Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1601–1606

TETRAHEDRON: *ASYMMETRY*

Ring-closing metathesis protocol for a diastereocontrolled preparation of the C_{28}–C_{34} segment of FK-506

Miwako Takeuchi, Takahiko Taniguchi and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Received 10 February 2000; accepted 3 March 2000

Abstract

A new synthesis of the C_{28}–C_{34} segment of FK-506 has been developed using a chiral building block having a 6,8-dioxabicyclo[3.2.1]octane framework by employing a ring-closing metathesis reaction as the key step.

1. Introduction

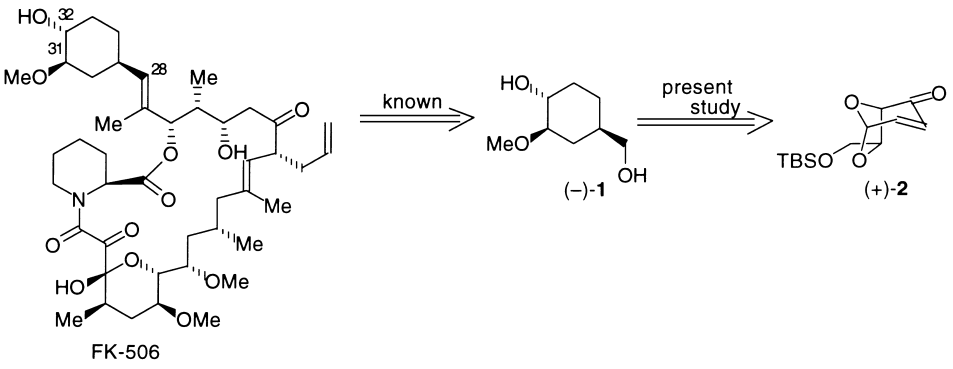
We recently developed the synthesis of the chiral building block **2** having a 6,8-dioxabicyclo[3.2.1]octane framework by employing either a catalytic[1] or an enzymatic[2] procedure. Owing to its high functionality confined in a biased framework, it allowed convex-face selective functionalization leading to diastereocontrolled construction of all of the eight possible aldohexoses[1,3] and (+)-L-noviose,[4] a sugar moiety of the antibiotic novobiocin. Herein we describe an alternative utilization of the building block on the basis of its convex-face selectivity for a diastereocontrolled preparation of the C_{28}–C_{34} segment (–)-**1** of FK-506,[5] a powerful immunosuppressant isolated from the soil bacterium *Streptomyces tsukubaensis*, by employing a ring-closing metathesis[6] as the key step. Because of the remarkable biological properties of FK-506, more than a dozen methods for the preparation of (–)-**1** have been reported during the course of its total synthesis[7] as well as of its partial synthesis.[8] However, the diastereocontrolled synthesis of (–)-**1** was found to be unexpectedly tedious and difficult.

2. Results and discussion

The present synthesis of (–)-**1** starting from our chiral building block (+)-**2** employing a ring-closing metathesis is easily carried out and is unprecedented (Scheme 1).

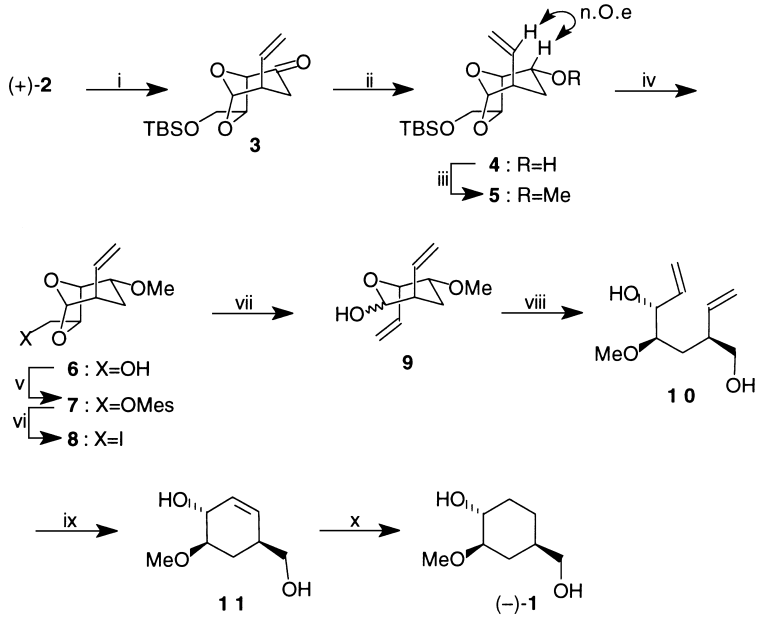
* Corresponding author. Fax: +81-22-217-6845; e-mail: konol@mail.cc.tohoku.ac.jp

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00093-8



Scheme 1.

