Total Synthesis

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Catalytic Asymmetric Total Synthesis of *ent*-Hyperforin**

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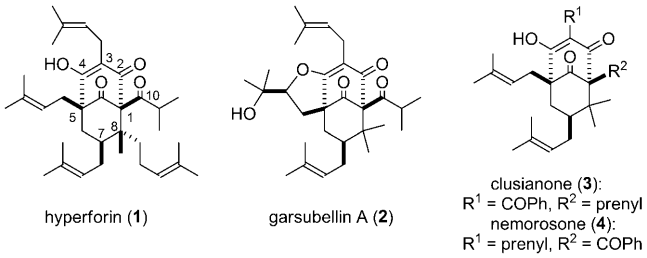
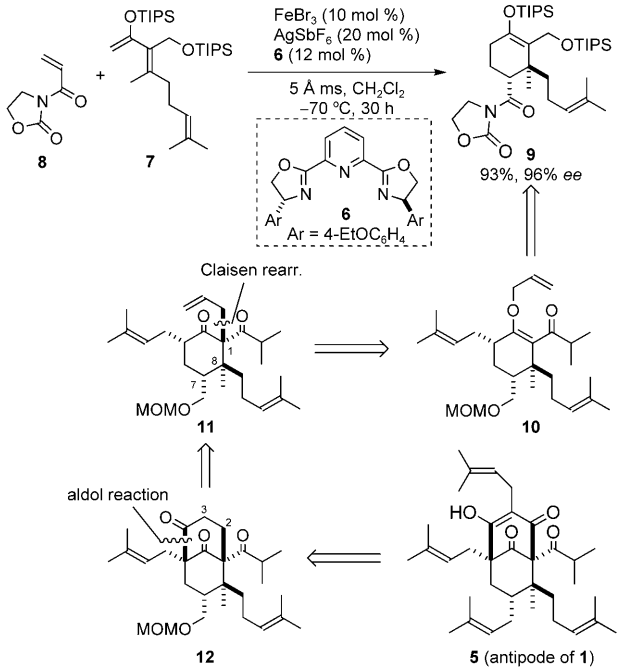
Naturally occurring polycyclic polyprenylated acylphloroglucinols (PPAPs: Scheme 1) commonly have a highly substituted bicyclo[3.3.1]nonanone core.[1] Hyperforin (**1**), a representative of this family, was isolated from the herb St. John's wort (*Hypericum perforatum*).[2a] Hyperforin exhibits various biological activities, including mild antidepressant activity,[3] antimalarial activity,[4] human histone deacetylase inhibitory activity,[5] and CYP3A4 induction activity.[6] Enhancement of a specific biological activity through structural modification is an important direction in drug-discovery research, and thus establishing a flexible, asymmetric total synthetic route is a fundamental prerequisite.



Scheme 1. Representative PPAPs.

Their structural complexity and potential utility as pharmaceutical leads make PPAPs very attractive synthetic targets. The total syntheses of garsubellin A (**2**),[7] clusianone (**3**),[8] and nemorosone (**4**)[8d] have been accomplished.[9] The use of elegant biomimetic approaches to construct the bicyclic core has resulted in some of these racemic syntheses being short and applicable for the production of structurally diverse analogues.[8b,e,9e] The catalytic asymmetric synthesis of PPAPs, however, remains a daunting challenge; there is only one asymmetric synthesis of PPAPs (that of **3**), which involved a late-stage kinetic resolution using a stoichiometric amount of chiral lithium amide.[8c] Hyperforin (**1**) contains an additional chiral quaternary center at C8 compared to **2**–**4**, thus providing a greater obstacle to its synthesis. We report herein the first catalytic asymmetric total synthesis of *ent*-hyperforin (**5**, the antipode of **1**).[10]

We previously developed a catalytic asymmetric Diels–Alder reaction between diene **7** and dienophile **8**, which was promoted by a cationic iron complex (10 mol%) derived from pybox ligand **6** (Scheme 2).[11] Product **9**, which contains



Scheme 2. Synthetic plan.

contiguous tertiary and quaternary stereocenters (corresponding to C7 and C8 of **5**), was obtained in 93% yield and 96% *ee* with complete *exo* selectivity (d.r. > 33:1).[12] This reaction is practical: reactions can be routinely conducted on up to 20 g scales (average 89% *ee*).[13] We thus planned our synthesis of **5** (Scheme 2) based on this powerful catalytic asymmetric reaction.

