A shortened synthesis of optically pure tricarbonyl[methyl (2*E*,4*E*)-6-oxo-2,4-hexadienoate]iron leading to improved yield

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Dedicated to Prof. James M. Cook on the occasion of his 65th birthday

Abstract
The (+)- and (–)-enantiomers of tricarbonyl[methyl (2*E*,4*E*)-6-oxo-2,4-hexadienoate]iron are prepared in 4 steps from commercially available hexadienal (26% and 25% yields, respectively).

Keywords: (Diene)iron complexes, resolution, asymmetric dihydroxylation

Introduction

Planar chiral organometallic complexes have found widespread use in asymmetric organic synthesis.[1] For example, the enantiomers of tricarbonyl(methyl 6-oxo-2,4-hexadienoate)iron **1** (Scheme 1) may be separated by classical or kinetic resolution[2] and have been used in the asymmetric synthesis of leukotrienes and AF toxins.[3] More recently, we reported a 5-step route from (*R*)-glyceraldehyde acetonide, which gave (+)-**1** and (–)-**1** (15% and 21%, respectively),[4] and we have utilized this route to these planar chiral scaffolds for the synthesis of the C9–C16 segment **2** of ambruticin and 2-(2'-carboxycyclopropropyl)glycine **3**.[5] We now report a shortened synthesis leading to improved yields of the enantiomers of **1**, which relies on asymmetric dihydroxylation as the source of chirality.

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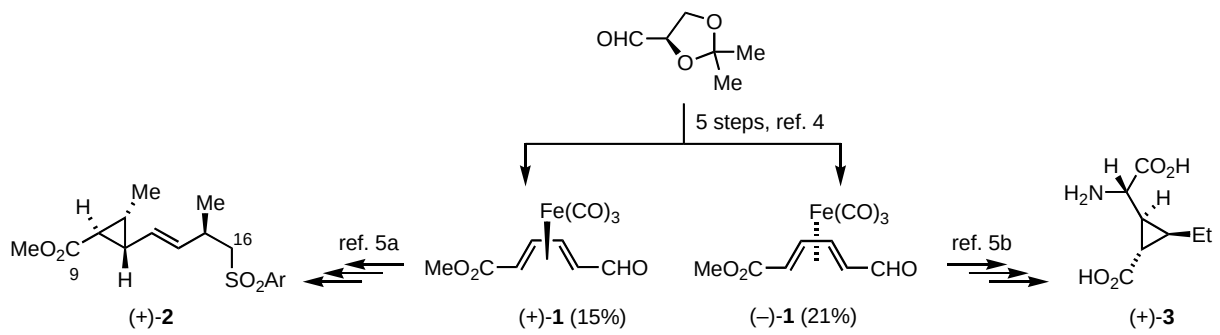
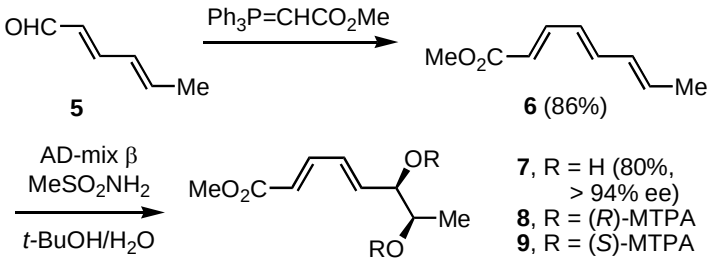


