mers.[15] Related systems also give good yields of Claisen products at room temperature in an apparently stereoselective manner.[17]

The synthesis is completed by a Wittig reaction, deprotection, and ring closure. The Wittig step proceeded to give diene **6**[18] without difficulty in 80% yield after purification on silica gel. Deprotection was attempted with methylmagnesium iodide[16,19] without success; however, trimethylsilyl iodide (Me_3SiI)[20] readily consumed the ether **6** and gave a *single product* (**7**)[21] in 94% yield.[22] Excess Me_3SiI does not affect this product. Removal of the remaining methyl ether is accomplished in 78% yield with excess NaSEt in DMF.[23,24] Thus, the overall yield of *trans*-Δ^1-THC from ester **3** is 37%. Conversion of THC **1** into the more stable isomer **2** was accomplished in 94% yield by using *p*-TsOH in anhydrous ether.[1,4,24]

Additional studies using optically active starting material are in progress as well as the synthesis of various analogues.

Acknowledgment. We gratefully acknowledge the assistance of Jim Spriggle with GC/MS determinations and Robert Zimmermann with ^{13}C NMR analyses.

(15) Mass spectral analysis of ketone **5** shows the molecular ion at *m/e* 344 and a base peak of *m/e* 43. The acetyl group is also in evidence in the ^1H NMR (δ 2.16) and IR (1715 cm^{-1}). The ratio is based on the relative peak areas from capillary GC analysis of hexane solutions. (The rearrangement does not occur in hexane.) Ketone **5** is a known compound.[16]

(16) Korte, F. Dlugosch, E.; Claussen, U. *Liebigs Ann. Chem.* **1966**, *693*, 165.

(17) These results will be discussed elsewhere.

(18) Diene **6** shows the loss of the carbonyl stretch characteristic of ketone **5** in the IR while mass spectral analysis gives a parent ion of *m/e* 342 and a base peak of *m/e* 287. The ^1H NMR is in accord with the reported values.[19a]

(19) (a) Mechoulam, R.; Gaoni, Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273. (b) Jen, T. Y.; Hughes, G. A.; Smith, H. *J. Am. Chem. Soc.* **1967**, *89*, 4551. (c) Mechoulam, R.; Braun, P.; Gaoni, Y. *Ibid.* **1967**, *89*, 4552; (d) **1972**, *94*, 6159.

(20) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

(21) Analysis of ether **7** by MS shows the expected parent ion at *m/e* 328 and a base peak at *m/e* 108. The benzylic (C-3) hydrogen appears at δ 3.15 (d of d, each J = 8 Hz) in the ^1H NMR confirming the trans stereochemistry (e.g., *trans*-Δ^1-THC has a δ 3.15 peak for this hydrogen).[4a]

(22) It is not yet clear where the epimerization of compound **6** occurs, but this conversion is currently under study. A possibly related process is the reaction of *trans*-cannabidiol dimethyl ether with HBr to give 9-bromo-*trans*-hexahydrocannabinol methyl ether.[3]

(23) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

(24) Spectral data are in accord with that published previously.[4]

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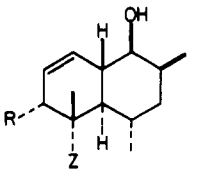
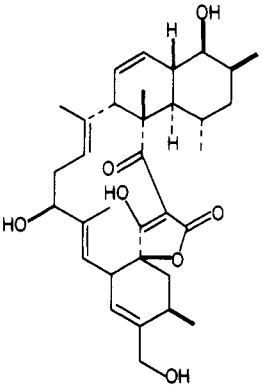
Intramolecular Diels-Alder Cyclization of Conjugated Aldehydes. Synthesis of a Chlorothricolide Intermediate

Summary: Various substituted 2,8,10-undecatrienals have been found to undergo facile intramolecular Diels-Alder cyclization in the presence of dialkylaluminum chlorides to give bicyclo[4.4.0]octahydronaphthalenecarboxaldehydes with high endo selectivity. The method has been applied to the synthesis of a synthetic intermediate related to the macrolide antibiotic aglycon chlorothricolide.

