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Tetrahedron Letters 48 (2007) 4855–4859
Tetrahedron Letters

Highly enantioselective preparation of tricyclo[4.4.0.0^{5,7}]decene derivatives via catalytic asymmetric intramolecular cyclopropanation reactions of α-diazo-β-keto esters

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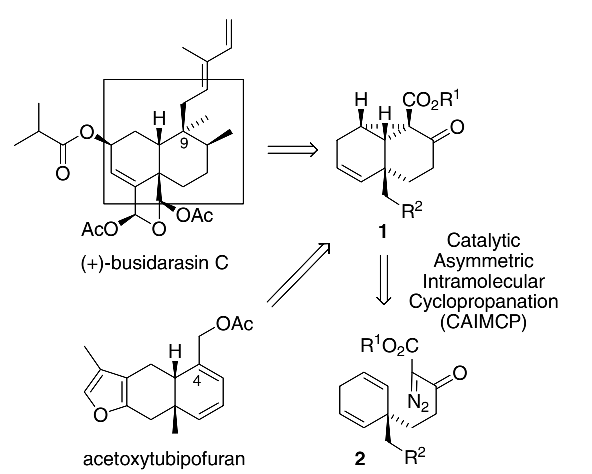
Received 12 April 2007; revised 2 May 2007; accepted 10 May 2007
Available online 16 May 2007

Abstract—The enantioselective preparation of the tricyclo[4.4.0.0^{5,7}]dec-2-ene derivatives via the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) reactions of α-diazo-β-keto esters with excellent ee (95–98% ee) is described. The chiral building blocks reported herein would be versatile intermediates for enantioselective natural products synthesis.

Convergent total synthesis of bioactive natural products would be facilitated by having suitable chiral precursors and, hence, preparation of new chiral building blocks is important in synthetic organic chemistry. Since the number of commercially available chiral compounds is limited, chiral building blocks prepared via asymmetric synthesis are important, and catalytic asymmetric synthesis would be ideal for this purpose because of its efficiency. We have prepared new chiral building blocks via biocatalysts[1] as well as artificial catalysts,[2,3] and have disclosed their applications to the enantioselective total synthesis of bioactive natural products.[3d,f,4] We herein report the highly enantioselective preparation of tricyclo[4.4.0.0^{5,7}]decene derivatives via the catalytic asymmetric intramolecular cyclopropanation (CAIMCP) reactions of α-diazo-β-keto esters.

Many polycyclic natural products incorporate a *cis*-dehydrodecalin skeleton and, thus, preparation of a chiral *cis*-dehydrodecalin derivative or its precursor would accelerate their enantioselective total syntheses. Indeed, we have reported the highly enantioselective CAIMCP reactions of α-diazo-β-keto sulfones[3a,b] providing tricyclo[4.4.0.0^{5,7}]decene derivatives, one of which was successfully converted to a *cis*-dehydrodecalin derivative, leading to the enantioselective total synthesis of (+)-digitoxigenin.[4c] However, other natural products, exemplified by (+)-busidarasin C[5] and acetoxytubipofuran[6] (Scheme 1), possess a *cis*-dehydrodecalin core including substituents at C9 of (+)-busidarasin C and at C4 of acetoxytubipofuran, prompting us to prepare new chiral tricyclo[4.4.0.0^{5,7}]decene derivatives **1** including an ester group as the one-carbon unit.[7] Compound **1** would not only be a potential synthetic intermediate for the natural products in Scheme 1, but would also be for other natural products because the functional groups incorporated in **1**, alkene, cyclopropane, and β-keto ester would allow further transformations.



Scheme 1.

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doi:10.1016/j.tetlet.2007.05.046

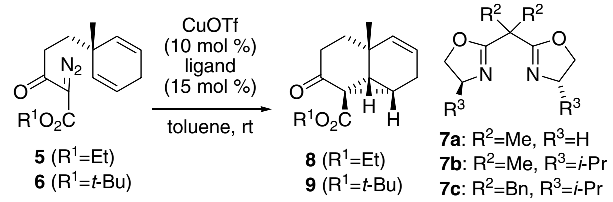
As reported earlier by us[3a] and others,[8] the enantioselectivity in the CAIMCP reactions of α-diazo-β-keto esters which generate carbocycle-fused cyclopropanes has been unsatisfactory (up to 56% ee[3a]) for synthetic purposes. However, our recent studies revealed that the enantioselectivity of these CAIMCP reactions depends on ester structure.[3h] Consequently, we reexamined the CAIMCP reactions of α-diazo-β-keto esters, starting with the studies of the CAIMCP reactions of **5** and **6** (Scheme 2) which were readily prepared from the reported **3**.[3e]

The carboxylic acid obtained from **3** was reacted with CDI to form the corresponding acylimidazolide, which was reacted in a 'one-pot' procedure with the magnesium salt of mono-ethyl malonate to provide **4** (96%, 3 steps),[9] followed by a diazo transfer reaction with *p*-toluenesulfonylazide to afford **5** (78%). Preparation of **6** was initiated with the hydrolysis of **4**, and the resultant carboxylic acid was condensed with *tert*-butyl alcohol by DCC, followed by a diazotransfer reaction to afford **6** (37%, 3 steps).

