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Expeditious and Practical Synthesis of Lycopene

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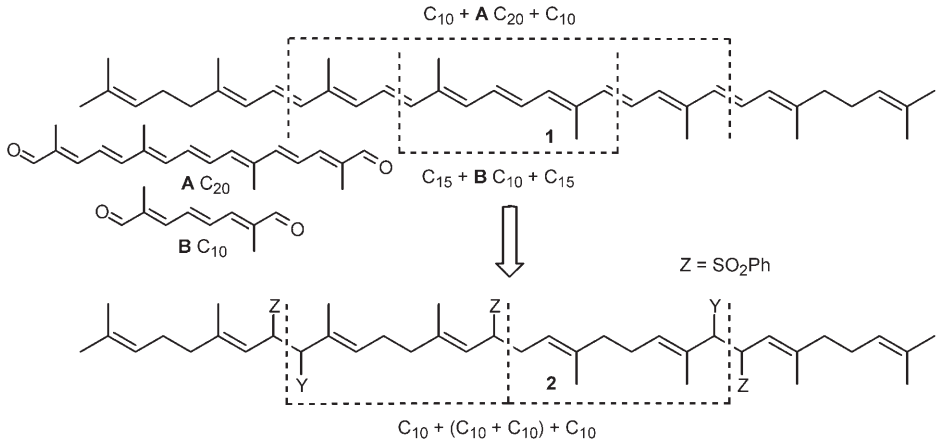
Abstract: Our lycopene synthesis highlights the expeditious assembly of the carbon skeleton by the use of a readily available ten-carbon unit, geraniol, rather than the original natural five-carbon building block, isopentenyl pyrophosphate. Furthermore, four oxidation steps by the enzyme desaturases to produce the conjugated carbon-carbon double bonds of lycopene are merged into one-pot double elimination reactions in our synthesis. These accomplished the highly efficient synthesis of all-(*E*)-lycopene from geraniol through a seven-step sequence in 51% overall yield.

Keywords: allylic oxidation; carotenoids; elimination; lycopene synthesis; olefination; sulfone chemistry

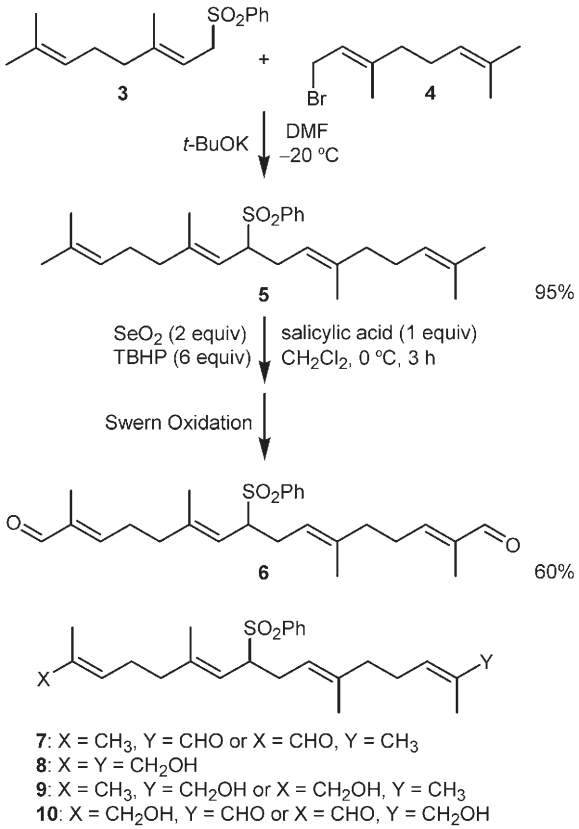
Nature utilizes the five-carbon building blocks of isopentenyl pyrophosphate and dimethylallyl pyrophosphate for the syntheses of more than 22,000 isoprenoid compounds.[1] The pinpoint controls by enzymes of the synthase, desaturase, and cyclase types make these biological processes highly efficient and selective. The biological functions of some of these isoprenoid compounds have been elucidated, and organic syntheses have been designed to produce a large quantity of these invaluable natural products for the purposes of medications and nutraceutical applications for human health. The carotenoid lycopene, a member of isoprenoid family and the key ingredient of tomato, is a strong antioxidant which relieves oxidative stresses.[2] It also shows a prophylactic effect on cancers of the prostate, breast, lung, and etc.[3] The intrinsic instability of the eleven conjugated carbon-carbon double bonds of lycopene under aerobic conditions did not allow an easy *in vitro* assembly of this biologically important natural product. Chemists have been challenged by the total synthesis of lycopene (**1**) for more than a half century, in which the main concern was how to generate the conjugated carbon-carbon double bonds.[4] The Wittig reaction has been mostly used for that purpose even though there had been an early report utilizing acetylide chemistry.[5] Two representative disconnections of lycopene (**1**) based on the available Wittig salts and the dialdehyde building blocks are shown in Scheme 1 as dotted lines.[4,6] Control of the *E*-configuration in the carbon-carbon double bond formation is a very important but difficult issue in the preparation and the reaction of Wittig salts.[7] Furthermore, non-trivial and tedious steps for the preparations of the C_{20} all-(*E*)-crocetin-dialdehyde (**A**)[4] or the C_{10} all-(*E*)-2,7-dimethyl-2,4,6-octatrienedial (**B**)[8] demanded a more efficient and practical organic synthetic pathway to lycopene (**1**).