Sir: In the course of studies on the synthesis of kijanolide and related natural products,[1] we wished to prepare hydronaphthalenes related to **1**. Others have explored the

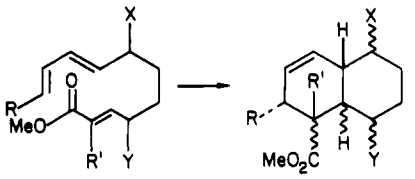


1a, Z = CO_2R
1b, Z = COR



kijanolide

highly attractive intramolecular Diels-Alder strategy for direct assemblage of such systems via dienyl acrylic esters such as **2**.[2] Unfortunately, the reaction requires high



2a, X = H; Y = OR
2b, X = OR; Y = H

temperatures and gives rise to a mixture of exo/endo adducts.[2a] Lewis acid catalysis has been successfully employed in **2a**-type systems,[2e] but the approach fails with the isomeric **2b** owing to destructive side reactions.[2a,d]

After due consideration of the foregoing results we decided to examine a slight variant of the intramolecular Diels-Alder approach to systems such as **1** by using a conjugated aldehyde as the internal dienophile with Lewis acid catalysis. It was our belief that the aldehyde group would serve as a more effective dienophile activator than an ester, particularly in conjunction with Lewis acids.[3] The aldehyde was also more in line with our projected synthetic use of the adducts. The dramatic improvements engendered through this relatively simple modification prompts this preliminary report of our findings which are potentially applicable to a variety of heretofore unattainable or inefficient intramolecular Diels-Alder cyclizations.

Initial studies were carried out on aldehyde **6**, prepared via selective addition of 4,6-heptadienylmagnesium bromide to isopropyl (*E*)-3-formylpropenoate[4a] along the lines

(1) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; MacFarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 497-1534. Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938-3940. Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Tetrahedron Lett.* **1980**, *21*, 2559-2560. Keller-Schierlein, P. W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127.

(2) (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200-5211. (b) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611-4621. (c) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825-4829. (d) Takeda, K.; Shinagawa, M.; Koizumi, T.; Yoshii, E. *Chem. Pharm. Bull.* **1982**, *30*, 4000-4005. (e) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180-182. (f) Burke, S. D.; Powner, T. H.; Kageyama, M. *Tetrahedron Lett.* **1983**, *24*, 4529-4532. (g) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370-4374. (h) For a recent review, see: Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183-234.

(3) Cf. Branchadell, V.; Oliva, A.; Bertran, J. *Chem. Phys. Lett.* **1983**, *97*, 378-380. Paido, L.; Branchadell, V.; Oliva, A.; Bertran, J. *Theochem.* **1983**, 255-260. Several examples of conjugated aldehydes in thermal intramolecular Diels-Alder additions leading to hydrindane systems have been reported. The stereoselectivity was not high. Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696-6704. Taber, D. F.; Campell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141-5144.

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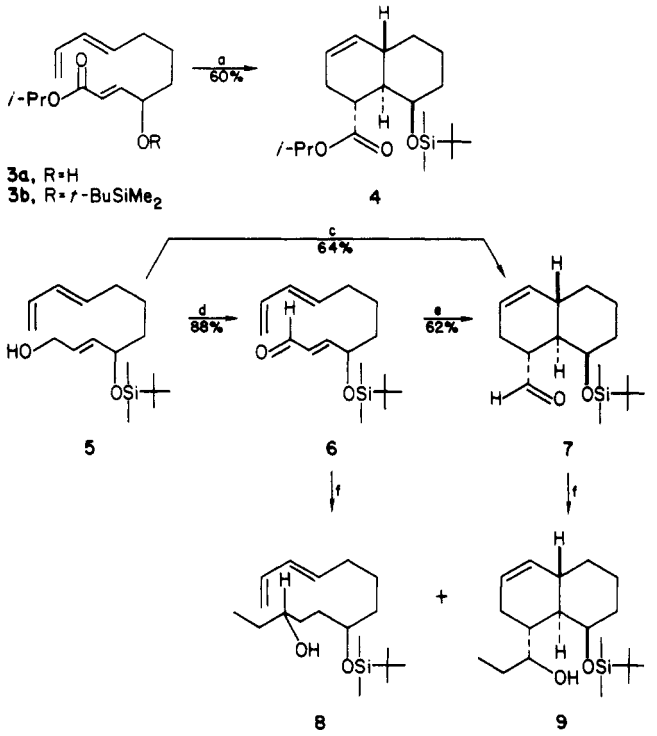
Scheme I[a]



