Table 1. In vitro antitumor activity[a] of complex **6**.

Cell line	Tumor of origin	MED[b] [μM]	
		6	Cisplatin
A2780S[c]	ovarian	2.5	3.3
A2780cP[c]	ovarian	112	36
MeWo[d]	melanoma	11.2	8

[a] Cytotoxicity was assessed by clonogenic survival assay as described.[12] [b] Median effect dose. [c] A2780S and its cisplatin-resistant variant, A2780cP, were obtained from Dr. Marshal Sklar (University of Miami) and maintained in Paul G. Braunschweiger's laboratory. [d] Obtained from Dr. Jorgen Fogh and maintained in Paul G. Braunschweiger's laboratory.

should open new avenues to explore this important area of cancer chemotherapy.

Moreover, complex **6** is, to the best of our knowledge, the first example of a carbohydrate-containing transition metal complex in which the carbohydrate moiety is not only unprotected, but also unbound to the metal center.[6, 14] Such complexes should be obtainable as single crystals, which can then be used to determine the solid-state structure of intact and unprotected carbohydrates.

Experimental Section

6: A mixture of **1** (2.2 g, 5.36 mmol), **2** (1.14 g, 8.0 mmol), and 4-Å molecular sieves (3.5 g) was stirred under Ar for 1 h at RT in CH_2Cl_2 (50 mL), and $HgBr_2$ (0.39 g, 1.07 mmol) and HgO (1.16 g, 5.36 mmol) were added. After being stirred in the dark for 2 d, the mixture was filtered through a layer of Celite. The filtrate was washed with aqueous $NaHCO_3$ solution, dried, and concentrated. Chromatography of the residue in hexanes/ethyl acetate (1/1) on silica gel afforded **3** (1.59 g, 63 %). Compound **3** (0.78 g, 2.56 mmol) and a catalytic amount of NaOMe were stirred in MeOH (30 mL) for 6 h at RT. The mixture was neutralized by addition of Dowex H^+ ion-exchange resin and filtered, and Pd/C (60 mg) was added. After being stirred under H_2 (35 psi) for 8 h, the mixture was filtered through a layer of Celite, and the filtrate concentrated. The residue was redissolved in H_2O and lyophilized to give **4** (0.4 g, 96 %). Compound **4** (0.18 g, 0.71 mmol) and **5** (0.3 g, 0.71 mmol) were stirred in H_2O (10 mL) for 2 d at RT, and concentrated. Chromatography of the residue on a gel filtration column with Bio-gel P2 resin afforded **6** (0.28 g, 75 %).

Received: January 13, 1999 [Z 12900 IE]
German version: *Angew. Chem.* **1999**, *111*, 1882 – 1884

Keywords: antitumor agents · bioinorganic chemistry · carbohydrates · N ligands · platinum