Thus, (+)-**2** was treated with vinylmagnesium bromide in THF containing 3 equivalents of hexamethylphosphoric triamide (HMPA) in the presence of 0.2 equivalent of a copper(I) bromide–dimethyl sulfide complex at –78°C to give the vinyl ketone **3** as the single product in 77% yield by diastereoselective reaction from the convex-face of the molecule. Reduction of **3** with sodium borohydride in the presence of cerium(III) chloride[9] gave a mixture of two epimeric alcohols containing the desired *endo*-alcohol **4** as the major component which could not be separated in pure form at this stage. Apparently, the introduced vinyl functionality hindered diastereoselective reduction of the ketone functionality from the convex-face owing to the 1,3-steric



Scheme 2. *Reagents and conditions*: (i) vinylmagnesium bromide, $CuBr{\cdot}SMe_2$, HMPA, THF, –78°C (77%); (ii) $NaBH_4$–$CeCl_3{\cdot}7H_2O$, MeOH, –30°C; (iii) MeI, NaH, THF, 0°C–rt (77% from **3**); (iv) TBAF, THF (95%); (v) MesCl, Et_3N, CH_2Cl_2, 0°C–rt; (vi) LiI, THF, reflux, 17 h (90% from **6**); (vii) Zn, AcOH:MeOH (1:10 v/v), rt; (viii) $LiAlH_4$, THF, 0°C (81% from **8**); (ix) Grubbs' reagent (10 mol%), CH_2Cl_2, reflux, 4 h; (x) H_2, PtO_2, AcOEt, rt (87% from **10**)

interaction. The mixture, therefore, was methylated without separation using iodomethane in the presence of sodium hydride, and the product was separated at this stage by silica gel column chromatography to give the *endo*-methoxy product **5** in 77% overall yield from **3**. Stereochemistry of **5** was confirmed by NOE experiments in which significant interaction between the 2-H and the 4-vinyl-(1-H) and no interaction between the 2-H and the 7-H were observed, thus supporting the assigned structure.

On desilylation with tetrabutylammonium fluoride (TBAF), **5** afforded the primary alcohol **6**, which was transformed into the iodide **8** via the mesylate **7** on sequential mesylation and substitution. Reductive cleavage of **8** with zinc in methanolic acetic acid proceeded without difficulty to give the hemiacetal **9**, which was treated with lithium aluminum hydride to afford the acylic diol **10** having two vinyl functionalities.

The key ring-closing metathesis of **10** using 10 mol% of Grubbs' catalyst in dichloromethane terminated after 4 h at reflux to bring about the expected cyclization to furnish the cyclohexenediol **11** which was accompanied by a minor amount of an inseparable coloring material originating from the catalyst. Thus, the product, without separation, was hydrogenated on Adams' catalyst to afford the target cyclohexanediol (–)-**1** in 87% overall yield from **10** after purification by column chromatography. Overall yield of the C_{28}–C_{34} segment (–)-**1** from the chiral building block (+)-**2** was 36% in 10 steps (Scheme 2).

In short, we have described an alternative utilization of our chiral building block having a 6,8-dioxabicyclo[3.2.1]octane framework for construction of the C_{28}–C_{34} segment of FK-506 on the basis of the inherent convex-face selectivity by employing ring-closing metathesis as the key step.

3. Experimental

Melting points were determined on a Yanagimoto hot-stage and are uncorrected. IR spectra were recorded on a JASCO-IR 700 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz) spectrometer. Optical resolutions were measured with a JASCO-DIP-370 digital polarimeter. Enantiomeric purities were determined on a Gilson Model-307 instrument equipped with a column with a chiral stationary phase.

*3.1. (+)-(1*R*,4*S*,5*R*,7*S*)-7-*tert*-Butyldimethylsiloxymethyl-4-vinyl-6,8-dioxabicyclo[3.2.1]oct-2-one **3***

