Structure Elucidation and Enantioselective Total Synthesis of the HMG-CoA Reductase Inhibitors FR901512 and FR901516

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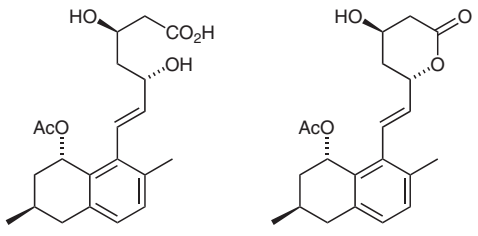
Abstract: The enantioselective total synthesis of the potent HMG-CoA reductase inhibitors FR901512 (**1**) and FR901516 (**2**) is reviewed. FR901512 was prepared in 15 steps from commercially available compound via **2** in 16.3% overall yield (89% average yield). This study validated the applicability and reliability of the catalytic asymmetric Nozaki–Hiyama reactions that were developed by us. These reactions enabled the concise, efficient, and protecting-group-free enantioselective total syntheses of these new statins.

Key words: asymmetric catalysis, enantioselective synthesis, Nozaki–Hiyama reaction, structure elucidation, total synthesis

Introduction

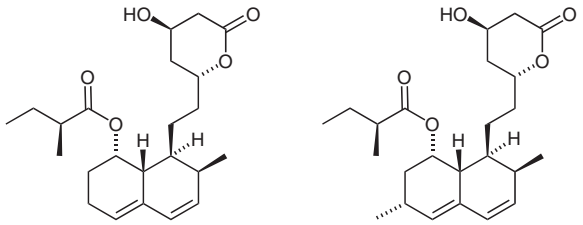
A research group at the Fujisawa (now, Astellas) Pharmaceutical Company isolated FR901512 (**1**) and FR901516 (**2**) (Figure 1) from the fermentation broth of agonomycete strain no. 14919.[1] Both these statins are new, specific, and strong inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (IC_{50} values of 0.95 and 14.0 nM, respectively). In addition, **1** inhibits cholesterol synthesis from [^{14}C]-acetate in Hep G2 cells with an IC_{50} value of 1.0 nM. Single oral administration of **1** strongly inhibits sterol synthesis in rats, and daily oral administration of **1** to beagle dogs reduces plasma cholesterol levels. Therefore, **1** is expected to have a hypolipidemic effect in humans.

Unlike previously reported naturally occurring HMG-CoA reductase inhibitors,[2] **1** and **2** possess a unique tetralin core with two stereogenic centers, while mevastatin and lovastatin possess a hexahydronaphthalene ring (Figure 2).[3] Furthermore, **1** and **2** contain 3,5-dihydroxyhept-6-enoic acid in the side chain, while mevastatin and lovastatin contain 3,5-dihydroxyheptanoic acid in the side chain.



FR901512 (**1**) FR901516 (**2**)

Figure 1 Structures of FR901512 (**1**) and FR901516 (**2**)



mevastatin (compactin) lovastatin (Mevacor®)

Figure 2 Structures of mevastatin (compactin) and lovastatin (Mevacor®)

New statins **1** and **2** are attractive compounds from the viewpoint of their potent bioactivity and unique structural features. In 2007, we carried out the enantioselective total synthesis of **1** and **2** and elucidated their absolute structures.[4] This article presents a detailed review of the enantioselective total synthesis of **1** and **2**.

Results and Discussion

Although **1** had been chemically correlated to **2**, the absolute structure of **1** had not been elucidated.[1a] Hence, we decided to elucidate the structure of **1** through enantioselective total synthesis. A divergent synthetic approach is required for this purpose, because all diastereomers and enantiomers of the target compound must be prepared in order to compare the spectroscopic data. A chiral starting material with a known absolute configuration has often been utilized for the total synthesis to elucidate the absolute structure.

However, total synthesis using enantioselective reactions is advantageous for introducing a stereogenic center into the target molecule when asymmetric induction is difficult. Although it is necessary to confirm the absolute configuration of the stereogenic center generated by the enantioselective reaction, it would be a powerful tool for enantiodivergent synthesis, because both enantiomers and/or diastereomers of the target compound could be produced when both enantiomers of the chiral reagent are available.