After conversion of **9** into allyl enol ether **10**, the key bicyclic compound **12** would be constructed by a Claisen rearrangement (**10**→**11**) and intramolecular aldol cyclization, according to previous model studies.[14] In the model studies, however, a simplified substrate containing geminal dimethyl substituents at C8 was utilized. The effect of the C8 quaternary stereocenter in **10** on the reactivity and stereoselectivity of the Claisen rearrangement was a major concern in this system. Moreover, the success in the construction of the bicyclic core intimately depended on the substitution pattern and conformation of the substrate.[15] In this sense, the C8

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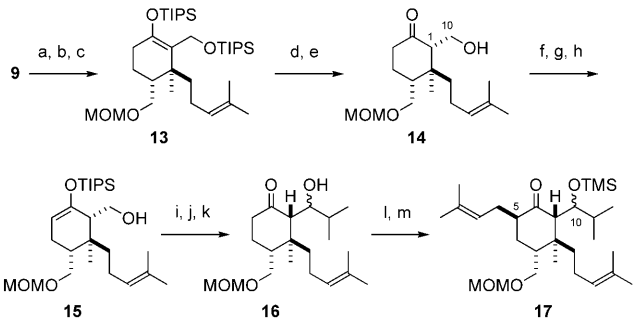
stereocenter could also affect the intramolecular aldol cyclization. From key intermediate **12**, introduction of an oxygen functionality at the extremely congested C2-position and installation of a prenyl group at the C3-position would lead to **5**.

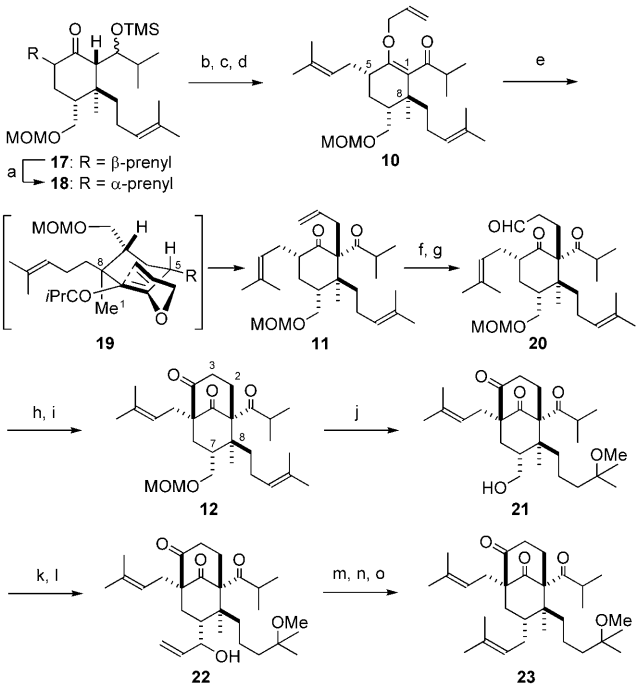
Based on the synthetic plan, we first converted enantiomerically enriched oxazolidinone **9** to MOM ether **13** over three steps with high efficiency (Scheme 3). Since the C10