[1] B. Rosenberg, L. VanCamp, J. E. Trosko, V. H. Mansour, *Nature (London)* **1969**, *222*, 385 – 386.
[2] a) *Metal Complexes in Cancer Chemotherapy* (Ed.: B. K. Keppler), VCH, Weinheim, **1993**; b) *Molecular Aspects of Anticancer Drug—DNA Interactions*, *Vol. 1* (Eds.: S. Neidle, M. Waring), Macmillian, Basingstoke, **1993**; c) J. Reedijk, *Chem. Commun.* **1996**, 801 – 806.
[3] Reviews: a) A. Pasini; F. Zunino, *Angew. Chem.* **1987**, *99*, 632 – 642; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 615 – 624; b) R. B. Weiss, M. C. Christian, *Drugs* **1993**, *46*, 360 – 377.
[4] a) J. Reedijk, *Inorg. Chim. Acta* **1992**, *198 – 200*, 873 – 881, and references therein; b) A. Iakovidis, N. Hadjiliadis, *Coord. Chem. Rev.* **1994**, *135/136*, 17 – 63, and references therein; c) K. F. Morris, L. E. Erickson, B. V. Panajotova, D. W. Jiang, F. Ding, *Inorg. Chem.* **1997**, *36*, 601 – 607.
[5] a) S. Hakamori, *Annu. Rev. Biochem.* **1981**, *50*, 733 – 764; b) Y.-T. Li, S.-C. Li, *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 235.
[6] For examples of platinum(II) complexes of diamino-dideoxy carbohydrates (coordination through the amino groups) as cisplatin analogues, see a) T. Tsubomura, M. Ogawa, S. Yano, K. Kobayashi, T. Sakurai, S. Yoshikawa, *Inorg. Chem.* **1990**, *29*, 2622 – 2626; b) S. Hanessian, J. Y. Gauthier, K. Okamoto, A. L. Beauchamp, T. Theophanides, *Can. J. Chem.* **1993**, *71*, 880 – 885; c) S. Hanessian, J.-G. Wang, *Can. J. Chem.* **1993**, *71*, 886 – 895.
[7] Compound **2** was prepared from 1,3-dibromo-2-propanol by reaction with NaN_3 in DMF.
[8] **6**: ^{1}H NMR (500 MHz, D_2O): $\delta = 4.39$ (d, J(H1,H2) = 8.0 Hz, 1H; H1), 4.23 (m, 1H; C*H*($CH_2NH_2)_2$), 3.70 (dd, J(H6a,H6b) = 12.5, J(H5,H6a) = 2.0 Hz, 1H; H6a), 3.55 (dd, J(H6a,H6b) = 12.5, J(H5,H6b) = 5.0 Hz, 1H; H6b), 3.34 – 3.23 (m, 3H; H3, H4, H5), 3.17 (dd, J(H2,H3) = 9.5, J(H1,H2) = 8.0 Hz, 1H; H2), 2.89 – 2.84, 2.72 – 2.65 (2m, 2 × 2H; CH(C*H*$_2$NH$_2$)$_2$); ^{13}C NMR (125 MHz, D_2O): $\delta = 102.2$ (C1), 76.5, 76.2 (C3, C5), 74.1 (*C*H($CH_2NH_2)_2$), 73.7 (C2), 70.1 (C4), 61.2 (C6), 46.2, 45.1 (CH(*C*H$_2$NH$_2$)$_2$).
[9] Crystal structure data (Bruker P4/CCD diffractometer) for **6** · 1.5 H_2O: $C_9H_{23}Cl_2N_2O_{7.5}Pt$, $M_r = 545.28$, crystal dimensions 0.32 × 0.22 × 0.06 mm^3, $T = 295(2)$ K, monoclinic, space group $P2_1$, $a = 690.390(10)$, $b = 3174.58(6)$, $c = 809.74(2)$ pm, $\beta = 115.0650(10)^\circ$, $Z = 4$, $V = 1.60758(6)$ nm^3, $\rho_{calcd} = 2.253$ g cm^{-3}, $Mo_{K\alpha}$ radiation ($\lambda_0 = 0.71073$ Å), $\mu = 9.096$ mm^{-1}, $2\theta = 2.56 – 56.68^\circ$; of 9952 reflections collected, 6498 were independent (R(int) = 0.031); refinement method: full-matrix least squares on F^2, 397 refined parameters, empirical absorption correction (SADABS software, T_{min} and T_{max} undefined), GOF = 1.008 (based on F^2), $R1 = 0.0383$, $\omega R2 = 0.0915$ ($\sigma > 2\sigma(I)$), absolute structure parameter 0.007(8), residual electron density −2.559/3.782 e Å^{-3}. The structure was solved and refined with the programs SHELXS-93 and SHELXTL. The hydrogen atoms were placed in their geometric positions (riding model), except that no hydrogen atoms were placed in the solvent molecules. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-113805. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[10] For examples, see reference [6].
[11] J. Wang, Y. L. Bennani, F. Belanger-Gariepy, S. Hanessian, *Acta Crystallogr. Sect. C* **1991**, *47*, 1067 – 1069, and references therein; see also reference [6].
[12] P. G. Braunschweiger, V. S. Basrur, O. Santos, J. P. Perras, A. M. Markoe, P. Houdek, J. G. Schwade, *Biotherapy* **1997**, *10*, 129 – 137.
[13] Solubility of **6** in water: > 20 mg mL^{-1} at 25 °C.
[14] Crystal structures of platinum(II) complexes of unprotected carbohydrate diolates have been reported, but there the carbohydrates are directly bound to platinum, and the complexes are not used in biological study. For examples, see a) A. Appelt, A. C. Willis, S. B. Wild, *J. Chem. Soc. Chem. Commun.* **1988**, 938 – 940; b) M. A. Andrews, G. L. Gould, *Organometallics* **1991**, *10*, 387 – 389; c) M. A. Andrews, E. J. Voss, G. L. Gould, W. T. Klooster, T. F. Koetzle, *J. Am. Chem. Soc.* **1994**, *116*, 5730 – 5740.