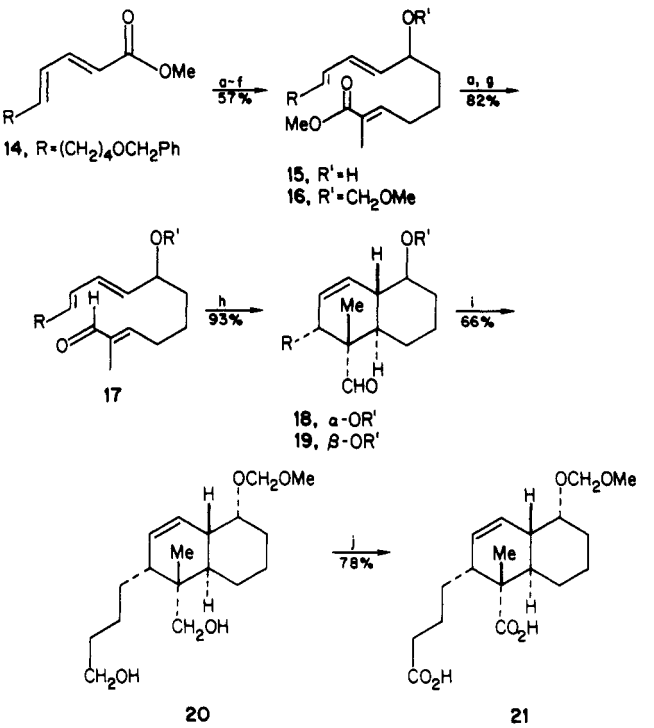
[a] (a) $EtAlCl_2$, CH_2Cl_2, 8 °C, 18 h; (b) *i*-Bu_2AlH, Et_2O; (c) MnO_2, CH_2Cl_2, 30 h; (d) $(COCl)_2$, Me_2SO, Et_3N, −78 to 25 °C; (e) $EtAlCl_2$, CH_2Cl_2, −50 °C, 1 min; (f) Et_2AlCl, CH_2Cl_2, −78 to −20 °C.

of Funk.[2e] Protection of the resulting alcohol **3a** as the *tert*-butyldimethylsilyl ether **3b** followed by reduction of the ester with diisobutylaluminum hydride afforded the allylic alcohol **5** (Scheme I). Oxidation of alcohol **5** with MnO_2 in methylene chloride at room temperature required 30 h and surprisingly yielded the intramolecular Diels–Alder adduct **7** as the sole product! The stereochemistry is assigned by analysis of the ^1H NMR spectrum. The fugitive aldehyde **6** could be prepared via Swern oxidation of alcohol **5**.[4b] Interestingly, this aldehyde proved to be stable, showing no tendency to cyclize upon prolonged storage at room temperature even with added MnO_2.[5] Ethylaluminum dichloride (0.2 equiv),[6] however, effected complete conversion of **6** to **7** (64% isolated yield) in methylene chloride at −50 °C in less than 1 min! In contrast, cyclization of the analogous ester **3** required a full equivalent of this catalyst at 8 °C for 18 h. The aldehyde grouping is thus seen to exert a profound rate enhancement of the intramolecular Diels–Alder cyclization.

As a more demanding test of the foregoing methodology, we prepared the aldehyde analogue **11** of Roush's triene ester **10**.[2a] Roush noted that ester **10** decomposed in contact with even mild Lewis acids and gave rise to a 15:13:23:49 mixture of the four possible epimeric products upon thermolysis.[2a] We found that aldehyde **11**, like its ester counterpart, was decomposed by ethylaluminum dichloride, even at low temperature. However, the milder catalyst diethylaluminum chloride[6] effected smooth cyclization of **11** in methylene chloride at −78 to −23 °C to afford an 8:1 mixture of the carbinyl epimers **12** and **13** in 75% yield.[7] Once again, the aldehyde grouping shows a profound rate enhancement of the intramolecular Diels–Alder cyclization, even in the more sterically demanding context of enal diene **11**.

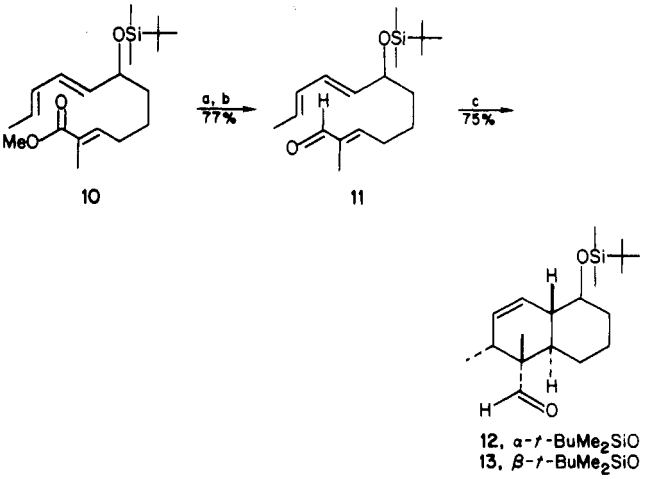
Diethylaluminum chloride also promoted the Diels–Alder cyclization of dienal **6** but with concomitant ethyl addition to give a 3:1 mixture of **8** and **9** in 79% yield. Evidently, ethyl addition to aldehydes **11**, **12**, and **13** is retarded by the α-methyl substituent.