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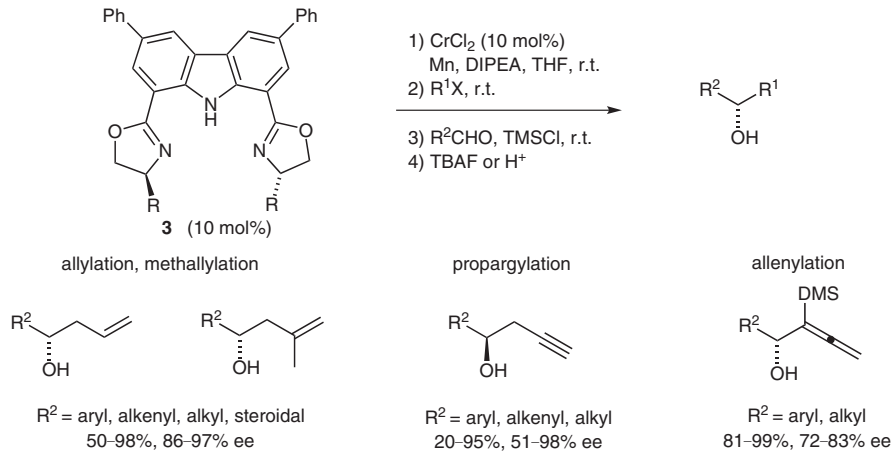
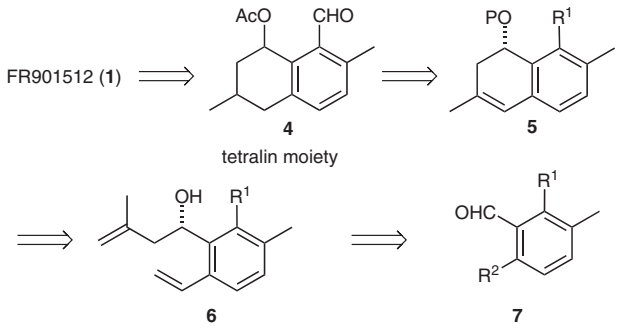


Scheme 1 Ligand **3** and catalytic asymmetric Nozaki–Hiyama reactions with **3**; DMS = dimethylsilyl

We have developed a new chiral ligand **3**[5] (Scheme 1) and used it for catalytic asymmetric Nozaki–Hiyama reactions, allylations,[5a,b] methallylations,[5a] propargylations,[5c] and allenylations;[5d] these reactions are reliable and have wide applicability.

These enantioselective reactions yield both enantiomers of the product with high enantioselectivity because the chiral ligand **3** can be readily prepared in both enantiomeric forms. Scheme 2 shows an outline of the retrosynthetic analysis of structurally unknown **1**.

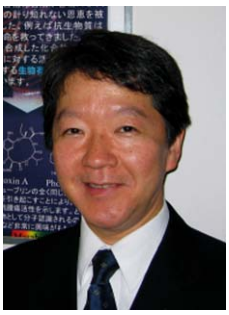
We expected that the side chain moiety of **1** would be connected at the benzylic position, and that both diastereomers of the tetralin moiety **4** would be derived from **5** via diastereoselective hydrogenation. In addition, we expect-



Scheme 2 Retrosynthetic analysis of FR901512 (**1**)

Biographical Sketches

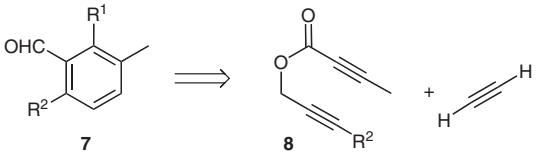
Masahiro Inoue was born in 1979 in Mie, Japan. He received his B.S. (2002), M.S. (2004), and Ph.D. (2007) degrees from Waseda University under the supervision of Prof. Masahisa Nakada. During his Ph.D. course, he was appointed as assistant professor (2005–2007) and worked with Prof. Masahisa Nakada. In 2007, he joined Daiichi Sankyo Co., Ltd., where he is currently a researcher. His current research interests are in the area of medicinal chemistry.



Masahisa Nakada was born in 1959 in Tokyo, Japan. He received his B.S. (1982) and M.S. (1984) degrees from the University of Tokyo, and was appointed as assistant professor at the University of Tokyo during his Ph.D. course in 1987. He received his Ph.D. degree in 1988 from the University of Tokyo (Prof. Masaji Ohno) and joined Prof. Shibasaki's group in 1991. He spent one year and four months from the beginning of 1992 as a postdoctoral fellow with Prof. K. C. Nicolaou at the Scripps Research Institute, USA. He was promoted to associate professor at Waseda University in 1995. Since 2000, he has been a professor at Waseda University. He was awarded the Pharmaceutical Society Award for Young Scientist (1997) and the SSOCJ Astellas Award for Organic Chemistry in Life Science 2008. His research interests include the total synthesis of bioactive complex natural products, asymmetric catalysis, new synthetic reactions, and chemical biology.

ed that alkene **5** would be obtained from **6** via ring-closing metathesis, and both enantiomers of **6** were anticipated to be produced by the catalytic asymmetric Nozaki–Hiyama methallylation of **7**. Consequently, we decided to first elucidate the absolute structure of the tetralin moiety **4**, and, hence, we commenced the catalytic asymmetric preparation of **6**.