Scheme 1

Results and Discussion

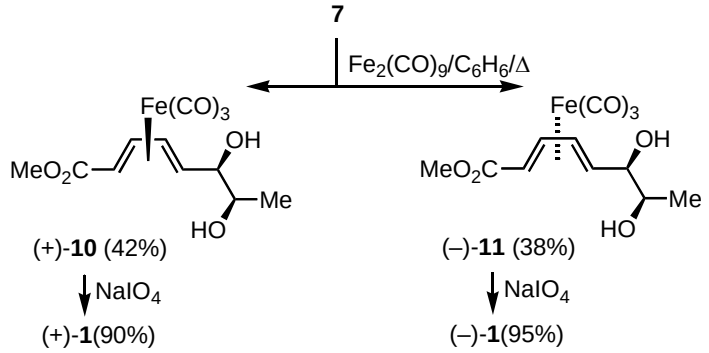
Wittig olefination of 2,4-hexadienal **5** afforded the known octadienoate **6** (Scheme 2). Asymmetric dihydroxylation of **6** using commercially available AD-mix β proceeded exclusively at the double bond most remote to the electron withdrawing ester substitutent to afford (2*E*,4*E*,6*R*,7*R*)-methyl 6,7-dihydroxyocta-2,4-dienoate **7** as a solid.[6] Analysis of the (*R*,*R*)- and (*S*,*S*)-bis-MTPA esters (**8** and **9**, respectively) by ^{1}H NMR indicated that each was >94% de.



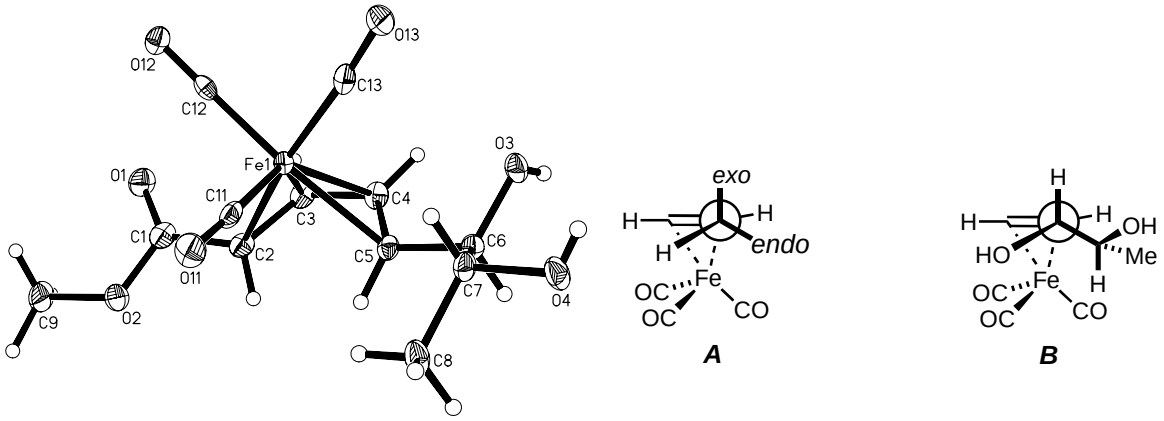
Scheme 2

Reaction of **7** with $Fe_2(CO)_9$ afforded a 1:1 mixture of diastereomeric complexes (+)-**10** and (–)-**11**, which were separable by column chromatography (Scheme 3). Use of toluene, ether, or THF as reaction solvent gave diminished yields and did not significantly change the ratio of the complexes. This lack of diastereoselectivity for the complexation was not unexpected as there are only two examples for the highly diastereoselective complexation of an acyclic *E*,*E*-diene.[7] On the basis of an empirical relationship between the optical rotation sign and the absolute configuration of (diene)$Fe(CO)_3$ complexes bearing terminal electron withdrawing groups,[8] complex (+)-**10** was tentatively assigned the 2*S* absolute configuration, while (–)-**11** was tentatively assigned the 2*R* absolute configuration. Finally, glycol cleavage of (+)-**10** gave the aldehyde complex (+)-**1**, while (–)-**11** gave (–)-**1**. The complexes (+)-**1** and (–)-**1** prepared by

this method were determined to be >94% ee by analysis of their ^{1}H NMR spectra with the chiral shift reagent [Eu(tfc)$_3$/acetone-d_6].[9]



Scheme 3



(a) (b)

Figure 1. (a) Molecular structure and crystallographic numbering scheme for compound (+)-**10**. (b) Conformation of (diene)Fe(CO)$_3$ complexes.