To a stirred solution of THF (4 ml) containing HMPA (616 μl, 3.54 mmol) was added CuBr·SMe (49 mg, 1.18 mmol) at 0°C, then after 30 min, vinylmagnesium bromide (1 M in THF, 3.42 ml, 3.42 mmol) was added at –20°C. After 30 min at the same temperature, the solution was cooled to –78°C and to this solution the enone (+)-**2** (318 mg, 1.18 mmol) in THF (2 ml) was added dropwise. After 30 min at the same temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with AcOEt:hexane, 1:30 v/v) to give the ketone **3** (269 mg, 77%) as a faint yellow oil: $[\alpha]_D^{25}$ +13.5 (*c* 1.06, $CHCl_3$). IR (film): $\nu = 1737$ cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.83$ (1H, ddd, $J = 17.0$, 10.4, 8.0 Hz), 5.46 (H, s), 5.18 (1H, dt, $J = 10.4$, 1.1 Hz), 5.16 (1H, dt, $J = 17.0$, 1.1 Hz), 4.38 (1H, s), 4.09 (1H, dd, $J = 8.2$, 5.5 Hz), 3.63 (1H, dd, $J = 10.2$, 5.5 Hz), 3.46 (1H, dd, $J = 10.2$, 8.2 Hz), 2.84 (1H, td, $J = 8.0$, 3.4 Hz), 2.68 (1H, dd, $J = 17.0$, 3.4 Hz), 0.89 (9H,

s), 0.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 204.8$, 136.9, 117.5, 10.4, 80.8, 78.2, 62.8, 46.3, 38.1, 25.8, 18.2, –5.4, –5.5. HRMS: m/z = calcd for $C_{15}H_{26}O_4Si$: 298.1600; found: 298.1605.

3.2. (+)-(1S,2R,4S,5R,7S)-7-tert-Butyldimethylsiloxymethyl-2-methoxy-4-vinyl-6,8-dioxabicyclo-[3.2.1]octane **5**

To a stirred solution of **3** (556 mg, 1.87 mmol) and $CeCl_3 \cdot 7H_2O$ (2.09 g, 5.60 mmol) in MeOH (11 ml) was added $NaBH_4$ (212 mg, 5.60 mmol) portionwise at –30°C and raised to room temperature. The mixture was evaporated under reduced pressure and the residue was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with AcOEt:hexane, 1:2 v/v) to give a mixture containing **4** as the major product. The mixture in THF (11 ml) was treated with NaH (60% oil dispersion, 119 mg, 2.99 mmol) at 0°C, then, after 10 min, with MeI (1.16 ml, 18.7 mmol) at the same temperature and the stirring was continued for 20 min at room temperature. The mixture was diluted with AcOEt and was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, elution with AcOEt:hexane, 1:50 v/v) to give the methyl ether **5** (454 mg, 77% from **3**) as a colorless oil: $[\alpha]_D^{27}$ +27.6 (c 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.86$ (1H, ddd, $J = 17.3$, 10.4, 7.8 Hz), 5.26 (1H, s), 5.13 (1H, d, $J = 17.3$ Hz), 5.12 (1H, d, $J = 10.4$ Hz), 4.43 (1H, d, $J = 3.3$ Hz), 4.21 (1H, dd, $J = 8.7$, 5.2 Hz), 3.65–3.58 (2H, m), 3.42 (1H, dd, $J = 9.8$, 8.7 Hz), 3.37 (3H, s), 2.50 (1H, t, $J = 7.1$ Hz), 1.90 (1H, dd, $J = 13.5$, 5.4 Hz), 1.77 (1H, ddd, $J = 13.5$, 10.7, 6.3 Hz), 0.89 (9H, s), 0.07 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.6$, 116.4, 103.8, 74.8, 74.5, 72.1, 63.5, 56.4, 45.1, 28.2, 25.8, 18.1, –5.5. HRMS: m/z = calcd for $C_{16}H_{30}O_4Si$: 314.1913; found: 314.1925.

3.3. (+)-(1S,2R,4S,5R,7S)-7-Hydroxymethyl-2-methoxy-4-vinyl-6,8-dioxabicyclo[3.2.1]octane **6**

To a stirred solution of **5** (454 mg, 1.45 mmol) in THF (9 ml) was added TBAF (1.0 M in THF, 2.17 ml, 2.17 mmol) at 0°C and the stirring was continued for 2 h at room temperature. The mixture was diluted with AcOEt and was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 9 g, elution with AcOEt:hexane, 1:2 v/v) to give the alcohol **6** (276 mg, 95%) as a colorless oil: $[\alpha]_D^{29}$ +0.6 (c 1.09, $CHCl_3$). IR (film): $\nu = 3450$ cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.85$ (1H, ddd, $J = 17.4$, 10.4, 8.0 Hz), 5.33 (3H, s), 5.14 (1H, d, $J = 10.4$ Hz), 4.34–4.30 (2H, m), 3.66–3.59 (3H, m), 3.37 (3H, s), 2.53 (1H, t, $J = 7.3$ Hz), 2.24 (1H, br.s), 1.96 (1H, dd, $J = 13.2$, 5.8 Hz), 1.78 (1H, ddd, $J = 13.2$, 10.7, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.2$, 116.5, 103.9, 75.1, 74.9, 72.0, 64.0, 56.1, 44.8, 27.8. HRMS: m/z = calcd for $C_{10}H_{16}O_4$: 200.1049; found: 200.1034.

