

Studies toward the Total Synthesis of GKK1032A₂, a Structurally Unique Antitumor Compound: Stereoselective Construction of the Tricarbo-cyclic System

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Abstract: The unique tricarbo-cyclic system in GKK1032A₂, an antitumor agent from *Penicillium* sp. GKK1032, was constructed in a highly stereoselective manner, starting from a readily available Hajos–Wiechert ketone analog.

Key words: antitumor agents, carbocycles, Diels–Alder reactions, natural products, stereoselective synthesis

GKK1032A₂ is a member of a novel class of antibiotic antitumor compounds recently isolated from *Penicillium* sp. GKK1032 (Figure 1).^{1,2} These compounds exhibit potent activity against bacteria including drug-resistant strain, as well as antitumor activity against epithelioid cell HeLa S3.^{1a} He et al. isolated pyrrocidines A and B, 3,6-bisepi-3-desmethyl analogues of GKK1032s, and reported that they showed similar bioactivity.³ From a pharmaceutical point of view, these bioactivities make GKK1032 family an expecting candidate for a drug to control multidrug-resistant *Staphylococcus aureus* and other nosocomial infections, and a new seed for anti-cancer drug. Structural feature of the compound was elucidated by NMR techniques and X-ray crystallographic analysis,^{1b} which includes an unusual 13-membered macrocyclic ether containing 1,4-disubstituted phenyl moiety. Recently, Oikawa disclosed that the unique backbone of GKK1032A₂ is biosynthetically constructed from L-tyrosine and a nonaketide chain with five methyl groups.⁴

These biologically and synthetically attracting features of GKK1032 family prompted us to embark on the total synthesis of GKK1032A₂.

The synthetic plan is shown in Scheme 1. The macrocyclic moiety of **1** could be constructed from an aldehyde **2** via carbon chain elongation followed by ring-closure. The cyclohexene ring in **2** is expected to be formed by Diels–Alder reaction between a diene **3** and an appropriate dienophile which may occur from the upper face of the diene taking advantage of a steric effect of the aromatic ring. The diene **3** would be readily accessible from a known bicyclic ketone **4** available with high optical

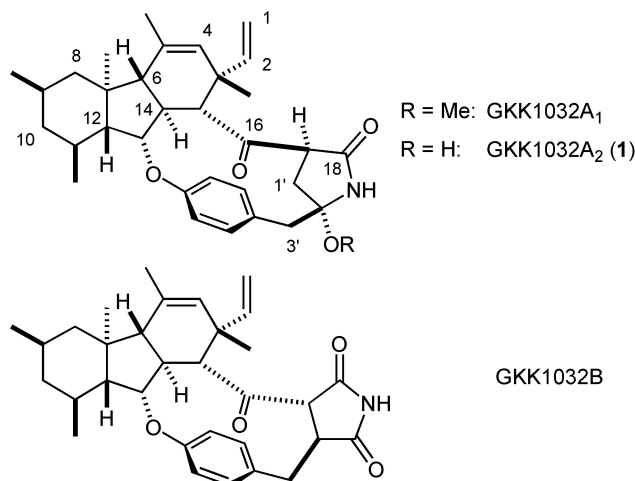
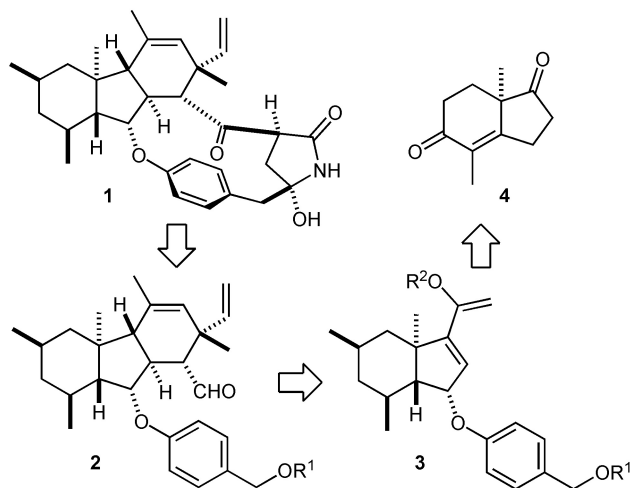


Figure 1 Structures of GKK1032 family.