The tentative structural assignment for (+)-**10** was eventually corroborated by single crystal X-ray diffraction (Figure 1a).[10] There are more than 40 crystal structures of acyclic (diene)Fe(CO)$_3$ complexes containing a methine group attached to C1 of the diene.[11] The vast majority of these structures reveal a conformation, in which the small hydrogen atom is oriented toward the bulky carbon monoxide ligand (***A***, Figure 1b). In sharp contrast, the crystal structure of (+)-**10** exhibits a conformation about the C5–C6 bond with the H6 oriented antiperiplanar with respect to the coordination of iron and the 6-hydroxyl group oriented toward the carbon monoxide ligand (***B***, Figure 1b). There are only two other examples of this relatively rarely observed conformer.[12]

Conclusions

The above route to the enantiomers of (methyl 6-oxo-2,4-hexadienoate)$Fe(CO)_3$ from hexadienal is both shorter (4 steps) and higher yielding [26% (+)-**1** and 25% (–)-**1**] then our previous route[4] from glyceraldehyde acetonide [5 steps, 15% (+)-**1** and 21% (–)-**1**].

Experimental Section

General. Spectrograde solvents were used without further purification with the exception of anhydrous methylene chloride, which was purchased from Aldrich. (Methoxycarbonylmethylene)triphenylphosphorane (95%) and 2,4-hexadienal were purchased from Avocado Research Chemicals/Alfa Aesar and Acros Organics, respectively. Column chromatography was performed on silica gel (Silicycle, P60, 40-63 μm).
Melting points were obtained on a Mel-Temp melting point apparatus. All ^{1}H and ^{13}C NMR spectra were recorded on Varian spectrometers at the indicated frequency. Elemental analyses were obtained from Midwest Microlabs, Indianapolis, IN, and high-resolution mass spectra were obtained from the University of Nebraska-Center for Mass Spectrometry.

Methyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (6). To a solution of (methoxycarbonylmethylene)-triphenylphosphorane (37.5 g, 0.112 mol) in dry THF (275 mL) at room temperature was added (2*E*,4*E*)-hexa-2,4-dienal (**5**; 7.00 g, 72.8 mmol). The mixture was stirred at room temperature, under nitrogen, for 36 h, after which the solvent was evaporated and the residue was dissolved in a minimal amount of dichloromethane. Petroleum ether (600 mL) was added to the stirred solution to precipitate triphenylphosphine oxide. The precipitate was separated by filtration and the filtrate was concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate 97.5:2.5) to afford the known trienoate **6** (8.55 g, 77 %) as a colorless solid. The NMR spectral data for this compound was consistent with the literature values.[13]
Methyl (2*E*,4*E*,6*R*,7*R*)-6,7-dihydroxyocta-2,4-dienoate (7). To a solution of methyl octatrienoate **6** (5.00 g, 32.9 mmol) in *t*-BuOH (165 mL) and H_2O (165 mL) at 0 °C was added AD-mix-β (46.5 g), followed by $MeSO_2NH_2$ (3.15 g, 32.9 mmol). The mixture was stirred at 0 °C for 24 h, at which time ethyl acetate (100 mL) was added, and the reaction was quenched with saturated aqueous sodium sulfite (50 mL). The layers were separated and the aqueous layer was extracted several times with ethyl acetate. The organic layers were combined, washed with 2N KOH, followed by brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate 3:2) to afford **7** (4.90 g, 80%) as a colorless gum, which solidified in the freezer; mp 52–55 °C [lit.[6a] 53–55 °C]. $[\alpha]_D$ + 68.5 (*c* 1.3, EtOH) [lit.[6a] $[\alpha]_D$ + 73.7 (*c* 1.3, EtOH)]. The NMR spectral data was identical to the literature values.[6a]
Bis-(*R*)-MTPA ester of methyl (2*E*,4*E*,6*R*,7*R*)-6,7-dihydroxyocta-2,4-dienoate (8). To a solution of methyl 6,7-dihydroxyocta-2,4-dienoate **7** (18.6 mg, 0.100 mmol) in CH_2Cl_2 was

