03011867 A1, 2003 (Hoffman-La Roche AG).

(8) Total synthesis: (a) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2466. (b) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Synthesis* **1999**, 188. Synthetic studies: (c) Diaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Peris, G.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 8130. (d) Lee, H. W.; Kim, Y. J. *Bull. Korean Chem. Soc.* **1996**, *17*, 1107. (e) Lee, H. W.; Lee, I.-C.; Kim, Y.-S.; Park, S.-U. *Bull. Korean Chem. Soc.* **2002**, *23*, 1197. (f) Park, S. H.; Lee, H. W.; Park, S.-U. *Bull. Korean Chem. Soc.* **2004**, *25*, 1613. (g) Gurjar, M. K.; Mainkar, A. S.; Srinivas, P. *Tetrahedron Lett.* **1995**, *36*, 5967. (h) Cao, Y.; Eweas, A. F.; Donaldson, W. A. *Tetrahedron Lett.* **2002**, *43*, 7831. (i) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Helv. Chim. Acta* **1995**, *78*, 122.

(9) Analogue work: (a) Hill, A. M.; Thompson, B. L.; Harris, P.; Segret, R. *Chem. Commun.* **2003**, 1358. (b) Böhlendorf, B.; Bedorf, N.; Höfle, G.; Schummer, D.; Sutter, M. US 4,997,820, 1991 (Ciba-Geigy AG). (c) Sutter, M.; O'Sullivan, A.; Höfle, G.; Böhlendorf, B.; Kiffe, M. EP0540469A1, 1992 (Ciba-Geigy AG). (d) Böhlendorf, B.; Bedorf, N.; Höfle, G.; Schummer, D.; Sutter, M. US 4,940,804, 1990 (Ciba-Geigy AG). (e) Böhlendorf, B.; Bedorf, N.; Höfle, G.; Schummer, D.; Sutter, M. US 4,-987,149, 1991 (Ciba-Geigy AG). (f) Böhlendorf, B.; Bedorf, N.; Höfle, G.; Schummer, D.; Sutter, M. EP 0358607A2, 1990 (Ciba-Geigy AG). (g) Schummer, D.; Jahn, T.; Höfle, G. *Liebigs Ann. Chem.* **1995**, 803. (h) Sutter, M.; Böhlendorf, B.; Bedorf, N.; Höfle, G. US 4,954,517, 1990 (Ciba-Geigy AG). (i) Höfle, G.; O'Sullivan, A. C.; Rihs, G.; Sutter, M.; Winkler, T. *Tetrahedron* **1995**, *51*, 3159. (j) Höfle, G.; O'Sullivan, A. C.; Sutter, M. *Pestic. Sci.* **1995**, 358. (k) Kiffe, M.; Schummer, D.; Höfle, G. *Liebigs Ann. Chem.* **1997**, 245. (l) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *J. Org. Chem.* **1995**, *60*, 953. (m) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Tetrahedron* **1995**, *51*, 3549.

(10) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (b) Itsuno, S. *Org. React.* **1998**, *52*, 395.

(11) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570. (b) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.

(12) Cf. Izzo, I.; Pironti, V.; Della Monica, C.; Sodano, G.; De Riccardis, F. *Tetrahedron Lett.* **2001**, *42*, 8977.

(13) Configurations and ee's were determined by the Mosher method: (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Kelly, D. R. *Tetrahedron: Asymmetry* **1999**, *10*, 2927. (c) Ichikawa, A.; Takahashi, H.; Ooi, T.; Kuzumi, T. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 881.

(14) Cf. Ellison, R. A.; Lukenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, *16*, 499.

(15) (a) Roush, W. R.; Grover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563. (b) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112.

(16) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957.

(17) Registered trade name for 1,8-bis-(*N*,*N*-dimethylamino)naphthalene.

(18) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

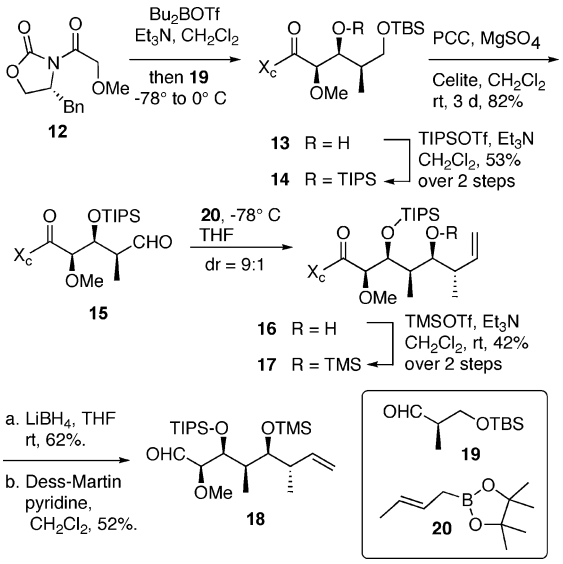
(19) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(20) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