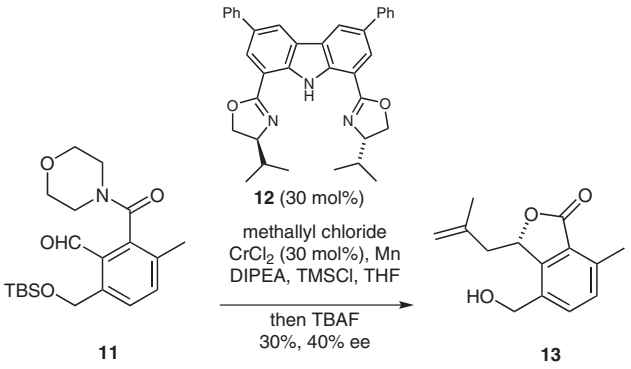
Initially, the starting material **7** was prepared via the transition-metal-mediated [2+2+2] cyclization of acetylene and diyne **8** (Scheme 3), because this reaction was expected to efficiently introduce four successive substituents on the benzene ring of **7**.



Scheme 3 Retrosynthetic analysis of aldehyde **7**

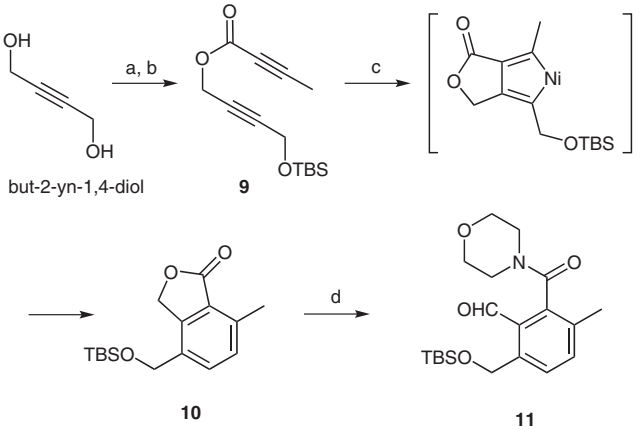
The monoprotection of a hydroxy group of but-2-yn-1,4-diol as a *tert*-butyldimethylsilyl ether (Scheme 4) and the subsequent condensation of the resulting alcohol with but-2-enoic acid yielded diyne **9**. Diyne **9** was subjected to transition-metal-mediated [2+2+2] cycloaddition with acetylene. Although reactions mediated by cobalt,[6] palladium,[7] and iridium[8] did not yield the desired products, mediation by a nickel catalyst prepared in situ from nickel(II) acetylacetonate and diisobutylaluminum hydride[9] yielded the desired lactone **10**. The ligand suitable for this reaction was found to be triphenylphosphine, and, interestingly, the reaction with tricyclohexylphosphine selectively afforded another structurally unidentified product. The ring-opening reaction of lactone **10** with morpholine proceeded smoothly; however, the product readily released morpholine to regenerate lactone **10**. Therefore, one-pot oxidation was carried out following the ring-opening reaction. Although most oxidizing reagents afforded lactone **10**, pyridinium dichromate successfully afforded aldehyde **11**.

The enantioselective methallylation of **11** was carried out with ligand **12** to afford a trimethylsilyl ether as the product; which was treated with tetrabutylammonium fluoride to afford lactone **13** (Scheme 5). The yield and enantiomeric excess of the product were unexpectedly low. This low ee could be attributed to steric hindrance, or the amide group, which could act as a ligand for the catalyst and disturb the transition state. In fact, we had observed the same phenomenon in the enantioselective allylation of a similar substrate.

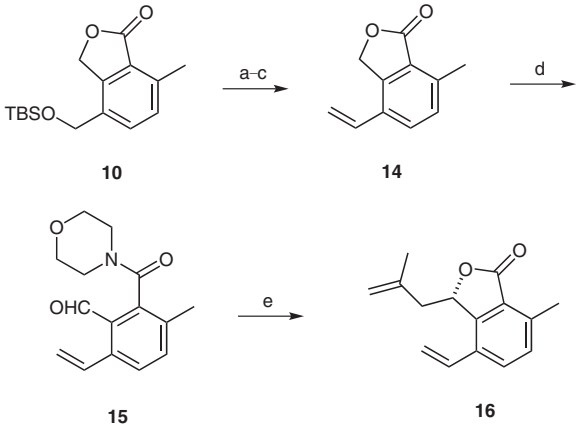


Scheme 5 Enantioselective methallylation of aldehyde **11** with ligand **12**. The ee of **13** was determined by HPLC [DAICEL CHIRALPAK AS-H, 0.46 cm × 25 cm; hexane–*i*-PrOH, 3:1; flow rate, 0.5 mL/min; t_R = 16.9 min (*S*), 23.7 min (*R*)].