The CAIMCP reaction of **5** was carried out under the conditions optimized for the reactions of α-diazo-β-keto sulfones (Table 1),[3a] providing **8** in 66% yield with 60% ee using ligand **7b** and in 34% yield with 69% ee using ligand **7c**. Hence, we expected that the enantioselectivity of the CAIMCP reaction of **6** would be higher because **6** possessed a bulky *t*-butyl ester group which would increase the enantioselectivity by the analogy of the CAIMCP reaction of α-diazo-β-keto sulfones.[3a] As predicted, the CAIMCP reaction of **6** with ligand **7b** produced **9** in 78% with 95% ee, although the reaction with **7c** proceeded more slowly, affording **9** in 64% yield with excellent ee (98% ee).[10]

The absolute configuration of **9** was determined as shown in Table 1 by X-ray crystallographic analysis of its derivative,[11] and the chemical correlation between **8** and **9**[12] elucidated the absolute configuration of **8** as shown in Table 1. Compound **9** would be a potential intermediate for the synthesis of acetoxytubipofuran.

Table 1. The CAIMCP reactions of **5** and **6**



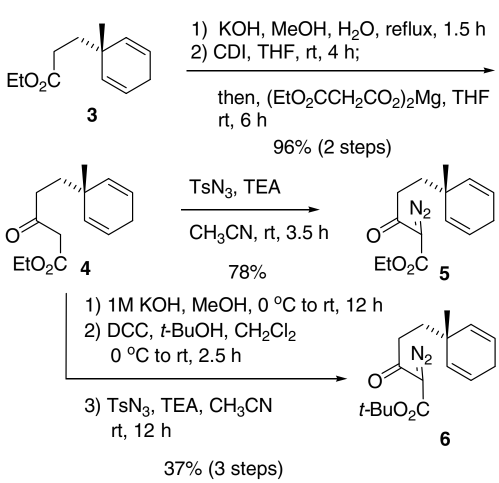
Entry	R^1	Ligand	Time (h)	Yield[a] (%)	ee (%)
1	Et	**7b**	8	66	60[c]
2	Et	**7c**	18.5	34[b]	69[c]
3	*t*-Bu	**7b**	4.5	78	95[d]
4	*t*-Bu	**7c**	26.5	64	98[d]

[a] Isolated yields.
[b] Some structurally unidentified products decreased the yield.
[c] ee determined by HPLC of the *p*-bromobenzoate corresponding to **9′**.[11] DAICEL CHIRALPAK AS-H (0.46 cm $\varphi \times 25$ cm; hexane/2-propanol = 29:1; flow rate = 0.4 mL/min); retention time: 17.5 min for the minor product, 20.6 min for the major product.
[d] ee determined by HPLC of **9′**. DAICEL CHIRALPAK AS-H (0.46 cm $\varphi \times 25$ cm; hexane/2-propanol = 49:1; flow rate = 0.4 mL/min); retention time: 13.3 min for the minor product, 15.5 min for the major product.

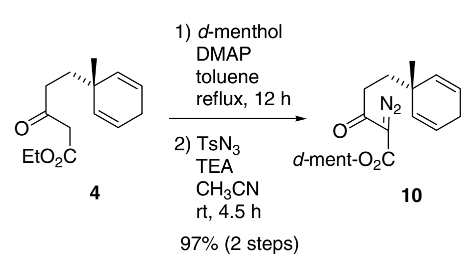
We then carried out the diastereoselective IMCP reaction of **10** to further investigate the relationship between the ester part in the substrate and the diastereoselectivity (Scheme 3). The α-diazo-β-keto ester **10** was prepared starting from **4**. Thus, DMAP catalyzed transesterification of **4** with *d*-menthol,[13] followed by the diazotransfer reaction to afford the *d*-menthyl ester **10** (97%, 2 steps).