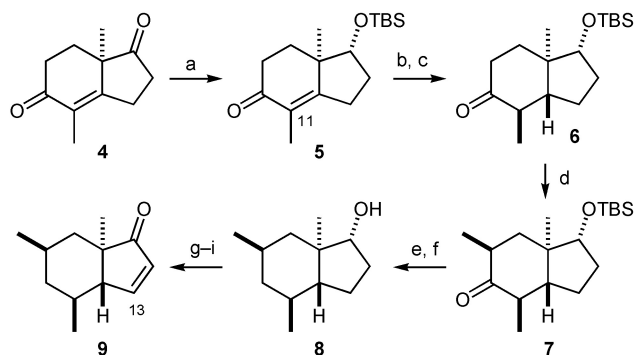


Scheme 1 Retrosynthetic analysis of GKK1032A₂.

purity. We describe herein a method to construct the tricarbo-cyclic system of GKK1032s in a highly stereoselective manner, starting from a readily available Hajos–Wiechert ketone analogue **4**.

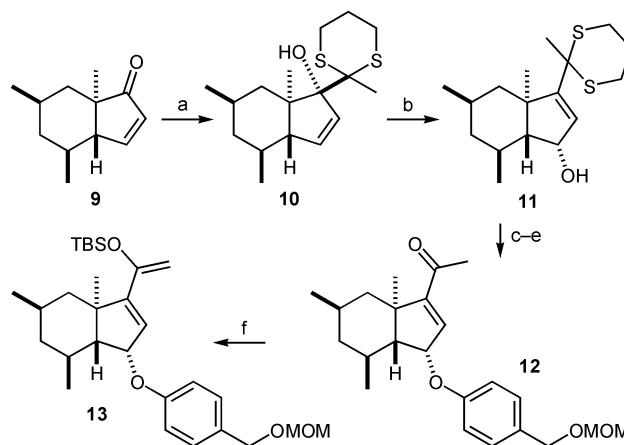
The bicyclic ketone **4** was regio- and stereoselectively reduced and protected with TBS group⁵ to afford an enone **5** (Scheme 2). For the *trans* selective reduction of 6–5

bicyclic enone related to **5**, we preferred a catalytic hydrogenation procedure convenient for multi-gram scale preparation at the early stage of the total synthesis. On the catalytic hydrogenation of this type of compounds, it was reported that the larger is a substituent at α -position of the enone [corresponding to C(11)-Me in **5**, GKK1032A₂ numbering], the higher *trans* selectivity is observed,⁶ though unsubstituted substrates gave *cis* major product.^{7,8} Indeed, the hydrogenation of **5** proceeded with high *trans* selectivity in THF to afford **6** via a subsequent epimerization under basic conditions. Use of the dry solvent was essential to achieve the high *trans* selectivity, otherwise the selectivity was markedly decreased, and in some case inverted. Methylation of **6** under kinetic conditions followed by epimerization produced a ketone **7** in good yield. A secondary alcohol **8** obtained by conventional deoxygenation⁹ of **7** was converted into an enone **9** via Swern oxidation¹⁰ and dehydrogenation under Tsuji's conditions.¹¹



Scheme 2 Reagents and conditions: a) ref. 5; b) H₂, Pd/C, THF, 0 °C, 1 d, *trans/cis* = ca.9:1; c) NaOEt, EtOH, reflux, 6 h, 77% (2 steps); d) LDA, THF, -78 °C, 3 h, then MeI, -78 °C to r.t., 85%; e) 1,2-ethanedithiol, BF₃·OEt₂, neat, 0 °C to r.t., 1 d, 85%; f) Raney Ni (W-2), EtOH, reflux, 14 h, 76%; g) (COCl)₂, DMSO, Et₃N, -78 to 0 °C, 1 h, 93%; h) LDA, THF, -78 °C, 3 h, then TMSCl; i) 10 mol% Pd(OAc)₂, allyl carbonate, MeCN, reflux, 67% (2 steps).