We have recently demonstrated the general and systematic synthesis of carotenoid compounds utilizing sulfone chemistry, in which the C_5 building blocks were designed and used for the chain-extension as a biomimetic approach.[9] This sulfone chemistry is ideally suited for carotenoid synthesis by providing an *E*-configuration of the carbon-carbon double bonds.[10] It would be definitely more efficient to use C_{10} building blocks than the shorter C_5 units in the chain-extension process. We thus envisioned that lycopene (**1**) might be more efficiently assembled by the use of the readily available C_{10} compound, geraniol, in proviso that we were able to efficiently make the C_{40} compound **2**, in which the elimination of the Z and Y functional groups would expeditiously produce lycopene (**1**) in one pot (Scheme 1).

Our research commenced with the synthesis of the novel C_{20} dialdehyde **6** as the key compound (Scheme 2). Geraniol was brominated quantitatively with PBr_3 to geranyl bromide **4**, which was sulfonylated with $NaSO_2Ph$ in DMF to geranyl sulfone **3** in 96% yield. These two geraniol derivatives coupled at −20 °C in DMF by *t*-BuOK to produce the C_{20} sulfone **5** in 95% yield. The double allylic oxidation reaction of **5** would produce the C_{20} dialdehyde **6**. Conditions using SeO_2 as an oxidant have been studied in order to secure the *E*-configuration of C=C bonds at the 2



Scheme 1. General disconnections of lycopene (**1**) utilizing the Wittig reaction and our synthetic plan by quadruple use of the geraniol derivatives.