Scheme II[a]



[a] (a) *i*-Bu_2AlH, Et_2O, −78 °C; (b) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 to 25 °C; (c) $BrMg(CH_2)_3CH(OEt)_2$, THF, 0 °C; (d) $(CO_2H)_2$, H_2O, 25 °C, 18 h; (e) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, 25 °C; (f) $MeOCH_2Cl$, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 to 25 °C; (g) MnO_2, CH_2Cl_2, 25 °C, 6 h; (h) Et_2AlCl, CH_2Cl_2, −78 to −23 °C, 14 h; (i) Li, NH_3; (j) CrO_3, H_2SO_4, acetone, 0 °C.

Diethylaluminum chloride also promoted the Diels–Alder cyclization of dienal **6** but with concomitant ethyl addition to give a 3:1 mixture of **8** and **9** in 79% yield. Evidently, ethyl addition to aldehydes **11**, **12**, and **13** is retarded by the α-methyl substituent.



(a) *i*-Bu_2AlH, Et_2O; (b) $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; (c) Et_2AlCl, CH_2Cl_2, −78 to −23 °C

(4) (a) The isopropyl ester gave considerably higher selectivity in the Grignard reagent addition than the reported ethyl ester.[2e] (b) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

(5) We believe that a byproduct in the oxidation reaction serves as a catalyst for the Diels–Alder reaction rather than the MnO_2 itself. A related reaction has been attributed to MnO_2 catalysis although the appropriate control experiment was not carried out. Vig, O. P.; Trehan, I. R.; Kumar, R. *Indian J. Chem.* **1977**, *15B*, 319–321.

(6) Cf. Snider, B. B.; Podini, D. J.; Karas, M.; Kick, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927–3934.

(7) The preference for the α(axial)-epimer **12** in a similar situation has been attributed to a stereoelectronic effect. Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251–4253. The effect appears to be absent in the seemingly related MOM derivative **17** as a 1:1 mixture of epimers **18** and **19** is obtained.

As a final preliminary test of the trienal approach to systems such as **1b**, we selected as a target the diacid **21**, an intermediate recently prepared by Ireland in connection with synthetic studies on chlorothricolide.[8] The sequence is outlined in Scheme II.

The benzyloxy ester **14** (>95% *E,E* according to high-field ^{1}H NMR analysis) was prepared via condensation of 5-(benzyloxy)pentanal[9] with methyl (*E*)-(4-diethoxyphosphinyl)-2-butenoate in 84% yield.[10] Reduction with diisobutylaluminum hydride at −78 °C followed by Swern oxidation[4b] to the aldehyde, addition of 4,4-diethoxybutylmagnesium bromide, hydrolysis of the acetal with 50% aqueous oxalic acid, and treatment of the resultant δ-lactol with methyl 2-(triphenylphosphylidene)propionate afforded the triene ester **15** in 57% overall yield.[2a] Reduction of the hydroxyl-protected ester **16** and subsequent MnO_2 oxidation gave the desired trienal **17** in 82% yield (>90% *E,E,E* according to high-field ^{1}H NMR). Diels–Alder cyclization effected with diethylaluminum chloride at −78 to −23 °C led to a chromatographically separable 45:55 mixture of the bicyclic aldehydes **18** and **19** in 93% yield.[7] Interestingly, the *tert*-butyldimethylsilyl-protected aldehyde **17** gave over 95% of the α-isomer **18** (R′ = *t*-Bu(Me)$_2$Si) in greater than 90% yield under comparable conditions.

Correlation of aldehyde **18** with Ireland's diacid **21** was effected via reductive cleavage of the benzyl protecting group and oxidation of the resulting diol **20**. The material thus obtained was judged identical with a comparison sample according to TLC and high-field ^{1}H NMR analysis.[8]

The foregoing examples establish the practical feasibility of preparing hydronaphthalenes related to **1** via an intramolecular Diels–Alder strategy. Applications to appropriate natural products are currently under investigation.

Acknowledgment. We thank Professor Robert E. Ireland for a comparison sample of diacid **21**. Support from the National Institutes of Health, National Cancer Institute, Research Grant CA34247, is gratefully acknowledged.

Supplementary Material Available: Spectral and physical data for compounds **3a**, **3b**, **4–7**, **11**, **12**, **14**, **15–18**, and **20** (7 pages). Ordering information is given on any current masthead page.