The IMCP reaction of **10** was carried out under the same conditions as those listed in Table 1 (Table 2). The IMCP reaction of **10** with achiral ligand **7a** showed no diastereoselectivity (entry 1). Hence, we next examined the IMCP reaction of **10** with chiral ligand **7b**, producing **11** in 67% with 60% de (entry 2), but use of ligand **7c** slightly decreased the diastereoselectivity (entry 3, 35%, 50% de).

Entries 1–3 in Table 2 clearly indicate that the IMCP reactions of **10** with ligand **7b** or ligand **7c** were the chiral ligand-controlled reactions. Consequently, the IMCP reactions of **10** with ligands *ent*-**7b** or *ent*-**7c** were also carried out, resulting in formation of *ent*-**11** as the major product in either 74% yield (−89% de) or 34% yield (−85% de), respectively. As expected, the diastereoselectivities of the IMCP reactions using ligand *ent*-**7b** or ligand *ent*-**7c** (entries 4 and 5) were reversed. Interestingly, either ligand *ent*-**7b** or *ent*-**7c** was more effective

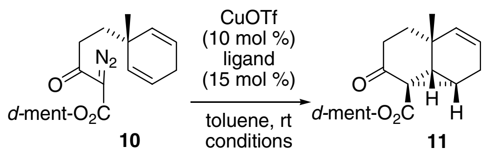


Scheme 2.



Scheme 3.

Table 2. The intramolecular cyclopropanation of **10**



Entry	Ligand	Temperature (°C)	Time (h)	Yield[a] (%)	de[b] (%)
1	**7a**	rt, 50	2, 10[c]	74 (91% conv)	0
2	**7b**	rt	15.5	67	60
3	**7c**	rt	25	35	50
4	*ent*-**7b**	rt	33	74	−89
5	*ent*-**7c**	rt	10.5	34	−85

[a] Isolated yields.
[b] de determined by 600 MHz ^{1}H NMR.
[c] Time at the corresponding reaction temperature.

than ligand **7b** or **7c**. Although the quantitative analysis of the difference between these results requires theoretical calculations, the results in entries 2-5 could be explained by the diastereomeric matching or mismatching between the chiral auxiliary in **10** and the chiral ligand in the transition state.[14]

The structure of *ent*-**11** obtained in entry 4 was elucidated by X-ray crystallographic analysis (Fig. 1).[15] This result indicated that the outcome of the enantioselectivity in the reactions of **5**, **6**, and **10** would be well explained by the model shown in Figure 2. The model was almost similar to that reported previously.[3a] The cyclopropanation reactions of **5**, **6**, and **10** are thought to occur preferentially at the *re*-face (defined by the Cu═C–C arrangement) of the chiral catalyst–carbene complexes, because steric hindrance will be encountered during cyclopropanation reactions at the *si*-face. That is, when the alkene approaches from the *si*-face, the resultant pyramidal conformation of the carbene C atom in the transition state means that the ester group will interact unfavorably with the isopropyl group. By contrast, the reaction at the *re*-face would be preferred because the unfavorable interaction of the isopropyl group with the ester group would be negligible in the transition state model depicted in Figure 2. For the reason described above, the excellent enantioselectivity would be observed in the reaction of the bulky *tert*-butyl ester **6**.

We finally examined the CAIMCP reaction of **16** to prepare **17**, which would be a potential chiral building

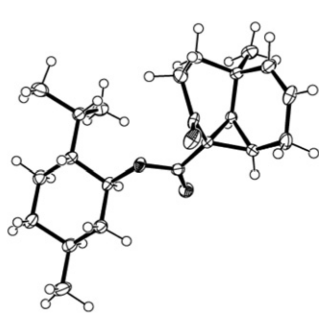


Figure 1.

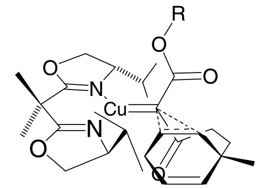
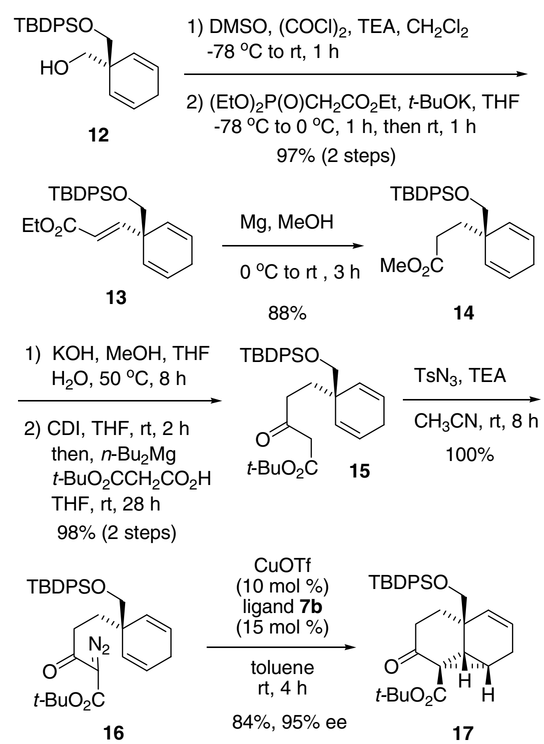