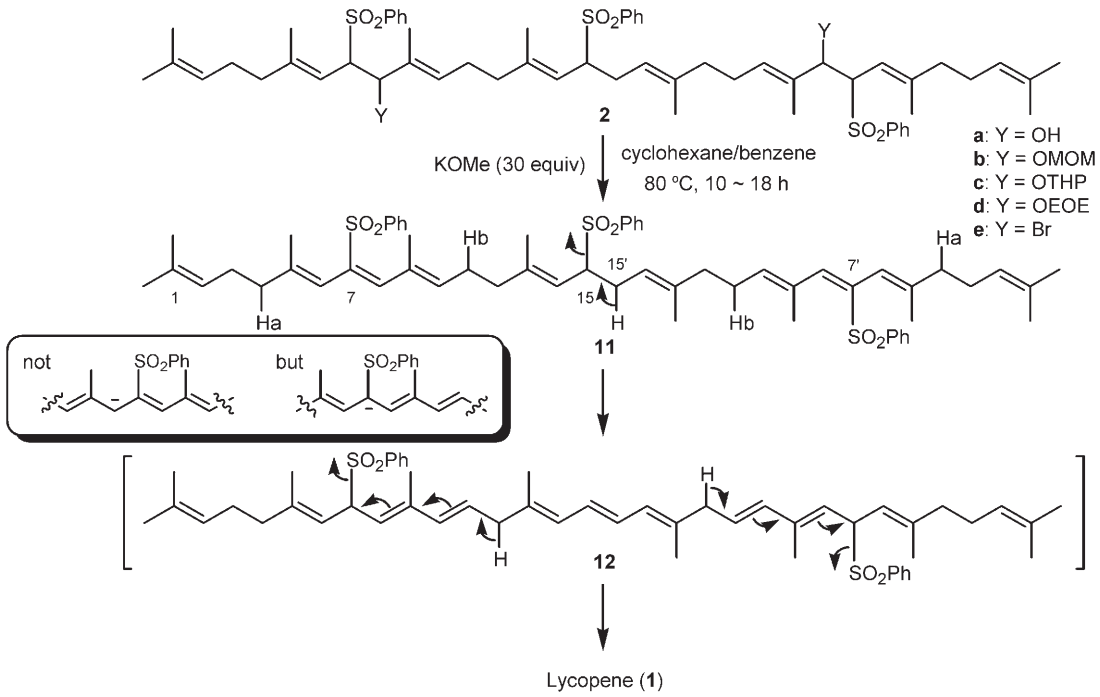


Scheme 2. Expeditious preparation of the novel C_{20} dialdehyde **6**.

and 2' positions of the dialdehyde.[11] The result of our preliminary study on the double allylic oxidation of **5** was, however, rather disappointing. The catalytic use of SeO_2 provided a large amount of the mono-alcohol **9** (see the structures in Scheme 2) regardless of the amount of *tert*-butyl hydrogen peroxide (TBHP, 70% aqueous solution) used. The oxidation utilizing two equivalents or more of SeO_2 was still slow and it took at least 24 h at room temperature to convert the intermediate oxidation products **7**–**10** to the desired dialdehyde **6**, in which the yield of **6** never reached above 20% and significant amounts of highly polar, unidentifiable side products were also obtained.

A major breakthrough for the allylic oxidation was found in an effort to optimize the formation of the diol **8** instead of the dialdehyde **6** by the use of excess oxidizing agents at 0 °C. Anhydrous TBHP[12] together with one equivalent of salicylic acid was used to speed up the oxidation reaction. The optimized conditions for the diol **8** (48% yield) were to use 2 equivalents of SeO_2 and 6 equivalents of TBHP at 0 °C for 3 h, in which the mono-alcohol **9** (28% yield) and the hydroxy-aldehyde **10** (12% yield) were also obtained. Since the diol **8** and the hydroxy-aldehyde **10** would lead to the same dialdehyde **6** after Swern oxidation, the two-step sequence of SeO_2-mediated allylic oxidation and Swern oxidation was conducted for the compound **5** to give the desired dialdehyde **6** in 60% yield (Scheme 2).

The second coupling reaction of the dialdehyde **6** with two equivalents of geranyl sulfone **3** produced the required C_{40} skeleton **2a** (Y = OH in Scheme 3) for lycopene synthesis in 93% yield. This coupling reaction was conducted at −78 °C with *n*-BuLi as a base to prevent the reverse reaction. The hydroxy groups of **2a** were then protected before the double elimination reactions.[13–15] Since the protection should be carried out under acidic conditions, the methoxymethyl (MOM) groups in **2b**, the tetrahydropyranyl (THP) groups in **2c**, and 1-ethoxyethyl (EOE) groups in **2d** can be selected as protecting groups. The hydroxy groups can also be transformed to Brs in **2e**. The elimination reaction proceeded smoothly with KOMe in a mixed solvent of cyclohexane and benzene at 80 °C. The reaction seemed to be completed within a



Scheme 3. The elimination reaction of **2** to produce lycopene (**1**).

few hours, but enough time (10–18 h) was given to allow the possible *Z* to *E* isomerization of the carbon-carbon double bonds. The yields of the protection (**2b**–**2e**) and the elimination reactions for each protecting group to produce all-(*E*)-lycopene (**1**) are listed in Table 1. The formation of 9-(*Z*)-lycopene (less than 15% yield) was confirmed in the crude product by ^{1}H NMR,[6] but this was easily removed by recrystallization from THF and MeOH to give all-(*E*)-lycopene.

The mechanism of the elimination reaction is delineated in Scheme 3. The initial step is the elimination of the protected hydroxy groups Y by deprotonation at the α-positions to the benzenesulfonyl groups to produce the intermediate compound **11**, which was isolated in 85% yield from **2e** under the carefully controlled conditions using 5 equivalents of KOMe in CH_2Cl_2 at 0 °C for 1 h. The compound **12** was then presumably formed after the dehydrosulfonylation at the 15 and 15' positions and the double bond migrations arising from the abstraction of the more acidic H_b atoms than the H_a atoms due to the anion-stabilizing effect of the benzenesulfonyl groups at the 7 and 7' positions. Final dehydrosulfonylation reactions provided the fully conjugated eleven carbon-carbon double bonds of lycopene (**1**).