Mixed Crossed Aldol Condensation between Conjugated Esters and Aldehydes Using Aluminum Tris(2,6-diphenylphenoxide)

Susumu Saito, Masahito Shiozawa, and Hisashi Yamamoto*

Crossed aldol condensation between two different carbonyl compounds is one of the earliest and synthetically most significant reactions for carbon – carbon bond formation.[1]

[*] Prof. Dr. H. Yamamoto, Dr. S. Saito, M. Shiozawa
Graduate School of Engineering, Nagoya University
CREST, Japan Science
and
Technology Corporation (JST)
Furo-cho, Chikusa
Nagoya 464-8603 (Japan)
Fax: (+81) 52-789-3222
E-mail: j45988a@nucc.cc.nagoya-u.ac.jp

  1433-7851/99/3812-1769 $ 17.50+.50/0

Our recent discovery[2] that aluminum tris(2,6-diphenylphenoxide)[3, 4] (ATPH, Figure 1) and lithium diisopropylamide (LDA) trigger mixed crossed aldol condensation of conjugated aldehydes or ketones with aldehydes encouraged us to

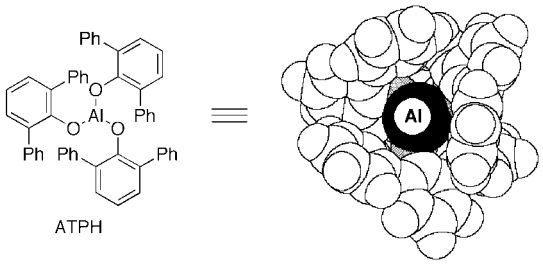
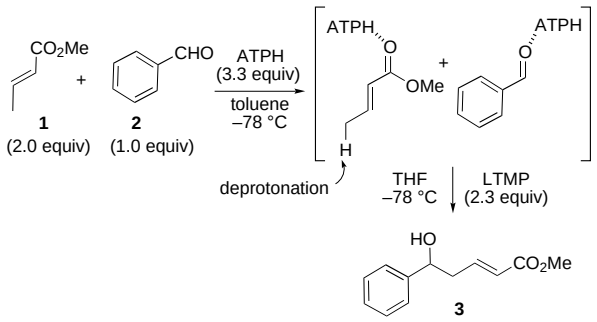


Figure 1. The molecular structure (left) and space-filling model of ATPH (right).

improve this reaction to a more synthetically useful level. Reported herein is the mixed aldol condensation between conjugated esters and aldehydes[5] in the presence of ATPH; lithium 2,2,6,6-tetramethylpiperidide (LTMP) instead of LDA has proven to be an effective reagent.

Precomplexation of methyl crotonate (**1**, 2.0 equiv) and benzaldehyde (**2**, 1.0 equiv) with ATPH (3.3 equiv) was followed by treatment with a solution of LTMP (2.3 equiv) in THF at $-78\,^{\circ}C$ under an argon atmosphere (Scheme 1). After stirring of the mixture at this temperature for 30 min, quenching with aq NH_4Cl, and purification by column chromatography on silica gel, aldol adduct **3** was obtained in



Scheme 1. Crossed-aldol condensation of methyl crotonate (**1**) with benzaldehyde (**2**) using ATPH and LTMP.