Figure 2.

block for (+)-busidarasin C. Preparation of **16** started from **12** (Scheme 4). That is, Swern oxidation of **12**, Horner–Wadsworth–Emmons reaction with triethylphosphonoacetate (97%, 2 steps), and reduction of the resultant unsaturated ester with magnesium in methanol afforded methyl ester **14** (88%). Conversion of **14** to **15** was successfully carried out using the modified Masamune's method (98%, 2 steps),[16] followed by a diazotransfer reaction of **15** to produce **16** in quantitative yield.

An oxygen atom is known to react with a carbene–metal complex to form an ylide, thereby resulting in the decreased yield of cyclopropanes.[17] However, the CAIMCP reaction of **16** fortunately afforded **17** with high yield and excellent ee (84%, 95% ee), proving that this reaction was applicable to a substrate possessing a TBDPS-protected hydroxyl group in **16**. The structure of **17** was fully characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra, and its absolute configuration was confirmed by converting it to the identical compound which had been derived from **9**.[12]



Scheme 4.

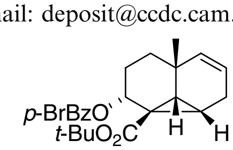
In conclusion, the tricyclo[4.4.0.0^{5,7}]dec-2-ene derivatives **9** and **17** have been synthesized with excellent ee (95–98% ee). To the best of our knowledge, this is the first example of preparing the tricyclo[4.4.0.0^{5,7}]dec-2-ene system via the CAIMCP reaction of the α-diazo-β-keto ester. The chiral cyclopropanes **9** and **17** would be versatile intermediates for the enantioselective natural product syntheses, including preparation of (+)-busidarasin C and acetoxytubipofuran.

Acknowledgments

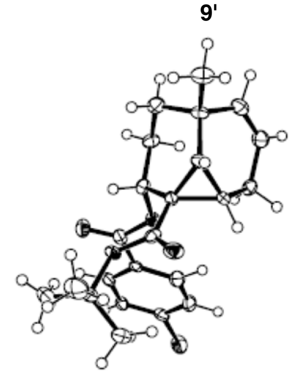
This work was financially supported in part by a Waseda University Grant for Special Research Projects and a Grant-in-Aid for Scientific Research on Priority Areas (Creation of Biologically Functional Molecules (No. 17035082)) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We are also indebted to 21COE 'Practical Nano-Chemistry'.