(8) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.* **1981**, *46*, 4863–4873.

(9) Prepared via oxidation of 5-(benzyloxy)pentanol (Sheehan, M.; Spangler, R. J.; Djerassi, C. *J. Org. Chem.* **1971**, *36*, 3526–3532) with pyridinium chlorochromate/3-Å sieves in methylene chloride (Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561–562).

(10) Sato, K.; Mizuno, S.; Hirayama, M. *J. Org. Chem.* **1967**, *32*, 177–180.

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Stereocontrolled Synthesis of Prostaglandins from Cyclopentadiene Monoepoxide[1]

Summary: Two complementary syntheses of prostaglandins from the same key intermediate **3**, available in four steps from cyclopentadiene monoepoxide, are described.

(1) A preliminary report of this work was presented at the 187th National Meeting, of the American Chemical Society St. Louis, MO, April 9, 1984; ORGN 7.

In one approach, a saturated α-chain is introduced via a 1,4-addition of an appropriately functionalized cyanocuprate reagent onto silyl enol ether **3**. The resulting prostanoid compound was converted into the bronchodilator 1-decarboxy-1-hydroxymethyl PGE_1, PGE_1, and $PGF_{1\alpha}$. The second approach involves the transformation of silyl enol ether **3** into the known prostanoid precursor **11** via selective addition of carbethoxycarbene and subsequent fluoride-induced ring opening of the resulting (silyloxy)cyclopropane carboxylate ester.

Sir: The past few years have witnessed an upsurge of interest in the general field of prostaglandin synthesis.[2] This high level of interest, sustained by the recognized therapeutic potential of these compounds, has more recently been stimulated by the unraveling of highly active and more selective analogues. Within this context, we report herein a new and stereocontrolled synthesis of prostaglandins, which offers maximum versatility for the attachment of a wide variety of side chains onto a preformed cyclopentane nucleus. The approach is primarily based on our observation of the high degree of regio- and stereoselectivity in the 1,4-addition of cyanocuprates to cyclic 1,3-diene monoepoxides.[3] Thus, conjugate addition of the cuprate reagent **1** onto cyclopentadiene monoepoxide, followed by cis-epoxidation and oxidation of the resulting allylic alcohol, provided the previously described[4] epoxy ketone **2**, which was quantitatively converted into its triethylsilyl enol ether **3**[5,6] by standard procedures. The introduction of the prostaglandin α-chain (or a readily convertible synthon for such a chain) onto this key intermediate was achieved by two different, albeit complementary, strategies, as illustrated in Scheme I.

In a "nucleophilic-type alkylation", a saturated α-chain was attached via a second conjugate addition of the cyanocuprate **4** derived from the timethylsilyl ether of 1-lithioheptan-7-ol.[7] After an ammonium chloride quench of the reaction mixture and subsequent hydrolysis of the resulting sily enol ether with a buffered potassium fluoride solution, an 80% yield of the 3-hydroxycyclopentanone derivative **5** was isolated.[8] The stereochemistry of the side chains in **5** was an 8:1 ratio of trans and cis epimers, respectively. The trans isomer was easily transformed into 1-decarboxy-1-hydroxymethyl PGE_1, **6**, by removal of the *tert*-butyldimethylsilyl group with aqueous HF in acetonitrile.[9] In addition, compound **5** could be selectively oxidized to the corresponding carboxylic acid with oxygen and platinum.[10] Deprotection of the C15 hydroxyl group as described before then yielded PGE_1.[11] Alternatively, stereoselective reduction of the C9 carbonyl of **5** with L-Selectride (Aldrich)[12] followed by selective oxidation of the primary alcohol and removal of the *tert*-butyldimethylsilyl group as indicated above provided $PGF_{1\alpha}$.[11]

In an "electrophilic-type alkylation", the enol ether derivative **7**, obtained in 90% overall yield by regiospecific reductive opening of the oxirane ring of **3** with $LiAlH_4$ and subsequent protection of the resulting 11-hydroxyl group, was cyclopropanated via the addition of carbethoxycarbene. It should be mentioned at this point that the direct introduction of a functionalized α-chain by regios-

(2) For recent reviews, see: (a) Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977. (b) Mitra, A. "The Synthesis of Prostaglandins"; Wiley-Interscience: New York, 1977. (c) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293.

(3) For previous examples, see: (a) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467. (b) Marino, J. P.; Abe, H. *Synthesis* **1980**, *11*, 872. (c) Marino, J. P.; Abe, H. *J. Org. Chem.* **1981**, *46*, 5379. (d) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907. (e) Marino, J. P.; Jaen, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 3165.

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