For the stereoselective introduction of an oxygen functionality at C(13)-position, we decided to utilize Krafft's procedures: they reported a suprafacial 1,3-rearrangement of the hydroxyl group of tertiary allylic alcohol obtained by addition of 2-lithio-2-methyl-1,3-dithiane to cyclopentenone moiety in a steroid derivative under dilute acidic conditions.¹² Their protocol worked well also in our case: Addition of the lithiodithiane to the enone **9** took place selectively from the opposite side of the angular methyl group and a subsequent treatment with dilute sulfuric acid afforded allylic alcohol **11** in excellent stereoselectivity (Scheme 3). Introduction of the aryl ether was effectively achieved by using aromatic S_N2 reaction between a fluoroarene chromium complex and an alkoxide of **11**,¹³ followed by decomplexation with CAN.¹⁴ The deprotection of the dithiane turned out to be somewhat troublesome, probably due to a steric factor and the instability of the aryl ether moiety under the reaction conditions.¹⁵ After several trials, it was found that application of Stork's method¹⁶ as well as Panek's protocol¹⁷

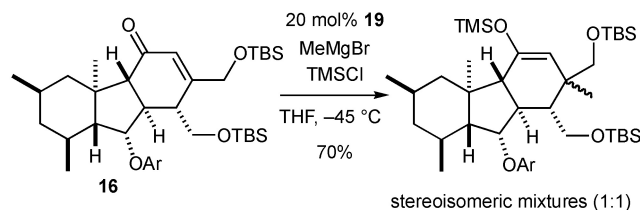


Scheme 3 Reagents and conditions: a) 2-lithio-2-methyl-1,3-dithiane, THF, -78 to -23 °C, 5 h, 97%; b) 0.5% H₂SO₄, aq THF, 0 °C to r.t., 1 d, 77% (3 recycles), >20:1 stereoselectivity; c) NaH, η^6 -4-FC₆H₄CH₂OMOM-Cr(CO)₃, THF, reflux, 7 h, 81%; d) CAN, NaHCO₃, MeCN, -23 °C, 20 min, 82%; e) Dess-Martin periodinane, MeCN-CH₂Cl₂-H₂O, r.t., 39 h, 70%; f) KHMDS, TBSCl, THF-HMPA, -78 °C to r.t., 95%.

gave enone **12** in an acceptable yield. The diene **13** was readily prepared by usual procedure from **12**.

Thus, the stage was set for the formation of the third 6-membered ring. In refluxing toluene, the [4+2]cycloaddition of dimethyl fumarate to the diene **13** took place selectively from the opposite side of OAr to afford the desired **14a** as a major product together with a small amount of its epimer **14b** (Scheme 4). The stereochemistry of each product was determined by NOE experiments. Reduction of **14a** to a diol followed by treatment with TBAF afforded a thermodynamically most favorable *trans*-fused ketone. Protection of the diol moiety with TBS provided **15**, which was converted into an enone **16**. A stereoselective introduction of methyl on the C(3)-position to form a quaternary carbon was a next critical aspect of our synthetic study. While usual procedures for conjugate addition (e.g., Me₂CuLi,¹⁸ MeMgBr-cat.Cu(I)-TMSCl¹⁹) did not work with the enone **16**, a Cu(II)-salicylidene-iminato complex **19** catalyzed reaction²⁰ effected the addition to afford methylation product in good yield. However, no stereoselection was observed (Equation 1), and we had to modify the structure of the substrate appropriate for the π -facial selection.

After various examinations, we found that the cyclic silyl ether **17**, easily available from **16** via a protective group manipulation,²¹ was the substrate of choice for the stereo-



Equation 1

selective 1,4-addition. When **17** was subjected to the above conditions, the addition product **18** was obtained as a sole product (Scheme 4). The complete stereoselectivity observed in this conjugate addition could be explained by considering the structural feature of **17** shown in Figure 2.