3.4. (+)-(1S,2R,4S,5R,7S)-7-Iodomethyl-2-methoxy-4-vinyl-6,8-dioxabicyclo[3.2.1]octane **8**

To a stirred solution of **6** (276 mg, 1.38 mmol) in CH_2Cl_2 (6 ml) was added Et_3N (577 μl, 4.14 mmol), followed by MesCl (160 μl, 2.07 mmol) at 0°C, and the stirring was continued for 1 h at room temperature. The mixture was diluted with AcOEt and washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave the mesylate **7**. Without purification, the crude **7** was dissolved in THF (6 ml) and was refluxed with LiI (1.85 g, 13.8 mmol) for 17 h. The mixture, after cooling, was diluted with AcOEt and was washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). After evaporation of the solvent under reduced

pressure the residue was chromatographed (SiO_2, 5 g, elution with AcOEt:hexane, 1:40 v/v) to give the iodide **8** (384 mg, 90% from **6**) as a colorless oil: $[\alpha]_D^{25}$ +59.4 (*c* 1.17, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.84$ (1H, ddd, $J = 17.6$, 9.9, 8.0 Hz), 5.38 (1H, s), 5.14 (1H, d, $J = 17.6$ Hz), 5.13 (1H, d, $J = 9.9$ Hz), 4.50–4.43 (2H, m), 3.59 (1H, ddd, $J = 11.0$, 6.0, 4.4 Hz), 3.42 (3H, s), 3.21 (1H, dd, $J = 9.6$, 5.2 Hz), 3.11 (1H, t, $J = 9.6$ Hz), 2.5 (1H, t, $J = 7.1$ Hz), 1.93 (1H, dd, $J = 13.5$, 6.0 Hz), 1.77 (1H, ddd, $J = 13.5$, 11.0, 6.6 Hz), 2.5 (1H, t, 7.1 Hz), 1.93 (1H, dd, $J = 13.5$, 6.0 Hz), 1.77 (1H, ddd, $J = 13.5$, 11.0, 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 137.0$, 116.8, 104.7, 77.1, 75.0, 72.0, 56.6, 44.7, 27.9, 7.1. HRMS: m/z = calcd for $C_{10}H_{15}IO_3$: 310.0066; found: 310.0082.

3.5. (+)-(3R,4R,6S)-3-Hydroxy-6-hydroxymethyl-4-methoxy-1,7-octadiene *10*

To a stirred solution of the iodide **8** (384 mg, 1.24 mmol) in methanolic acetic acid (10:1 v/v, 4.4 ml) activated Zn powder (1.62 g, 24.8 mmol) was added portionwise at room temperature. After stirring for 1 h at the same temperature, the mixture was diluted with AcOEt and, after filtration through a Celite pad, was washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 8 g, elution with AcOEt:hexane, 1:2 v/v) to give the hemiacetal **9**.

The hemiacetal **9** was dissolved in THF (4 ml), which was treated with $LiAlH_4$ (94 mg, 2.48 mmol) at 0°C with stirring. After 90 min at the same temperature, the mixture was diluted with Et_2O and the excess $LiAlH_4$ was decomposed by addition of H_2O. After filtration through a Celite pad, the organic layer was separated, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 8 g, elution with AcOEt:hexane, 1:1 v/v) to give the diol **10** (210 mg, 91% from **8**) as a colorless oil: $[\alpha]_D^{27}$ +26.4 (*c* 1.05, $CHCl_3$). IR (film): $\nu = 3396$ cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.89$ (1H, ddd, $J = 16.5$, 10.4, 6.0 Hz), 5.62 (1H, ddd, $J = 17.0$, 10.3, 8.9 Hz), 5.35 (2H, dt, $J = 17.0$, 1.4 Hz), 5.25–5.17 (3H, m), 3.57 (1H, ddd, $J = 10.4$, 7.7, 5.5 Hz), 3.50–3.36 (4H, m), 3.25 (1H, ddd, $J = 9.3$, 5.5, 3.0 Hz), 2.54–2.36 (1H, m), 1.62–1.43 (3H, m), 2.26 (1H, d, $J = 4.9$ Hz), 1.69–1.56 (2H, m), 1.46 (1H, ddd, $J = 14.3$, 9.9, 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 139.7$, 137.8, 117.9, 116.6, 81.8, 74.5, 66.0, 58.9, 43.6, 32.4. HRMS: m/z = calcd for $C_{10}H_{19}O_3$: 187.1334; found: 187.1333.