Scheme 3. Conversion of the catalytic asymmetric Diels–Alder product. Reagents and conditions: a) EtSLi, THF, 96%. b) LAH, THF, 99%. c) MOMCl, TBAI, iPr$_2$NEt, CH_2Cl_2, 94%. d) TBAF, AcOH, THF. e) HF·py, py, THF, 91% (over 2 steps; d.r. = 1:1). f) TMSCl, NEt_3, CH_2Cl_2. g) TIPSOTf, iPr$_2$NEt, CH_2Cl_2. h) K_2CO_3, MeOH. i) TPAP (10 mol%), NMO, 4Å MS, CH_3CN/CH_2Cl_2. j) 2-bromopropane, Li, THF (d.r. = 5:1). k) TBAF, AcOH, THF, 58% (over 6 steps). l) TMSCl, imidazole, DMF, 94%. m) LDA, HMPA, prenyl bromide, THF, 89% (d.r. > 33:1). LAH = lithium aluminum hydride, MOM = methoxymethyl, TBAI = tetrabutylammonium iodide, TBAF = tetrabutylammonium fluoride, py = pyridine, TMS = trimethylsilyl, TIPS = triisopropylsilyl, OTf = trifluoromethanesulfonate, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, HMPA = hexamethyl phosphoramide.

hydroxy group readily eliminated to give the corresponding enone under various reaction conditions, cleavage of the two TIPS groups was conducted by a two-step sequence, which afforded primary alcohol **14**.[16] Direct oxidation of **14** and subsequent addition of an isopropyl group to C10 were difficult because of the instability of the intermediate aldehyde derived from **14**. Hence, **16** was synthesized via **15**, which was produced from **14** by temporary protection of the primary alcohol with a TMS group, protection of the ketone as an enol silyl ether, and selective cleavage of the TMS ether. After oxidation of **15** with TPAP [17] followed by introduction of the isopropyl group under Barbier conditions (d.r. = 5:1), hydrolysis of the enol silyl ether afforded ketone **16**. Although multiple steps were required for the apparently simple conversion from **14** into **16**, the overall yield was reasonable (58% over 6 steps). After protection of the C10 hydroxy group of **16** with a TMS group, prenylation of the kinetically produced lithium enolate proceeded exclusively from the axial β face at C5 to give **17**. The two diastereomers derived from the C10 stereocenter exhibited distinctly different reactivity in this step, and the ratio of the product diastereomers was enriched to 9:1.

Previous studies indicated that the configuration at C5 controls the approach of an allyl group to C1 in the Claisen rearrangement.[14] Therefore, β-prenyl **17** was converted into α-prenyl **18** through a deprotonation/kinetic protonation sequence (Scheme 4). Cleavage of the TMS ether, Dess–Martin oxidation,[18] and O-allylation produced **10**, the



Scheme 4. Construction of the bicyclic core. Reagents and conditions: a) LDA, THF; aq NH_4Cl, 88% (d.r. > 33:1). b) HF·py, py, THF. c) DMP, CH_2Cl_2, 96% (over 2 steps). d) NaHMDS, allyl bromide, HMPA, THF, > 99%. e) toluene, *N*,*N*-diethylaniline, 170°C, > 99% (d.r. = 12:1). f) $(Sia)_2BH$, THF; aq H_2O_2, aq NaOH, EtOH, 81%. g) DMP, CH_2Cl_2, 91%. h) NaOEt, EtOH. i) DMP, CH_2Cl_2, 86% (over 2 steps). j) (+)-CSA, MeOH, 66% (over 3 cycles). k) $(COCl)_2$, DMSO, CH_2Cl_2; NEt_3, 95%. l) vinylmagnesium bromide, THF, 92% (d.r. > 33:1). m) Ac_2O, DMAP, iPr$_2$EtN, CH_2Cl_2, 98%. n) $[Pd(PPh_3)_4]$ (20 mol%), HCO_2NH_4, toluene, 95%. o) Hoveyda–Grubbs 2nd generation cat. (15 mol%), 2-methyl-2-butene, CH_2Cl_2, > 99%. DMP = Dess–Martin periodinane, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, CSA = camphorsulfonic acid, DMAP = 4-dimethylaminopyridine.