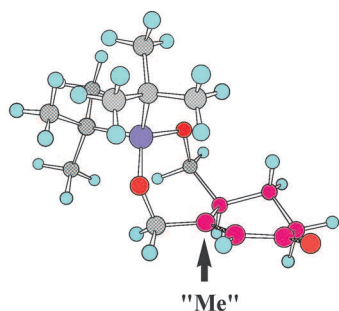
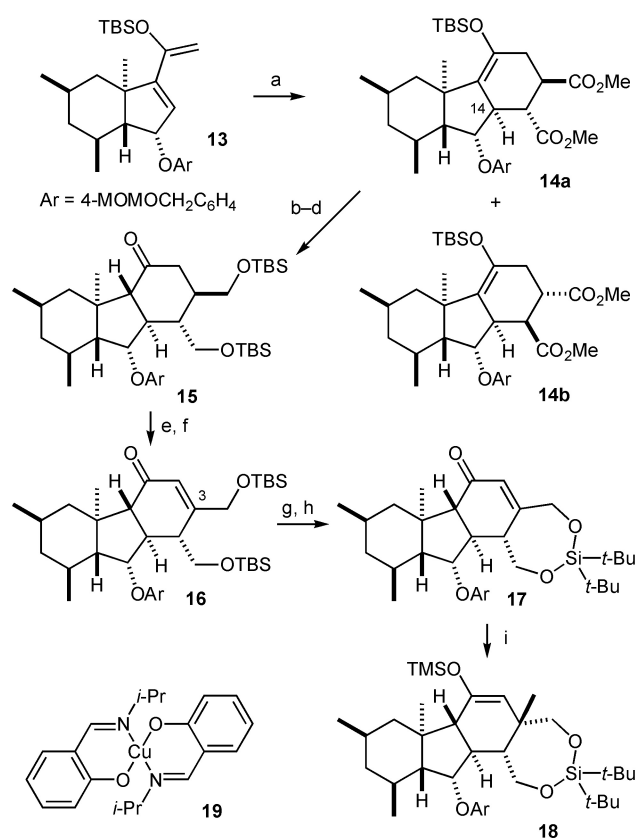


Figure 2 An optimized structure of the right half of **17**.



Scheme 4 Reagents and conditions: a) dimethyl fumarate, toluene, reflux, 10 h, **14a** 83%, **14b** 17%; b) LiBH_4 , THF–MeOH, 0 °C to r.t., 1 d, 91%; c) TBAF, THF, 0 °C to r.t., 2 h; d) TBSCl, imidazole, DMF, r.t., 1 h, 97% (2 steps); e) LDA, TMSCl, THF, –78 °C, 3 h; f) $\text{Pd}(\text{OAc})_2$, MeCN, 50 °C, 10 h; g) TBAF, THF, 0 °C to r.t., 2 h; h) $(t\text{-Bu})_2\text{Si}(\text{OTf})_2$, 2,6-lutidine, CH_2Cl_2 , –78 to –45 °C, 4 h, 58% (based on **15**); i) MeMgBr , TMSCl, 10 mol% **19**, THF, –45 °C, 44 h, 84% (single stereoisomer).

The trimethylsiloxy group in **18** was replaced with methyl group via three sequential steps, silyl–lithium exchange,²² triflation with Comins reagent,²³ $\text{Pd}(0)\text{--Me}_2\text{Zn}$ reagents,²⁴ affording **20** (Scheme 5). Compound **20** carries all required functionalities in the tricyclic core of

GKK1032s with correct stereochemistry. Since **20** was isolated as a crystalline compound, the relative configuration was unambiguously determined by X-ray crystallographic analysis (Figure 3).²⁵