Table 1. Protection and elimination reactions of **2a** to produce all-(*E*)-lycopene (**1**).

Entry	**2**	Y	Yield of **2** [%]	Yield of **1** [%][a]	Purified **1** [%][b]
1	**2a**	OH	93[c]	-	-
2	**2b**	OMOM	91[c]	74	56
3	**2c**	OTHP	98[c]	100	79
4	**2d**	OEOE	95[c]	73	52
5	**2e**	Br	96[a]	76	57

[a] Crude yield.
[b] Recrystallization yield from MeOH and THF.
[c] Purification yield by SiO_2 flash column chromatography.

In conclusion, we have demonstrated the use of C_{10} geraniol in the expeditious chain-extension for the synthesis of the carotenoid, lycopene. The initial tail-to-tail coupling of the geranyl derivatives formed the central structure of the carotenoids. The double allylic oxidation of the C_{20} coupling product enabled the second coupling reactions with two equivalents of geranyl sulfones, and thereby established the required C_{40} skeleton for lycopene. The benzenesulfonyl and protected hydroxy functional groups in the coupling product are ideally placed for double elimination reactions to give rise to the fully conjugated carbon-carbon double bonds of lycopene in one pot. All-(*E*)-lycopene (**1**) was obtained from geraniol through the total seven-step sequence in 51% overall yield based on the total amount of geraniol used (see synthetic Scheme in the supporting information). This is the most efficient, practical, and expeditious synthetic method for lycopene (**1**). The process utilizing the coupling reaction with the novel C_{20} dialdehyde compound **6** and the double elimination reactions can be

applied to the expeditious assembly of other carotenoid natural products.

Experimental Section

General Experimental Methods

^{1}H (300 MHz or 400 MHz) and ^{13}C NMR (75.5 MHz or 100 MHz) spectra were recorded in $CDCl_3$ with Me_4Si ($\delta =$ 0 ppm) as an internal standard. Solvents for extraction and chromatography were reagent grade and used as received. Column chromatography was performed by the method of Still using silica gel 60, 230–400 mesh ASTM supplied by Merck. Solvents used as reaction media were dried over pre-dried molecular sieve (5 Å) in a microwave oven. All reactions were performed under dry argon in oven-dried glassware, except for those reactions with H_2O as a solvent, which were run in air.

Double Allylic Oxidation: 8-Benzenesulfonyl-2,6,11,15-tetramethylhexadeca-2,6,10,14-tetraenedial (6)

To a stirred suspension of SeO_2 (3.48 g, 31.34 mmol, 2 equivs.) and salicylic acid (2.20 g, 15.67 mmol, 1 equiv.) in MeCN (50 mL) at 0 °C was added a 3.0 M solution of TBHP in toluene (31.3 mL, 94.02 mmol, 6 equivs.). The mixture was stirred at that temperature for 1.5 h, and a solution of **5** (6.50 g, 15.67 mmol, 1 equiv.) in MeCN (10 mL) was slowly added for 10 min. The reaction mixture was stirred at 0 °C for 3 h, and diluted with EtOAc (50 mL). The EtOAc solution was washed with 10% NaOH solution (20 mL × 3) and then saturated $Na_2S_2O_3$ solution (20 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude allylic oxidation product; yield: 7.50 g.

Swern Oxidation

To a stirred solution of DMSO (5.77 g, 73.87 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added oxalyl chloride (3.28 mL, 36.93 mmol). The mixture was stirred for 5 min, and a solution of the above allylic oxidation product (7.50 g) in CH_2Cl_2 (10 mL) was added. The resulting mixture was stirred at −78 °C for 15 min, and Et_3N (23 mL, 167.9 mmol) was added. Stirring for 5 min at that temperature, the mixture was then warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with 1 M HCl solution (20 mL × 3) and then H_2O (20 mL × 2), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the dialdehyde **6** (yield: 4.10 g, 9.26 mmol; 60%), together with the mono-aldehyde **7** (yield: 1.20 g, 2.71 mmol, 17%).