added (*R*)-α-methoxy-(trifluoromethyl)phenyl acetic acid (70.2 mg, 0.300 mmol), DMAP (7.0 mg), and DCC (61.8 mg, 0.321 mmol). The reaction mixture was stirred for 3.5 h, and then quenched by addition of water (5 drops). The mixture was extracted several times with ether, the extracts were combined, washed with 3% aqueous HCl followed by water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate 7:3) to afford diester **8** (35 mg, 56%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49–7.36 (m, 10H), 7.13 (dd, *J* = 10.8, 15.2 Hz, 1H), 6.17 (dd, *J* = 11.2, 15.2 Hz, 1H), 5.83 (dd, *J* = 6.4, 15.2 Hz, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 5.65 (br t, *J* = 5.6 Hz, 1H), 5.36–5.30 (m, 1H), 3.77 (s, 3H), 3.48 (s, 3H), 3.45 (s, 3H), 1.28 (d, *J* = 6.8 Hz, 3H). This compound was not further characterized.

Bis-(*S*)-MTPA ester of methyl (2*E*,4*E*,6*R*,7*R*)-6,7-dihydroxyocta-2,4-dienoate (9). The preparation of the (*S*)-MTPA diester **9** (55%) was carried out in the same fashion as the preparation of (*R*)-MTPA diester **8**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.35 (m, 10H), 7.06 (dd, *J* = 11.0, 15.0 Hz, 1H), 6.22 (dd, *J* = 10.8, 15.2 Hz, 1H), 5.82 (d, *J* = 14.8 Hz, 1H), 5.73 (dd, *J* = 6.8, 15.6 Hz, 1H), 5.57 (dd, *J* = 3.6, 7.6 Hz, 1H), 5.30-5.23 (m, 1H), 3.78 (s, 3H), 3.49 (s, 3H), 3.47 (s, 3H), 1.29 (d, *J* = 7.2 Hz, 3H). This compound was not further characterized.

Tricarbonyl[methyl (2E,4E,6*S*,7*R*)-dihydroxyoctadienoate]iron (10 and 11). To a solution of methyl 6,7-dihydroxyocta-2,4-dienoate **7** (5.10 g, 27.4 mmol) in benzene (110 mL) was added $Fe_2(CO)_9$ (20.0 g, 55.0 mmol). The reaction mixture was heated at reflux for 2 h. The mixture was cooled to room temperature and additional $Fe_2(CO)_9$ (5.00 g, 13.7 mmol) was added. The resulting mixture was heated at reflux for an additional 1 h. The mixture was cooled, filtered through a pad of SiO_2, and the filter bed was washed with methanol. The filtrate was concentrated and the residue was passed through a short column (SiO_2, hexanes/ethyl acetate 7:3 to 5:5 gradient) to afford a mixture of **10** and **11** (ca. 1:1, 8.20 g, 91.7 %) as an orange syrup. The mixture was separated by column chromatography in 4.1 g batches (SiO_2, hexanes/ethyl acetate 17:3) to afford (+)-**10** (3.75 g, 42%) followed by (–)-**11** (3.40 g, 38%), both as an orange syrup.

10. Crystallization from hexanes/ethyl acetate gave a crystalline solid **10**; mp 78–80 °C. R_f 0.36 (Al_2O_3 plates, hexanes/ethyl acetate 3:2). $[\alpha]_D$ +217.4 (*c* 1.078, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86 (ddd, *J* = 1.2, 5.2, 8.2 Hz, 1H), 5.48 (dd, *J* = 5.2, 8.6 Hz, 1H), 3.67 (s, 3H), 3.59 (br q, *J* = 6.0 Hz, 1H), 3.37 (dt, *J* = 3.1, 7.2 Hz, 1H), 2.55 (*J* = 3.0 Hz, OH), 2.18 (d, *J* = 5.1 Hz, OH), 1.31 (d, *J* = 6.8 Hz, 3H), 1.31–1.19 (m, 1H), 0.99 (dd, *J* = 0.8, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.7, 208.2, 206.7, 172.9, 85.1, 83.6, 77.4, 72.9, 65.0, 52.0, 45.9, 19.7. Anal. calcd. for $C_{12}H_{14}FeO_7$: C, 44.20; H, 4.33. Found: C, 44.63; H, 4.28.