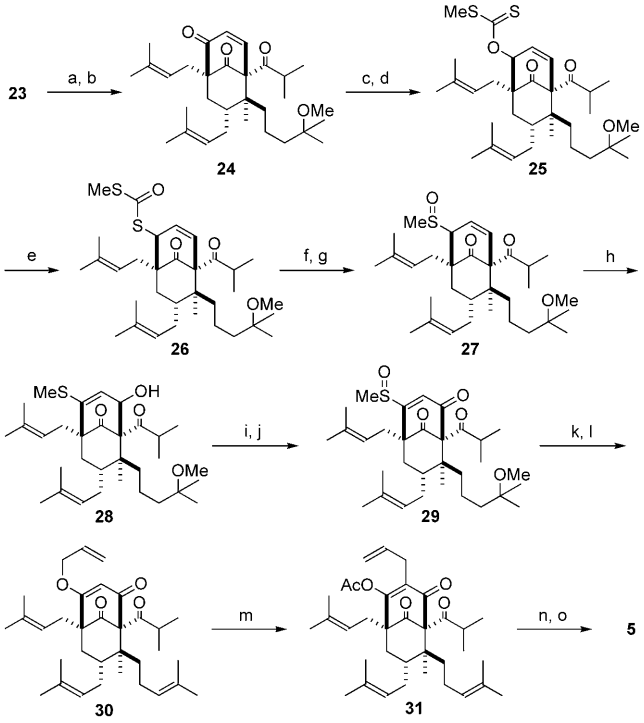
precursor for the key Claisen rearrangement. The thermal Claisen rearrangement of **10** proceeded with high selectivity (12:1) from the β face, and **11**, which contains the requisite three contiguous stereocenters (two of which are quaternary), was obtained with high fidelity. This excellent stereoselectivity was consistent with the model studies,[14] and attributable to the pseudoaxial methyl group at C8 blocking the α face (**19**). The key bicyclic intermediate **12** was synthesized uneventfully from **11** through a selective hydroboration at the terminal double bond using disiamylborane [$(Sia)_2BH$], Dess–Martin oxidation, intramolecular aldol cyclization of resulting aldehyde **20**, and oxidation.

From **12**, the remaining tasks were: 1) to convert the C7 MOM ether moiety into a prenyl group, 2) oxidize C2, and 3) install a prenyl group at C3. Of these tasks, conversion of the C7 MOM ether into a prenyl group was conducted first. Cleavage of the MOM ether under acidic conditions pro-

ceeded with concomitant protection of the homoprenyl group at C8 to give **21**. This unplanned selective protection was desirable because the reactive homoprenyl group caused side reactions at a later metathesis stage. Swern oxidation of **21**, followed by the addition of a vinyl Grignard reagent produced allylic alcohol **22** as a single isomer, which was deoxygenated through acetylation and a palladium-catalyzed allylic reduction.[8e,19] The subsequent cross-metathesis with isobutene using the Hoveyda–Grubbs catalyst[20] afforded **23** containing the prenyl group at C7.

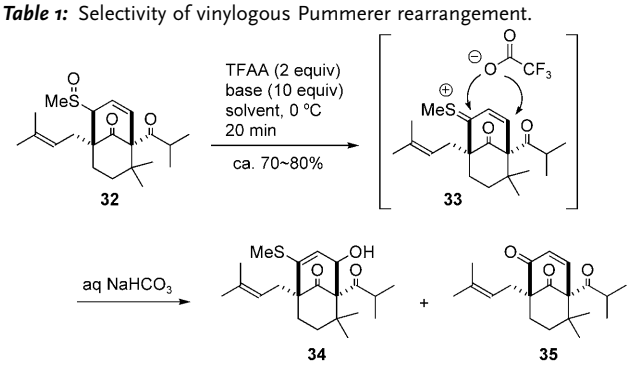
The oxidation of C2 was studied next; however, this task proved to be extremely difficult. After the conversion of **23** into **24** under the palladium-mediated conditions (Scheme 5),[21] inter- and intramolecular conjugate addition of various heteronucleophiles (such as Si, O, and N reagents) was attempted, but without success.[13a] Finally, we attempted a [3,3] sigmatropic rearrangement of xanthate **25**, which was produced efficiently from **24**. Thermal rearrangement of **25** proceeded cleanly; however, the expected functionalization at C2 did not occur. Instead, dithioate **26** was obtained by a [1,3] rearrangement.[22] This result again illustrated the highly congested nature of the C2-position. This finding, however, allowed us to attempt a vinylogous Pummerer rearrangement[23] for the oxidation of C2. The intermediate thionium cation would be highly electrophilic, thus making it possible to introduce an oxygen functionality at the C2-position.