(21) Cf. (a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974. (b) Karimi, B.; Rajabi, J. *Org. Lett.* **2004**, *6*, 2841. (c) Deng, G.; Xu, B.; Liu, C. *Tetrahedron* **2005**, *61*, 5818. (d) Wu, Y.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141. (e) Cossio, F. P.; Aizpura, J. M.; Palomo, C. *Can. J. Chem.* **1986**, *64*, 225.

(22) Direct oxidation of silyl ethers: Muzart, J. *Synthesis* **1993**, 11.

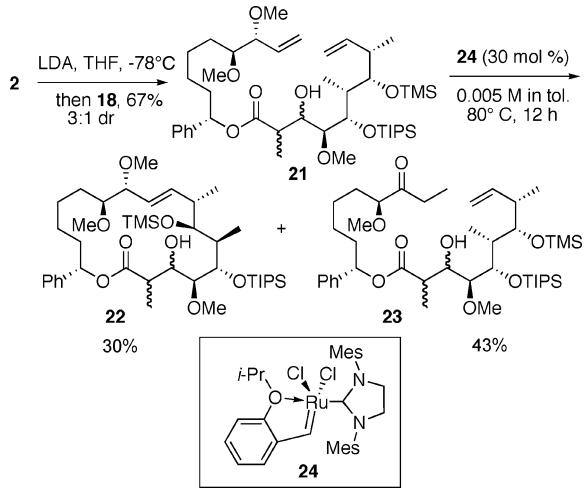
**Scheme 2.** Synthesis of Fragment **3**




Wuts-type[23] crotylboration of **15** proceeded with a 9:1 Cram−Felkin diastereoselectivity to afford alcohol **16**,[24] which was uneventfully elaborated to analogue **18** of fragment **3**. The TMS O-protecting group present in **18** was crucial for the success of the metathesis step employed in the formation of the macrocycle (vide infra).

The successful avenue to a soraphen-like macrocycle is delineated in Scheme 3. Deprotonation of **2** and aldol

**Scheme 3.** Assembly of the Soraphen A Framework

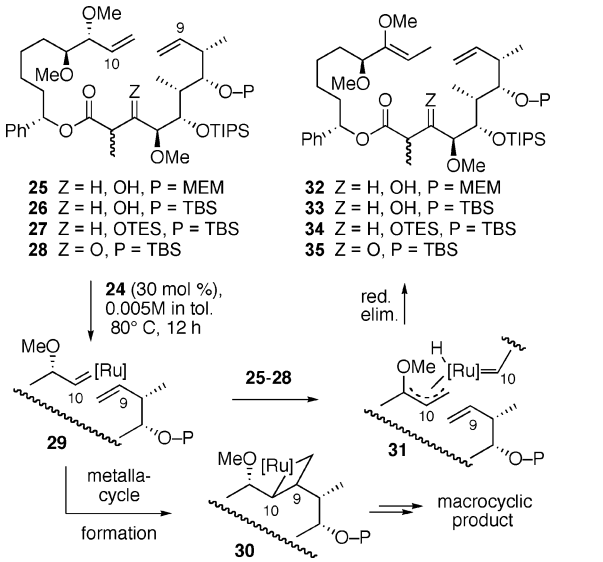



addition of the corresponding enolate to **18** proceeded normally to afford **21** as a mixture of diastereomers at the level of the C-2 and C-3 stereogenic carbons (soraphen numbering). Recall that the C-3 alcohol must ultimately be oxidized to a ketone, thereby removing C-3 stereogenicity, whereas spontaneous C-2 epimerizaton of the emerging $\beta$-ketoester will ultimately secure the correct configuration.

A great deal of experimental work was necessary to identify conditions suitable for the metathetical closure of the macrocyclic ring, a step that proved to be quite sensitive to the nature of the blocking group present on the homoallyl alcohol in **21**. In the end, it transpired that macrocyclization may be best effected through reaction of **21** with Hoveyda catalyst **24**,[25] in toluene at 80 °C.[26] After 12 h, the desired **22** was formed in 30% chromatographed yield, together with ketone **23** (43% yield).