11. R_f 0.30 (Al_2O_3 plates, hexanes/ethyl acetate 3:2). $[\alpha]_D$ –142.1 (*c* 1.078, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87 (ddd, *J* = 0.8, 5.2, 8.0 Hz, 1H), 5.58 (dd, *J* = 4.8, 9.0 Hz, 1H), 3.82–3.75 (m, 1H), 3.68 (s, 3H), 3.40 (dt, *J* = 3.5, 6.1 Hz, 1H), 2.35 (*J* = 6.8 Hz, OH), 1.84 (d, *J* = 5.2 Hz, OH), 1.43 (ddd, *J* = 0.8, 6.0, 8.4 Hz, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.30-1.24 (m, 1H), 1.07 (dd, *J* = 0.8, 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 85.5, 84.0, 76.2, 71.4, 63.8, 52.0, 46.2, 20.4 (the signal for the metal carbonyls was not observed). FAB-HRMS: *m/z* 327.0160 (calcd. for $C_{12}H_{15}O_7Fe$ ($M+H^+$) *m/z* 327.0159).

Tricarbonyl [methyl (2*E*,4*E*,2*S*,5*R*)-6-oxo-2,4-hexadienoate]iron [(+)-1]. To a solution of (+)-**10** (1.0 g, 3.086 mmol) in THF (13 mL) was added distilled water (13 mL). Solid $NaIO_4$ (0.991 g, 4.6 mmol) was added to the clear yellow clear solution. The formation of a fine white precipitate was observed. The reaction mixture was stirred at room temperature for 1.5 h, at which time TLC monitoring indicated no remaining starting material. The reaction mixture was filtered through the filter-aid, and the filtrate was poured into brine. The aqueous layer was extracted several times with ethyl acetate, the organic layers were combined, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate 5:1) to afford (+)-**1** as a yellow oil (0.775 g, 90%, 2.76 mmol). The ^{1}H NMR spectral data for this product was identical to the literature spectral data.[3a]

Tricarbonyl [methyl (2*E*,4*E*,2*R*,5*S*)-6-oxo-2,4-hexadienoate]iron [(–)-1]. The glycol cleavage of (–)-**11** (1.0 g, 3.086 mmol) was carried out in a fashion similar to the preparation of (+)-**1** from (+)-**10** to give (–)-**1** (0.816 g, 95%) as a yellow oil. The ^{1}H NMR spectral data for this product was identical to the literature spectral data.[3a]

Acknowledgements

This work was supported by the National Science Foundation. High-resolution mass spectra were obtained at the University of Nebraska-Center for Mass Spectrometry.