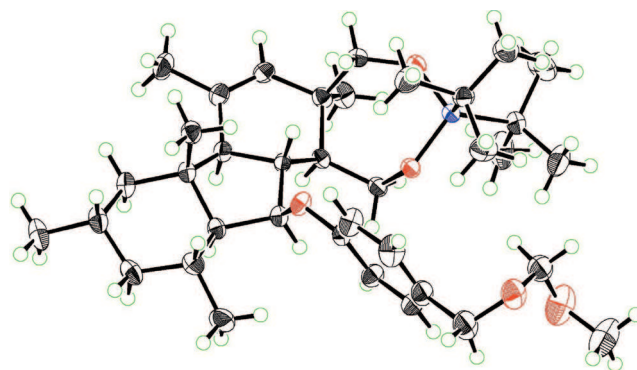
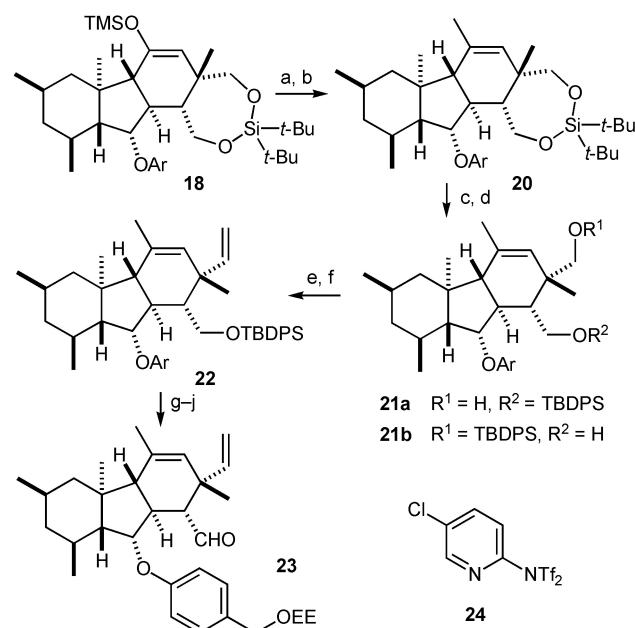


Figure 3 ORTEP drawing of **20**.

After deprotection of the silylene in **20** with TBAF, regioselective TBDPS ether formation was nicely carried out under low temperature conditions to give **21a** in preference to **21b**. Oxidation of the remaining hydroxy group in **21a** followed by Wittig reaction²⁶ led to **22**, which was converted into aldehyde **23** via usual protecting group manipulation. Thus, we established a highly stereoselective synthetic route from the known ketone **4** to the aldehyde **23**, which could be a useful common intermediate in the total synthesis of GKK1032 family.



Scheme 5 Reagents and conditions: a) MeLi , THF, –78 °C to r.t., 2 h, then **24**, –78 °C, 16 h, 86%; b) Me_2Zn , $\text{Pd}(\text{PPh}_3)_4$, THF, 0 °C to r.t., 28 h, 95%; c) TBAF, THF, r.t., 20 h; d) TBDPSCl, Et_3N , 10 mol% DMAP, CH_2Cl_2 , –78 °C to –45 °C, 4 h, **21a** 80%, **21b** 13%; e) $(\text{COCl})_2$, DMSO, Et_3N , –78 °C to 0 °C, 1 h, 95%; f) MePh_3PBr , BuLi, THF, 0 °C, 2 h, 96%; g) 2 M HCl, aq THF, 35 °C, 8 h, 95% (3 recycles); h) ethyl vinyl ether, 10 mol% PPTS, CH_2Cl_2 , r.t., 3 h; i) TBAF, MS 4 Å, THF, 40 °C, 17 h, quant. (2 steps); j) SO_3 ·pyridine, Et_3N , DMSO, r.t., 1.5 h, 89%.

We are now investigating the total synthesis of GKK1032s, and will describe this in the near future.