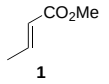
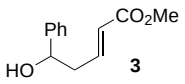
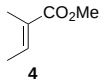
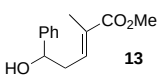
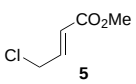
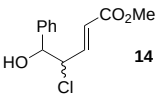
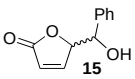
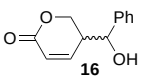
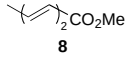
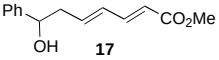
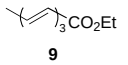
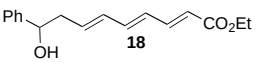
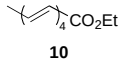
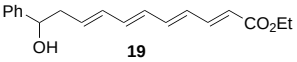
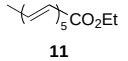
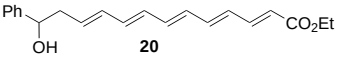
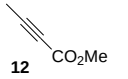
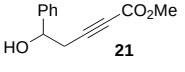
97% yield with retention of the *E* configuration at the olefin moiety (see entry 1 of Table 1). None of the *Z* isomer was detected by ^1H NMR spectroscopy or GC-MS analysis.

Similar to the case of the conjugated aldehyde–aldehyde aldol system,[2] deprotonation and subsequent alkylation occurred exclusively at the allylic terminus of the unsaturated ester, and not at the α-carbon atom. The use of a smaller amount of the ester, ATPH, and LTMP (1.0:2.2:1.2) proved disappointing (yield of **3** 57%). Under otherwise identical conditions, the reaction with other lithium amides such as LDA, lithium hexamethyldisilazide (LHMDS), and lithium dicyclohexylamide proceeded less efficiently than with LTMP, producing **3** with consistently lower yields of 33, 23, and 42%, respectively. It should be emphasized that the ester and aldehyde must be precomplexed with ATPH: when benzaldehyde (**2**) was exposed to the ATPH complex ($-78\,^{\circ}C$, 5 min) prior to treatment with LTMP, the desirable aldolization was obtained with similar ineffectiveness (recovery of **2** 90%, yield of **3** 10%).

We thus chose to focus on the use of LTMP, and various examples of ester–aldehyde combinations are listed in Tables 1 and 2. Benzaldehyde (**2**) and pivalaldehyde (**22**) were particularly well suited to this process. In contrast, valeraldehyde (**24**) might suffer from competitive deprotonation at the α-carbon atom. This difficulty was easily circumvented when cyclohexanecarboxaldehyde (**23**) branched at the α-carbon atom was used to provide **28** (90%) and **29** (87%) with equal effectiveness. Aldolization at the γ-positions of lactones proceeded with similar success, despite low diastereoselectivities (Table 1, entries 4 and 5). Highly conjugated esters including dienoate **8**, trienoate **9**, tetraenoate **10**, and even pentaenoate **11** participated in this transformation; however, the reaction proceeded less readily with **11** to give **20** in moderate yield (Table 1, entries 9–12).[6]

One area where this system could be applied with particular benefit is the rapid elaboration of elongated conjugated esters, which have been demonstrated to be of great synthetic potential.[7] For example, tosylation of aldol adduct **34**, which was obtained in 93% yield by the standard procedure (see

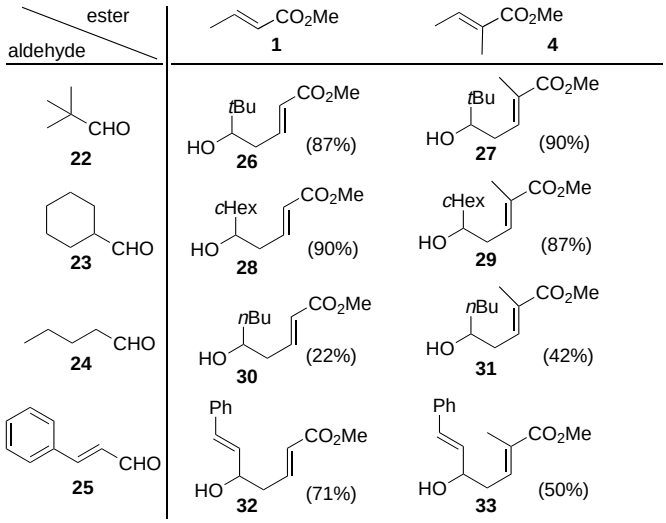
Table 1. Mixed aldol condensation of unsaturated esters with benzaldehyde (**2**).