References and Notes

1. (a) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465. (b) Bromfield, K. M.; Graden, H.; Hagverg, D. P.; Olsson, T.; Kann, N. *Chem. Comm.* **2007**, 3183. (c) Baba, Y.; Sata, G.; Nakao, S.; Iwata, C.; Tanaka, T.; Ibuka, T.; Ohishi, H.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 81. (d) Chen, M.-J.; Narkunan, K.; Liu, R.-S. *J. Org. Chem.* **1999**, *64*, 8311. (e) Roe, C.; Sandoe, E.; Stephenson, G. R.; Anson, C. E. *Tetrahedron Lett.* **2008**, *49*, 650. (f) Dehmel, F.; Schmalz, H.-G. *Org. Lett.* **2001**, *3*, 3579. (g) Ley, S. V.; Cleator, E.; Harter, J.; Hollowood, C. J. *Org. Biomol. Chem.* **2003**, 3263. (h) Franck-Neumann, M.; Geoffroy, P.; Hanss, D. *Tetrahedron Lett.* **2002**, *43*, 2277. (i) Kocienski, P.; Bell, R.; Bourque, E.; Christopher, J. A.; Cooksey, J.; Gunn, A.; Kuhl, A.; Li, Y. Uppal, S.; Yuen, J. *Pure Appl. Chem.* **2004**, *76*, 477. (j) Crevisy, C.; C.; Herbage, B.; Marrel, M.-L.; Toupet, L.; Gree, R. *Eur. J. Org. Chem.* **1998**, 1949.
2. (a) Monpert, A.; Martelli, J.; Grée, R.; Carrié, R. *Tetrahedron Lett.* **1981**, *22*, 1961. (b) Xu, M.; Tran, C. D. *J. Chromatography* **1991**, *543*, 233. (c) Roush, W. R.; Park, J. C. *Tetrahedron Lett.*, **1990**, *31*, 4707. (d) Howell, J. A. S.; Palin, M. G.; Jaouen, G.; Top, S.; El Hafa, H.; Cense, J. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1241. (e) Whitlock, H.W.; Markezich, R.L.; *J. Am. Chem. Soc.* **1971**, *93*, 5290.

3. (a) Laabassi, M.; Grée, R. *Tetrahedron Lett.* **1988**, *29*, 611 (b) Tao, C.; Donaldson, W. A. *J. Org. Chem.* **1993**, *58*, 2134. (c) Gigou, A.; Beaucourt, J.-P.; Lellouche, J.-P.; Grée, R. *Tetrahedron Lett.* **1991**, *32*, 635. (d) Nunn, K.; Mosset, P.; Grée, R.; Saalfrank, R. W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1188. (e) Laabassi, M.; Grée, R. *Tetrahedron Lett.* **1989**, *30*, 6683. (f) Laabassi, M.; Grée, R. *Bull. Soc. Chim. Fr.* **1992**, *129*, 47.
4. Godula, K.; Barmann, H.; Donaldson, W. A. *J. Org. Chem.* **2001**, *66*, 3590.
5. (a) Lukesh, J. M.; Donaldson, W. A. *Chem. Comm.* **2005**, 110. (b) Yun, Y. K.; Godula, K.; Cao, Y.; Donaldson, W. A. *J. Org. Chem.* **2003**, *68*, 901
6. (a) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447. (b) For asymmetric dihydroxylation of the ethyl ester of **6** see: Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570.
7. Two examples of diastereoselective complexation of acyclic dienes have been reported. Each of these reactions generates <50% complexed product. (a) Pearson, A. J.; Chang, K.; McConville, D. B.; Youngs, W. J. *Organometallics* **1994**, *13*, 4. (b) Tsai, M.-S.; Rao, U. N.; Shueh, P.-Y.; Yeh, M. C. P. *Organometallics* **2001**, *20*, 289.
8. (a) Djedaini, F.; Gree, D.; Martelli, J.; Gree, R.; Leroy, L.; Bolard, J.; Toupet, L. *Tetrahedron Lett.* **1989**, *30*, 3781. (b) Nakanishi, S.; Kumeat, K.; Nakanishi, J.-I.; Takata, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2097.
9. Tao, C.; Donaldson, W. A. *J. Org. Chem.* **1993**, *58*, 2134.
10. The crystallographic data for (+)-**10** has been deposited with the CCDC (CCDC 665758). This data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retreiving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB12 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.ccdc.cam.ac.uk.
11. For a complete list of structures and references see the Supplementary Material.
12. (a) Messager, P. J. C.; Toupet, L. *Acta Cryst. B* **1986**, *B42*, 371. (b) Xiao, N.; Wang, B.; Yin, J.; Xu, Q.; Tsumori, N.; Sun, J.; Chen, J. *Organometallics* **2004**, *23*, 257.
13. (a) Moorhoff, C. M. *Synlett* **1997**, 126. (b) Kobayashi, N.; Kuniyoshi, H.; Ishigami, K.; Watanabe, H. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2708.