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References

- (1) (a) Koizumi, F.; Hasegawa, A.; Ando, K.; Ogawa, T.; Hara, M. *Jpn. Kokai Tokkyo Koho*, JP 2001247574 A2 20010911, **2001**; *Chem. Abstr.* **2001**, 135, 209979. (b) Hasegawa, A.; Koizumi, F.; Takahashi, Y.; Ando, K.; Ogawa, T.; Hara, M.; Yoshida, M. *43rd Symposium on the Chemistry of Natural Products, Symposium Papers*; Osaka: Japan, **2001**, 467.
- (2) Omura, S.; Komiyama, H.; Hayashi, M.; Masuma, R.; Fukaumi, A. *Jpn. Kokai Tokkyo Koho*, JP 2002255969 A2 20020911, **2002**; *Chem. Abstr.* **2002**, 137, 231476.
- (3) He, H. Y.; Yang, H. Y.; Bigelis, R.; Solum, E. H.; Greenstein, M.; Carter, G. T. *Tetrahedron Lett.* **2002**, 43, 1633.
- (4) Oikawa, H. *J. Org. Chem.* **2003**, 68, 3552.
- (5) Hagiwara, H.; Sakai, H.; Uchiyama, T.; Ito, Y.; Morita, N.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. I* **2002**, 583.
- (6) McKenzie, T. C. *J. Org. Chem.* **1974**, 39, 629.
- (7) Renoud-Grappin, M.; Vanucci, C.; Lhommet, G. *J. Org. Chem.* **1994**, 59, 3902.
- (8) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, 38, 3239.
- (9) (a) Provita, J.; Ocadlik, R.; Klinotova, E.; Klinot, J.; Vystreil, A. *Collect. Czech. Chem. Commun.* **1987**, 52, 501. (b) Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *J. Org. Chem.* **1987**, 52, 3346. (c) Mehta, G.; Murthy, A. N. *J. Org. Chem.* **1987**, 52, 2875. (d) Ihara, M.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1990**, 55, 4497.
- (10) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
- (11) (a) Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, 42, 2971. (b) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, 43, 1011.
- (12) Krafft, M. E.; Dasse, O. A.; Fu, Z. *J. Org. Chem.* **1999**, 64, 2475.
- (13) (a) Nicholls, B.; Whiting, M. C. *J. Chem. Soc.* **1959**, 551. (b) Ghavshou, M.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. I* **1983**, 3065.
- (14) Tanaka, T.; Mikamiyama, H.; Maeda, K.; Ishida, T.; In, Y.; Iwata, C. *Chem. Commun.* **1997**, 2401.
- (15) (a) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, 36, 3553. (b) Ho, T.-L.; Wong, C. M. *Can. J. Chem.* **1972**, 50, 3740. (c) Ho, T.-L.; Ho, C. H.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791. (d) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.
- (16) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, 30, 287.
- (17) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, 5, 575.
- (18) Posner, G. H. *Org. React.* **1972**, 19, 1.
- (19) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Org. Synth., Coll. Vol. IX*; Wiley and Sons: New York, **1998**, 564.
- (20) Sakata, H.; Aoki, Y.; Kuwajima, I. *Tetrahedron Lett.* **1990**, 31, 1161.
- (21) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, 23, 4871.
- (22) (a) Torneiro, M.; Fall, Y.; Castedo, L.; Mourino, A. *Tetrahedron Lett.* **1992**, 33, 105. (b) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, 4, 3473.
- (23) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, 33, 6299.
- (24) Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, 66, 8037.
- (25) Crystallographic data for **22**: formula, C₃₇H₆₀O₂Si; FW, 612.94; crystal system, orthorhombic; space group, P2₁2₁2₁; *a* = 11.7726 (4) Å, *b* = 12.9543 (4) Å, *c* = 23.5023 (8) Å; *V* = 3584.2 (2) Å³; *Z* = 4; *T* = 170 K; *D*_{calcd} = 1.136 g cm⁻³; λ(MoK_α) = 0.71070 Å; *R*1 = 0.0418 [*I* > 2σ(*I*)]; *wR*2 = 0.1082; GOF(*F*²) = 1.064.
- (26) (a) Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, 99, 6066. (b) Stevens, R. V.; Albizzati, K. F. *J. Org. Chem.* **1985**, 50, 632.