Data for **6**: ^{1}H NMR: $\delta = 1.27$ (d, $J = 1.3$ Hz, 3H), 1.63 (s, 3H), 1.72 (d, $J = 1.1$ Hz, 3H), 1.73 (d, $J = 0.9$ Hz, 3H), 2.15 (t, $J = 7.4$ Hz, 4H), 2.30–2.46 (m, 5H), 2.86 (ddd, $J = 14.4$, 7.2, 3.7 Hz, 1H), 3.77 (ddd, $J = 10.3$, 10.3, 3.7 Hz, 1H), 5.02 (dt, $J_d = 1.1$, $J_t = 7.4$ Hz, 1H), 5.06 (dd, $J = 10.3$, 1.2 Hz, 1H), 6.39 (dt, $J_d = 1.3$, $J_t = 7.0$ Hz, 1H), 6.41 (dt, $J_d = 1.3$, $J_t =$ 7.2 Hz, 1H), 7.48–7.68 (m, 3H), 7.81–7.87 (m, 2H), 9.36 (s, 1H), 9.38 (s, 1H) ppm; ^{13}C NMR: $\delta = 9.2$, 9.2, 16.2, 16.4, 26.7, 26.9, 27.1, 37.9, 38.0, 64.4, 118.0, 119.7, 128.8, 128.9, 133.5, 137.2, 137.9, 139.4, 139.6, 143.8, 152.8, 153.7, 194.8, 195.0; IR (KBr): $\nu = 2944$, 1686, 1447, 1303, 1145, 1084 cm^{-1}; HR-MS (FAB$^+$): $m/z = 443.2248$, calcd. for $C_{26}H_{35}O_4S$: 443.2256.

Data for **7**: ^{1}H NMR: $\delta = 1.16$ (d, $J = 1.3$ Hz, 3H), 1.59 (s, 3H), 1.66 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 1.94 (br s, 4H), 2.15 (dd, $J = 7.7$, 6.8 Hz, 2H), 2.32–2.48 (m, 3H), 2.83–2.96 (m, 1H), 3.73 (ddd, $J = 10.5$, 10.3, 3.5 Hz, 1H), 4.93–5.14 (m, 3H), 6.42 (t, $J = 5.5$ Hz, 1H), 7.46–7.70 (m, 3H), 7.76–7.92 (m, 2H), 9.35 (s, 1H).

Coupling Reaction: 8,16,25-Tris(benzenesulfonyl)-2,6,10,14,19,23,27,31-octamethyldotriaconta-2,6,10,14,18,22,26,30-octaene-9,24-diol (2a)

To a stirred solution of geranyl sulfone **3** (2.41 g, 8.65 mmol, 2.2 equivs.) in THF (30 mL) at −78 °C was added 1.6 M solution of *n*-BuLi in hexane (6.14 mL, 9.83 mmol, 2.5 equivs.). The resulting orange solution was stirred at that temperature for 1 h, and a solution of the dialdehyde **6** (1.74 g, 3.93 mmol, 1 equiv.) in THF (10 mL) was added for 5 min. The resulting mixture was stirred at −78 °C for 1 h, and quenched with 1 M HCl solution (10 mL). The mixture was warmed to room temperature, extracted with EtOAc (30 mL × 2), washed with 1 M HCl solution (20 mL × 2), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give **2a**; yield: 3.65 g (3.66 mmol, 93%). ^{1}H NMR: $\delta = 1.07$ (s, 3H), 1.12 (s, 3H), 1.19 (d, $J = 1.5$ Hz, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 1.56 (s, 6H), 1.58 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 1.80–2.07 (m, 16H), 2.24–2.40 (m, 1H), 2.77–2.90 (m, 1H), 3.71 (br t, $J =$ 9.5 Hz, 1H), 3.93 (dd, $J = 9.1$, 7.0 Hz, 1H), 3.96 (dd, $J = 9.1$, 6.6 Hz, 1H), 4.59 (d, $J = 9.2$ Hz, 1H), 4.60 (d, $J = 8.9$ Hz, 1H), 4.68 (d, $J = 10.1$ Hz, 1H), 4.72 (d, $J = 9.0$ Hz, 1H), 4.90–5.05 (m, 5H), 5.30–5.43 (m, 2H), 7.45–7.68 (m, 9H), 7.78–7.90 (m, 6H); ^{13}C NMR: $\delta = 10.5$, 10.5, 13.0, 15.8, 15.9, 16.2, 16.4, 16.5, 17.6, 25.7, 25.7, 25.8, 26.0, 26.2, 26.2, 26.5, 39.0, 39.5, 39.8, 64.7, 67.7, 68.4, 72.4, 76.4, 112.0, 114.2, 117.1, 119.0, 123.3, 123.6, 128.7, 128.7, 128.8, 129.0, 129.1, 129.2, 129.3, 129.5, 130.1, 131.9, 132.0, 132.0, 133.1, 133.4, 133.6, 133.7, 133.9, 137.4, 138.1, 144.4, 144.5, 144.7; IR (KBr): $\nu =$ 3497, 2930, 1447, 1300, 1143, 1083 cm^{-1}; HR-MS (FAB$^+$): $m/z = 697.4645$, calcd. for $C_{46}H_{65}O_3S$ [$C_{58}H_{79}O_8S_3 - 2(C_6H_6SO_2) - H_2O$]: 697.4654.