References and notes

1. (a) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239–7243; (b) Watanabe, H.; Iwamoto, M.; Nakada, M. *J. Org. Chem.* **2005**, *70*, 4652–4658; (c) Noguchi, N.; Nakada, M. *Org. Lett.* **2006**, *8*, 2039–2042.
2. (a) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140–1141; (b) Suzuki, T.; Kinoshita, A.; Kawada, H.; Nakada, M. *Synlett* **2003**, 570–572; (c) Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977–2980; (d) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252–255.
3. (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860–2861; (b) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007–9011; (c) Sawada, T.; Nakada, M. *Adv. Synth. Catal.* **2005**, *347*, 1527–1532; (d) Miyamoto, H.; Iwamoto, M.; Nakada, M. *Heterocycles* **2005**, *66*, 61–68; (e) Abe, M.; Nakada, M. *Tetrahedron Lett.* **2006**, *47*, 6347–6351; (f) Takeda, H.; Watanabe, H.; Nakada, M. *Tetrahedron* **2006**, *62*, 8054–8063; (g) Takeda, H.; Nakada, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2896–2906; (h) Takeda, H.; Honma, M.; Ida, R.; Sawada, T.; Nakada, M. *Synlett* **2007**, 579–582.
4. (a) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897–4900; (b) Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359–362; (c) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2007**, *48*, 1541–1544; (d) Inoue, M.; Nakada, M. *J. Am. Chem. Soc.* **2007**, *129*, 4164–4165.
5. Hayashi, K.-I.; Nakanishi, Y.; Bastow, K. F.; Cragg, G.; Nozaki, H.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 345–348.
6. Iguchi, K.; Mori, K.; Suzuki, M.; Takahashi, H.; Yamada, Y. *Chem. Lett.* **1986**, 1789–1790.
7. Total synthesis of *cis*-clerodane diterpenoides, see: (a) Tokoroyama, T. *Synthesis* **2000**, 611–633, and references cited therein; (b) Kato, M.; Kosugi, H.; Ichiyanagi, T.; Hagiwara, H.; Kodaira, A.; Kusakari, T.; Suzuki, T.; Ando, M.; Lee, J.; Drechsel, P.; Vogler, B. *Tetrahedron* **2001**, *57*, 8243–8256; (c) Liu, H.-J.; Ho, Y.-L.; Wu, J.-D.; Shia, K.-S. *Synlett* **2001**, 1805–1807; (d) Nakatani, M.; Nakamura, M.; Suzuki, A.; Fuchikami, T.; Inoue, M.; Katoh, T. *ARKIVOC* **2003**, *8*, 45–57; (e) Ly, T. W.; Liao, J.-H.; Shia, K.-S.; Liu, H.-J. *Synthesis* **2004**, 271–275.
8. (a) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969–6972; (b) He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307–13314; (c) Mühler, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093–1111.
9. Brooks, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72–74, and references cited therein.
10. The experimental procedure for the IMCP reaction of **6**: A toluene azeotroped $[CuOTf]_2{\cdot}C_6H_5CH_3$ (24.1 mg; 0.0465 mmol, 10 mol % as CuOTf) was placed in a dried flask (20 mL) and to this flask was added a solution of toluene azeotroped ligand **7b** (37.2 mg, 0.140 mmol, 15 mol %) in toluene (7.7 mL) via a cannula. The mixture was stirred at room temperature for 0.5 h and then to the light blue solution was added a solution of toluene azeotroped **6** (0.273 g, 0.930 mmol) in toluene (10.8 mL) via a cannula. The reaction mixture was stirred at room temperature for 4.5 h, quenched with aqueous NH_4OH solution (5.0 mL) and saturated aqueous NH_4Cl solution (2.5 mL), and extracted with ether (15 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/AcOEt = 100:1) to afford **9** (0.192 g, 78%, 95% ee) as a white solid: mp = 74 °C (hexane); $[\alpha]_D^{24}$ +181.7 (*c* 0.98, $CHCl_3$); IR (KBr): 2926, 1717, 1693, 1338, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.54$ (dddd, $J = 10.5$, 3.5, 3.5, 0.7 Hz, 1H), 5.18 (dddd, $J = 10.5$, 1.2, 1.2, 1.2 Hz, 1H), 2.42 (ddd, $J = 19.8$, 2.9, 2.9 Hz, 1H), 2.35 (ddd, $J = 15.1$, 7.0, 1.2 Hz, 1H), 2.23–2.02 (m, 4H), 1.80 (dd, $J = 9.3$, 1.2 Hz, 1H), 1.62 (dd, $J = 12.1$, 6.6 Hz, 1H), 1.43 (s, 9H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.2$, 169.6, 131.7, 124.6, 81.6, 37.3, 36.3, 33.8, 33.2, 29.2, 29.1, 28.0, 22.8, 20.0; HRMS(FAB): *m*/*z* calcd for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1467. Found: 285.1462.
11. Preparation of **9′** (below) from **9**: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 12 h, 90%. (b) 4-BrBzCl, DMAP, CH_2Cl_2, rt, 2 h, 95%. Crystallographic data (excluding structure factors) for compound **9′** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 643687. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].



9'



ORTEP of **9'**

12. Compounds **8**, **9**, and **17** were converted to the same diol by $LiAlH_4$ reduction. The spectra of these compounds were identical in all respects.
13. Although *l*-menthol was less expensive, a readily available bottle of *d*-menthol in our laboratory was used.
14. (a) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076–7077; (b) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079; (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.
15. The diastereomer of **11**, *ent*-**11**, is shown in Figure 1. Crystallographic data (excluding structure factors) for compound *ent*-**11** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 643686. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. Ghosh, M.; Miller, M. J. *Tetrahedron* **1996**, *52*, 4225–4238.
17. Reviews for the preparation and use of cyclopropanes: (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198; (b) Davies, H. M. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 1031–1067, Chapter 4.8; (c) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160; (d) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919–7946; (e) Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; YHC Publishers: New York, 2000; pp 191–228, Chapter 5, and references cited therein.