The genesis of **23** is attributable to isomerization of the "left-hand side" olefin[27] in **21** to a vinyl ether, followed by hydrolytic cleavage of the latter during workup. Such vinyl ethers are isolable and characterizable: examples appear in Scheme 4. Thus, representative compounds **25**−**28** were

**Scheme 4.** Olefin Isomerization during Metathesis




cleanly converted to **32**−**35** upon contact with metathesis catalysts: no macrocyclic product was detected in the corresponding reaction mixtures. Additives such as Ti(OiPr)$_4$[28] or ($c$-C$_6$H$_{11}$)$_3$P=O[29] can reduce the extent of olefin isomerization during metathesis. However, these agents had essentially no effect on the outcome of the reactions of Schemes 3 and 4. Microwave irradiation[30] (no additives) also offered no advantage in the present case.

(23) Wuts, P. G. M.; Thompson, P. A.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398.

(24) Lactone **36** (cf. Scheme 5) was also obtained as a byproduct in this reaction (ca. 20%).

(25) Hoveyda, A. H.; Gillinhham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, B. G.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8.

(26) Grubbs and Schrock catalysts were less effective in this reaction.

(27) Olefin isomerization during metathesis is precedented: (a) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 725. (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H. J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(28) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

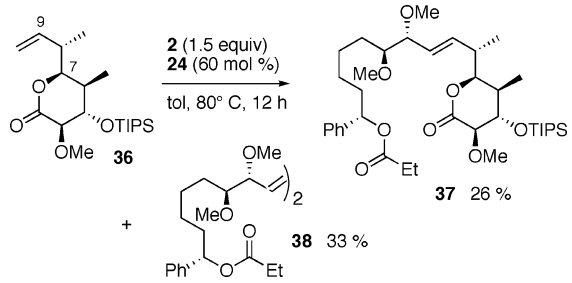
(29) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643*−*644*, 247.

(30) (a) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

Precedent[29] suggests the following rationale for the formation of **32**−**35**. The olefin containing the ultimate C-10 of soraphen is less sterically encumbered than the one that contributes C-9 of **1**,[31] and steric crowding around the latter increases with an increasing steric demand of protecting group P. Accordingly, exposure of the substrate to catalyst **24** probably results in selective formation of carbene complex **29**. This agent partitions between two reaction pathways: cyclization to a metallacycle (cf. **30**; an event that would ultimately yield the desired macrocyclic product) or coordination of the metal in **29** to the less-hindered olefin of an intact molecule of substrate. This promotes formation of $\pi$-allyl complex **31**, which may undergo reductive elimination to form the observed vinyl ethers. Consistent with the observations of Gennari,[32] the rate of metallacycle formation is anticipated to be sensitive to the steric demand of P: for large Ps, olefin isomerization becomes the dominant reaction pathway.

On a final note, olefinic lactone **36**[33] proved to be moderately competent in a cross-metathesis reaction[34] with **2** (Scheme 5), yielding a mixture of **37** (26%) and **38** (33%). The carbonyl group in **36** functions as a protecting group of modest steric demand for the ring oxygen, which correlates with the C-7 OH substituent of **1**. Consonant with the picture developed in Scheme 4, this alleviates steric barriers to metathesis, permitting formation of **37**. Significantly, no homodimer arising from **36** was detected in the product mixture, reflecting the preferential interaction of catalyst **24**

**Scheme 5.** Cross-Metathesis Avenue to *seco*-Soraphen A




with the less sterically encumbered alkene present in **2**. Compound **37** is a seco form of **1** that could be advanced to the ultimate target through a Meinwald−Dieckmann[35] reaction.

In summary, we have devised a concise and convergent avenue to soraphen A congeners that involves the union of fragments **2** (available in six steps from **4**) and **18** (seven steps from **19**) through an aldol−metathesis sequence. Further details of this chemistry will be disclosed in a forthcoming full paper.

**Acknowledgment.** We thank Bayer CropScience and the CNRS (BDI fellowship to G.V.), the MENRT, and the Région Rhône-Alpes for support. M.A.C. is the recipient of a Merck & Co. Academic Development Prize.

**Supporting Information Available:** Experimental procedures, characterization data, and spectra of all the compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) A methoxy group (A-value ≈ 0.6 kcal/mol) is less sterically demanding than a methyl group (A-value = 1.8 kcal/mol). Cf.: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−697.

(32) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Tesler, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913.

(33) Obtained quantitatively upon treatment of **16** with 1.0 equiv of LDA.

(34) (a) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2003**, *43*, 5351.

(35) Duggan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, *19*, 4323.