Entry[a]	Ester	Product	Yield [%][b]
1	 **1**	 **3**	97
2	 **4**	 **13**	90
3	 **5**	 **14**	72[c]
4	 **6**	 **15**	88[d]
5	 **7**	 **16**	70[e]
6	 **8**	 **17**	97
7	 **9**	 **18**	88
8	 **10**	 **19**	80
9	 **11**	 **20**	40[f]
10	 **12**	 **21**	86

[a] The reaction was performed using aldehyde (1 equiv), ester (2 equiv), ATPH (3.3 equiv), and LTMP (2.3 equiv) in toluene/THF (1/1) at $-78\,^{\circ}C$ for 30 min. [b] Yield of isolated, purified products. [c] Diastereomeric ratio = 76:24. [d] Diastereomeric ratio = 70:30. [e] Diastreomeric ratio = 66:33. [f] An unidentified isomer was also obtained (23%).

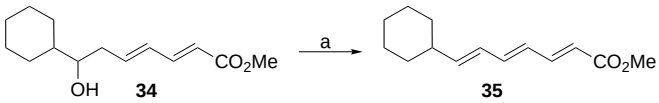
  1433-7851/99/3812-1770 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 12

Table 2. Mixed aldol condensation of various aldehydes with conjugated esters.[a, b]



[a] The reaction was performed using aldehyde (1 equiv), ester (2 equiv), ATPH (3.3 equiv) and LTMP (2.3 equiv) in toluene/THF (1/1) at $-78\,^{\circ}C$ for 30 min. [b] The yields in parentheses are of isolated, purified products.

Experimental Section), followed by elimination with DBU at $90\,^{\circ}C$ gave (2*E*,4*E*,6)-trienoate **35**, one of the synthetic intermediates for asukamycin,[7a] in 90% yield (6*E*:6*Z* = 97:3, Scheme 2).



Scheme 2. A rapid route to **35**, the synthetic intermediate of asukamycin. Reagents and conditions: a) 4-methylbenzenesulfonyl chloride (TsCl, 2.0 equiv), 4-(dimethylamino)pyridine (DMAP, 5.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 18 h, 90%; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5 equiv), toluene, $90\,^{\circ}C$, 5 h, >99%.

In summary, a directed access to δ-hydroxy-α,β-unsaturated esters and their derivatives using two different ATPH–carbonyl complexes in place of carbonyl compounds themselves has been demonstrated. Such a strategy has proven to be quite general with respect to both the aldehyde component and the unsaturated esters. Moreover, this method should be of practical value as a straightforward route to important classes of synthetic intermediates such as highly polyenic esters, and thus potentially useful for a short-step convergent approach to complex natural products.[8]

Experimental Section

The reaction of methyl crotonate (**1**) with benzaldehyde (**2**) is representative. To a solution of ATPH (1.65 mmol) in toluene (6.0 mL) was added **1** (106 μL, 1.0 mmol) and **2** (51 μL, 0.50 mmol) at $-78\,^{\circ}C$ under argon. After the mixture was stirred for 20 min, LTMP—generated by treatment of a solution of 2,2,6,6-tetramethylpiperidine (194 μL, 1.15 mmol) in THF (6.0 mL) with a 1.60 M solution of *n*BuLi (0.72 mL, 1.15 mmol) in hexane at $-78\,^{\circ}C$ for 30 min—was transferred by a steel cannula to the solution of ATPH-**1** and ATPH-**2** in toluene at $-78\,^{\circ}C$. The reaction mixture was stirred at this temperature for 30 min and quenched with aq NH_4Cl, and the resulting suspension was filtered through a celite pad. The filtrate was extracted with diethyl ether. The organic layer was dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography on silica gel (diethyl ether/hexane 1/2 → 1/1 → 5/1) to give **3** (99.2 mg, yield 97%) as a colorless liquid. 2,6-Diphenylphenol could be isolated in more than 90% yield before the aldol product came off the column. The obtained aldol adduct **3** showed identical spectral and analytical data with those reported in the literature.[9]