Based on this hypothesis, we studied the critical vinylogous Pummerer rearrangement intensively by using sulfoxide **32** as a model substrate (Table 1). Treatment of **32** with



Scheme 5. Completion of the total synthesis. Reagents and conditions: a) TMSCl, NEt_3, DMAP, CH_2Cl_2, 84%. b) $Pd(OAc)_2$, DMSO, O_2, >99%. c) $NaBH_4$, MeOH, 95% (d.r. > 33:1). d) CS_2, NaH, THF; MeI, >99%. e) toluene, 150°C. f) EtSLi, THF; MeI, NEt_3, 98% (over 2 steps). g) $NaBO_3 \cdot 4H_2O$, AcOH (d.r. = 1.3:1), 95%. h) TFAA, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, −40°C; H_2O, 65% (d.r. > 33:1). i) H_2O_2, HFIP, 87% (d.r. = 9:1). j) DMP, CH_2Cl_2, 86%. k) Amberlyst 15DRY, toluene, 55%. l) LiH, allyl alcohol, 67%. m) $[Pd_2(dba)_3]$ $CHCl_3$ (10 mol%), (*S*)-tol-binap (20 mol%), THF; Ac_2O, pyridine, 50%. n) Hoveyda–Grubbs 2nd generation cat. (15 mol%), 2-methyl-2-butene, CH_2Cl_2, 34%. o) K_2CO_3, MeOH, 94%. dba = *trans*,*trans*-dibenzylideneacetone, binap = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

Table 1: Selectivity of vinylogous Pummerer rearrangement.



Entry	Solvent	Base	**34/35**[a]
1	toluene	Et_3N	1:1.1
2[b]	toluene	pyridine	3.0:1
3	CH_2Cl_2	2,6-lutidine	3.6:1
4[c]	CH_2Cl_2	2,6-di-*tert*-butylpyridine	8.3:1

[a] Determined by ^1H NMR spectroscopy. [b] 5 equiv of TFAA were used. [c] 3 equiv of TFAA were used.

trifluoroacetic anhydride (TFAA) in the presence of NEt_3 resulted in the vinylogous Pummerer rearrangement and normal Pummerer rearrangement proceeding at comparable rates, thereby affording, after hydrolysis, a 1:1.1 mixture of the desired allylic alcohol **34** and enone **35** (entry 1). Encouraged by this result, we then optimized the reaction conditions. The regioselectivity was greatly influenced by the base used. Among these examined, pyridine preferentially afforded **34** in moderate selectivity (entry 2; **34**/**35** = 3:1). The selectivity was improved by increasing the steric bulkiness of the pyridine-derived bases. 2,6-Di-*tert*-butylpyridine was finally found to be the optimum base, giving **34** as the major product with a selectivity of 8.3:1 (entry 4).

Having optimized the vinylogous Pummerer rearrangement with model substrate **32**, we applied the conditions to the actual substrate **27**, which was synthesized from **26** through thiolysis followed by S-methylation and S-oxidation[24] (Scheme 5). As expected, the vinylogous Pummerer rearrangement of **27** proceeded preferentially (4:1) to the normal Pummerer rearrangement under the optimized conditions, thereby providing the desired allylic alcohol **28** in 65% yield.