3.6. (–)-(1R,2R,4R)-4-Hydroxymethyl-2-methoxycyclohexan-1-ol *1*

A solution of the diene **10** (55 mg, 0.30 mmol) and Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene-ruthenium(IV) dichloride, 24 mg, 0.03 mmol] in CH_2Cl_2 (degassed, 15 ml) was refluxed for 4 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, 2 g, elution with AcOEt:hexane, 2:1 v/v) to give the cyclohexenol **11**. Without further purification, the **11** obtained was hydrogenated over PtO_2 (4 mg) in AcOEt (2 ml) at room temperature to give the cyclohexane **1**, which was purified by column chromatography (SiO_2, 2 g, elution with AcOEt:MeOH, 95:5 v/v) to give pure product (–)-**1** (40 mg, 87% from **10**) as a colorless oil: $[\alpha]_D^{30}$ –56.9 (*c* 0.40, $CHCl_3$) [lit.[7c] $[\alpha]_D^{23}$ –57.0 (*c* 0.30, $CHCl_3$)]. IR (film): $\nu = 3390$ cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.53$–3.38 (3H, m), 3.42 (3H, s), 3.02 (1H, ddd, $J = 11.3$, 8.8, 4.4 Hz), 2.93 (1H, br.s), 2.23–2.20 (1H, m), 2.04 (1H, dq, $J = 12.9$, 3.6 Hz), 1.95 (3H, br.s), 1.80–1.74 (1H, m), 1.61–1.55 (1H, m), 1.42–1.39 (1H, m), 1.08 (1H, qd, $J = 12.4$, 3.6 Hz), 0.86 (1H, q, $J = 12.4$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 84.32$, 73.83, 67.31, 56.32, 38.64, 31.15, 30.79, 26.72. HRMS: m/z = calcd for $C_8H_{16}O_3$: 160.1099; found: 160.1090.

References

1. Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341.
2. Takeuchi, M.; Taniguchi, T.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synthesis* **1999**, 1325.
3. Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Chirality*, in press.
4. Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett*., in press.
5. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc*. **1987**, *109,* 5031.
6. For a pertinent review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
7. (a) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc*. **1989**, *111*, 1157. (b) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc*. **1990**, *112*, 2998. (c) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc*. **1990**, *112*, 5583. (d) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem*. **1996**, *61*, 6856. (e) Ireland, R. E.; Liu, L.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13 221; Ireland, R. E.; Liu, L.; Roper, T. D.; Glearson, J. L. *Tetrahedron* **1997**, *53*, 13 257.
8. For partial syntheses focused on the C_{28}–C_{34} segment and the related segments, see: (a) Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett*. **1988**, *29*, 281. (b) Corey, E. J.; Huang, H.-C. *Tetrahedron Lett*. **1989**, *30*, 5235. (c) Smith III, A. B.; Hale, K. J.; Laakso, L. M.; Chen, K.; Riera, A. *Tetrahedron Lett*. **1989**, *30*, 6963. (d) Linde II, R. G.; Egbertson, M.; Coleman, R. S.; Jones, A. B.; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 2771. (e) Kocienski, P.; Stocks, M.; Donald, D.; Perry, M. *Synlett* **1990**, 38. (f) Gu, R.-L.; Sih, C. J. *Tetrahedron Lett*. **1990**, *31*, 3287. (g) Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S.-H.; Danishefsky, S. J. *J. Org. Chem*. **1991**, *56*, 5826. (h) Maier, M. E.; Schöffling, B. *Tetrahedron Lett*. **1990**, *31*, 3007. (i) Maruoka, K.; Saito, S.; Ooi, T.; Yamamoto, H. *Synlett* **1991**, 579. (j) Ireland, R. E.; Highsmith, T. K.; Gegnas, L. D.; Gleason, J. L. *J. Org. Chem*. **1992**, *57*, 5071. (k) White, J. D.; Toske, S. G.; Yakura, T. *Synlett* **1994**, 591. (l) Marshall, J. A.; Xie, S. *J. Org. Chem*. **1995**, *60*, 7230. (m) Haller, B.-U.; Kruber, S.; Maier, M. E. *J. Prakt. Chem*. **1998**, *340*, 656.
9. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc*. **1981**, *103*, 5454.