Received: December 29, 1998 [Z12839IE]
German version: *Angew. Chem.* **1999**, *111*, 1884–1886

Keywords: aldol reactions · C–C coupling · cross-coupling · enols

[1] a) O. H. House in *Modern Synthetic Reactions* (Ed.: R. Breslow), Benjamin, Menlo Park, NJ, USA, **1972**, chap. 10, and references therein; b) C. H. Heathcock in *Comprehensive Organic Synthesis*, *Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, chap. 1.5, and references therein; c) C. H. Heathcock in *Modern Synthetic Methods 1992*, *Vol. 6* (Ed.: R. Scheffold), VHCA, Basel, **1992**, chap. 1, and references therein.

[2] S. Saito, M. Shiozawa, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 813.

[3] For a general review of bulky aluminum reagents, including ATPH, see: S.Saito, H. Yamamoto, *Chem. Commun*. **1997**, 1585.

[4] ATPH was prepared as follows: To a solution of 2,6-diphenylphenol (3 equiv) in toluene was added a 1 M solution of Me_3Al (1 equiv) in hexane at room temperature under argon. The resulting pale yellow solution was stirred at this temperature for 30 min and used without further purification. a) S. Saito, M.Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 611; b) T. Ooi, K. Hokke, K. Maruoka, *Angew. Chem*. **1997**, *109*, 1230; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1181; c) K. Maruoka, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 9091; d) K. Maruoka, S. Saito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 1165; e) K. Maruoka, H. Imoto, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 12115; f) K. Maruoka, H. Imoto, S. Saito, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 4131.

[5] With the exception of our case, the extended dienolates of esters are invariably prone to α-functionalization: a) D. Caine in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming, G. Pattenden), Pergamon, Oxford, **1991**, chap. 1.1, and references therein; b) S. Saito, H. Yamamoto, *Chem. Eur. J.*, in press.

[6] Preparation of **5**: a) H. O. House, V. K. Jones, G. A. Frank, *J. Org. Chem*. **1964**, *29*, 3327. Highly conjugated esters **8**–**11** were prepared as described in the literature, through a Horner–Emmons olefination with diethyl phosphonoacetic acid ethyl ester (methyl ester for **8**): b) M. Bellassoued, A. Majidi, *J. Org. Chem*. **1993**, *58*, 2517.

[7] a) P. Wipf, P. D. G. Coish, *Tetrahedron Lett*. **1997**, *38*, 5073; b) B. H. Lipshutz, C. Lindsley, *J. Am. Chem. Soc*. **1997**, *119*, 4555; c) J. Thibonnet, M. Abarbi, J. L. Parrain, A. Duchêne, *Synlett* **1997**, 771; d) D. Boschelli, T. Takemasa, Y. Nishitani, S. Masamune, *Tetrahedron Lett*. **1985**, *26*, 5239.

[8] There are many examples of δ-hydroxy-α,β-unsaturated esters and their related units involved in the synthesis of important natural products: a) X. Fan, G. R. Flentke, D. H. Rich, *J. Am. Chem. Soc.* **1998**, *120*, 8893; b) T. I. Richardson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1997**, *119*, 12360; c) A. B. Smith III, G. R. Ott, *J. Am. Chem. Soc.* **1996**, *118*, 13095; d) C. S. Poss, S. D. Rychnovsky, S. L. Schreiber, *J. Am. Chem. Soc*. **1993**, *115*, 3360; e) G. E. Keck, J. A. Murry, *J. Org. Chem*. **1991**, *56*, 6606; f) K. C. Nicolaou, T. K. Chakraborty, Y. Ogawa, R. A. Daines, N. S. Simpkins, G. T. Furst, *J. Am. Chem. Soc*. **1988**, *110*, 4660; g) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, Y. Ogawa, *J. Am. Chem. Soc*. **1988**, *110*, 4685.

[9] P. R. Johnson, J. D. White, *J. Org. Chem*. **1984**, *49*, 4424.

  1433-7851/99/3812-1771 $ 17.50+.50/0