The final task was the installation of the prenyl group at C3. S-Oxidation using H_2O_2 in hexafluoroisopropanol (HFIP)[25] followed by Dess–Martin oxidation of the allylic alcohol afforded sulfoxide **29**. After deprotection of the homoprenyl group through elimination of the methoxy group by treatment with an acidic resin, an addition/elimination sequence using allyl alcohol afforded allyl ether **30**. The catalyzed intramolecular allyl transfer presumably proceeded

via a π-allyl-palladium intermediate, and enol acetate **31** was obtained in 50% yield after O-acetylation in a one pot reaction. It is noteworthy that thermal, microwave-assisted, and Lewis acid mediated Claisen rearrangement of **30** only produced a trace amount of the product (giving either complex mixtures or no product). Finally, cross-metathesis to introduce the prenyl group at C3, and methanolysis of the acetate under basic conditions completed the total synthesis of *ent*-hyperforin (**5**). ^{1}H, ^{13}C NMR, and IR spectroscopic data as well as mass spectrometric data were all identical with the reported values. The optical rotation of synthesized **5** was opposite to that of the natural isomer ($[\alpha]_D^{23} = -36.8$ ($c = 0.38$, EtOH); Lit. $+41$).[2]

In conclusion, we have achieved the first catalytic asymmetric total synthesis of *ent*-hyperforin. The key reactions were: 1) an iron-catalyzed asymmetric Diels–Alder reaction to produce contiguous C7 and C8 stereocenters; 2) a stereoselective Claisen rearrangement to produce the bridgehead quaternary carbon atom at C1; 3) an intramolecular aldol reaction to produce the highly substituted bicyclic core; and 4) a vinylogous Pummerer rearrangement to install the oxygen functionality at the C2-position. These basic methods are applicable to the asymmetric synthesis of other PPAPs and analogues of hyperforin. However, further improvements in the efficiency of the reactions may be necessary for such aplications. Studies are ongoing and will be reported in due course.