Double Elimination Reactions to Lycopene (1)

From 2c: To a stirred solution of **2c** (0.44 g, 0.38 mmol) in cyclohexane (20 mL) and benzene (10 mL) was added KOMe (0.79 g, 11.3 mmol). The mixture was heated to 70~80 °C for 13 h, cooled to room temperature, and 1 M HCl (20 mL) was carefully added. The reaction mixture was extracted with a 2:1 (v:v) solution (30 mL) of hexane and benzene, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting red solid was diluted with hexane (50 mL) and washed with CH_3CN (10 mL × 3). The hexane layer was concentrated under reduced pressure to give lycopene **1**; crude yield: 0.20 g (0.37 mmol, 97%), which presumably contained a small amount of 9-(*Z*)

isomers. The crude product was purified by recrystallization from MeOH and THF to provide all (*E*)-lycopene **1** as dark red crystals; yield: 0.16 g (0.29 mmol, 79%).

Supporting Information

Experimental procedures for **1** (from **2b**, **2d**, **2e**), **2b**, **2c**, **2d**, **2e**, **5**, **8**, and **11**, and $^{1}H/^{13}C$ spectra for all compounds.

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References

[1] D. E. Cane, in: *Comprehensive Natural Products Chemistry*, Vol. 2, (Eds.: D. Barton, K. Nakanishi), Elsevier, Oxford, **1999**.
[2] A. V. Rao, L. G. Rao, *Pharmacol. Res.* **2007**, *55*, 207–216.
[3] O. Kucuk, *Cancer Met. Rev.* **2002**, *21*, 189–197.
[4] O. Isler, H. Gutmann, H. Lindlar, M. Montavon, R. Rüegg, G. Ryser, P. Zeller, *Helv. Chim. Acta* **1956**, *39*, 463–473.
[5] P. Karrer, C. H. Eugster, E. Tobler, *Helv. Chim. Acta* **1950**, *33*, 1349–1352.
[6] U. Hengartner, K. Bernhard, K. Meyer, G. Englert, E. Glinz, *Helv. Chim. Acta* **1992**, *75*, 1848–1865.
[7] H. Ernst, *Pure Appl. Chem.* **2002**, *74*, 1369–1382.
[8] H. Pomer, *Angew. Chem.* **1977**, *89*, 437–443.
[9] M. Ji, H. Choi, M. Park, M. Kee, Y. C. Jeong, S. Koo, *Angew. Chem. Int. Ed.* **2001**, *40*, 3627–3629.
[10] M. H. Ji, H. Choi, Y. C. Jeong, J. Jin, W. Baik, S. Lee, J. S. Kim, M. Park, S. Koo, *Helv. Chim. Acta* **2003**, *86*, 2620–2628.
[11] M. A. Umbreit, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.
[12] J. G. Hill, B. E. Rossiter, K. B. Sharpless, *J. Org. Chem.* **1983**, *48*, 3607–3608.
[13] J. Otera, H. Misawa, T. Mandai, T. Onishi, S. Suzuki, Y. Fujita, *Chem. Lett.* **1985**, 1883–1886.
[14] J. Otera, H. Misawa, T. Onishi, S. Suzuki, Y. Fujita, *J. Org. Chem.* **1986**, *51*, 3834–3838.
[15] S. K. Guha, S. Koo, *J. Org. Chem.* **2005**, *70*, 9662–9665.