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[1] Review: R. Ciochina, R. B. Grossman, *Chem. Rev.* **2006**, *106*, 3963.
[2] a) A. I. Gurevich, V. N. Dobrynin, M. N. Kolosov, S. A. Popravko, I. D. Ryabova, B. K. Chernov, N. A. Derbentseva, B. E. Aizenman, A. D. Garagulya, *Antibiotiki* **1971**, *16*, 510; b) N. S. Bystrov, B. K. Chernov, V. N. Dobrynin, M. N. Kolosov, *Tetrahedron Lett.* **1975**, *16*, 2791; c) I. Brondz, T. Greibrokk, P. A. Groth, A. J. Aasen, *Tetrahedron Lett.* **1982**, *23*, 1299; d) I. Brondz, T. Greibrokk, P. A. Groth, A. J. Aasen, *Acta Chem. Scand. A* **1983**, *37*, 263; e) P. Adam, D. Arigoni, A. Bacher, W. Eisenreich, *J. Med. Chem.* **2002**, *45*, 4786.
[3] W. E. Muller, A. Singer, M. Wonnemann, U. Hafner, M. Rolli, C. Schafer, *Pharmacopsychiatry* **1998**, *31* (suppl. 1), 16.
[4] L. Verotta, G. Appendino, E. Bombardelli, R. Brun, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1544.
[5] C. Gey, S. Kyrylenko, L. Henning, L. D. Nguyen, A. Büttner, H. D. Pham, A. Giannis, *Angew. Chem.* **2007**, *119*, 5311; *Angew. Chem. Int. Ed.* **2007**, *46*, 5219.
[6] L. B. Moore, B. Goodwin, S. A. Jones, G. B. Wisely, C. J. Serabjit-Singh, T. M. Willson, J. L. Collins, S. A. Kliewer, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 7500.
[7] a) A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 14200; b) D. R. Siegel, S. J. Danishefsky, *J. Am. Chem. Soc.* **2006**, *128*, 1048; c) N. M. Ahmad, V. Rodeschini, N. S. Simpkins, S. E. Ward, A. J. Blake, *J. Org. Chem.* **2007**, *72*, 4803.
[8] a) V. Rodeschini, N. M. Ahmad, N. S. Simpkins, *Org. Lett.* **2006**, *8*, 5283; b) P. Nuhant, M. David, T. Pouplin, B. Delpech, C. Marazano, *Org. Lett.* **2007**, *9*, 287; c) V. Rodeschini, N. S. Simpkins, C. Wilson, *J. Org. Chem.* **2007**, *72*, 4265; d) C. Tsukano, D. R. Siegel, S. J. Danishefsky, *Angew. Chem.* **2007**, *119*, 8996; *Angew. Chem. Int. Ed.* **2007**, *46*, 8840; e) J. Qi, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 12682.
[9] Synthetic studies of PPAPs (representative examples): a) K. C. Nicolaou, J. A. Pfefferkorn, S. Kim, H. X. Wei, *J. Am. Chem. Soc.* **1999**, *121*, 4724; b) S. J. Spessard, B. M. Stoltz, *Org. Lett.* **2002**, *4*, 1943; c) M. Abe, M. Nakada, *Tetrahedron Lett.* **2007**, *48*, 4873; d) G. Mehta, M. K. Bera, *Tetrahedron Lett.* **2009**, *50*, 3519; e) E. A. Couladouros, M. Dakanali, K. D. Demadis, V. P. Vidali, *Org. Lett.* **2009**, *11*, 4430.
[10] In this study, chiral ligand **6** derived from inexpensive (*R*)-4-hydroxyphenylglycine was used in the catalytic asymmetric Diels–Alder reaction between **7** and **8**, thus resulting in the synthesis of the antipode of natural **1**.
[11] H. Usuda, A. Kuramochi, M. Kanai, M. Shibasaki, *Org. Lett.* **2004**, *6*, 4387.
[12] During the scale-up studies, it was found that the enantioselectivity of this catalytic Diels–Alder reaction was improved to up to 96% *ee* (87% *ee* in Ref. [11]) by using strict temperature control and moisture exclusion.
[13] a) See the Supporting Information for details; b) when the catalytic asymmetric Diels–Alder reaction was conducted on greater than 10 g scales, a decline in the *ee* value was observed, probably because of the slight increase in the reaction temperature during the addition of substrates.
[14] Y. Shimizu, A. Kuramochi, H. Usuda, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2007**, *48*, 4173.
[15] a) H. Usuda, M. Kanai, M. Shibasaki, *Org. Lett.* **2002**, *4*, 859; b) H. Usuda, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 3621.
[16] The hydrolysis of the enol TIPS ether provided a 1:1 mixture of C1 isomers. Although further conversion was described from one isomer (**14**) in the text, the other isomer was also utilized for the synthesis of intermediate **10** with comparable efficiency; see the Supporting Information for details.
[17] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625.
[18] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.
[19] G. Hughes, M. Lautens, C. Wen, *Org. Lett.* **2000**, *2*, 107.
[20] a) A. K. Chatterjee, D. P. Sanders, R. H. Grubbs, *Org. Lett.* **2002**, *4*, 1939; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168.
[21] a) Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011; b) R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn, D. A. Zheng, *Tetrahedron Lett.* **1995**, *36*, 2423.
[22] T. Taguchi, Y. Kawazoe, M. Nakao, *Tetrahedron Lett.* **1963**, *4*, 131.
[23] K. Feldman, M. D. Fodor, *J. Am. Chem. Soc.* **2008**, *130*, 14964.
[24] A. McKillop, J. A. Tarbin, *Tetrahedron Lett.* **1983**, *24*, 1505.
[25] K. S. Ravikumar, Y. M. Zhang, J. P. Bégué, D. Bonnet-Delpon, *Eur. J. Org. Chem.* **1998**, 2937.