Consequently, another aldehyde **15** that contained a vinyl group instead of a (*tert*-butyldimethylsiloxy)methyl group was prepared to examine the enantioselective reaction (Scheme 6). The *tert*-butyldimethylsilyl ether **10** was treated with tetrabutylammonium fluoride, and, subsequently, Parikh–Doering oxidation and the Wittig reaction were carried out to afford lactone **14**; lactone **14** was



Scheme 4 *Reagents and conditions*: (a) TBSCl, Et_3N, CH_2Cl_2, 0 °C, 71%; (b) but-2-enoic acid, DCC, DMAP, CH_2Cl_2, –25 to –10 °C, 98%; (c) acetylene, Ni(acac)$_2$ (20 mol%), DIBAL-H (40 mol%), Ph_3P (80 mol%), THF, hexane, 0 °C, 82%; (d) morpholine, *i*-PrMgCl, CH_2Cl_2, 0 °C, then PDC, 0 °C, 75%.

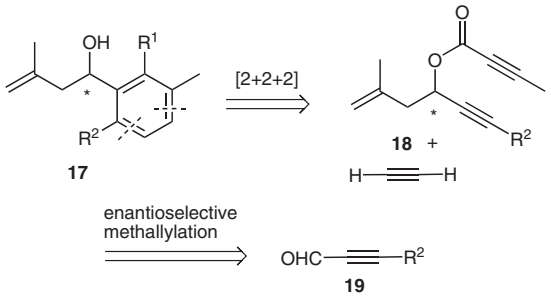


Scheme 6 *Reagents and conditions*: (a) TBAF, THF, 0 °C, 97%; (b) SO_3·py, Et_3N, DMSO, CH_2Cl_2, 90%; (c) Ph_3PMeBr, *t*-BuOK, THF, 0 °C, 91%; (d) morpholine, *i*-PrMgCl, CH_2Cl_2, 0 °C, then PDC, 0 °C, 60%; (e) **12** (30 mol%), methallyl chloride, $CrCl_2$ (30 mol%), Mn, DIPEA, TMSCl, THF, then TBAF, 8%.

converted into aldehyde **15** according to the same procedure as that shown in Scheme 4.

The enantioselective methallylation of aldehyde **15** gave a low yield because the pinacol coupling reaction of aldehyde **15** was the major pathway for the decreased yield. This result could be attributed to the increased stability of the radical anion derived from aldehyde **15**, in which a vinyl group was incorporated.

Next, we tried to synthesize compound **17** via the transition-metal-mediated [2+2+2] reaction of acetylene with diyne **18**, which would be prepared from aldehyde **19** by enantioselective methallylation with ligand **12** (Scheme 7).



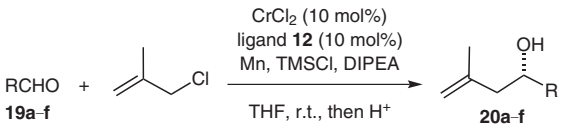
Scheme 7 Retrosynthetic analysis of **17**

The enantioselective methallylation of aldehyde **19a** afforded the desired product **20a**; however, the yield and enantioselectivity were low (Table 1, entry 1). The low yield was attributed to the concomitant pinacol coupling of aldehyde **19a**. Moreover, the enantioselective reaction of ynal **19b** gave the same results as those shown in entry 1. The low yield and enantioselectivity of aldehydes **19a** and **19b** (entries 1 and 2) could be attributed to their less bulky structures. Therefore, we carried out the enantioselective methallylation of a more bulky aldehyde, namely hexacarbonylcobalt complex **19c** (entry 3), which was readily available from **19a**. However, aldehyde **19c** decomposed during the reaction, and no desired product was obtained.

Next, we carried out the reactions of enals **19d–f**, which are ynal equivalents. The reactions of **19d** (Table 1, entry 4) and **19e** (entry 5) yielded the same results as that of **19c** (entry 3), but the reaction of enal **19f** yielded the desired product **20f** (entry 6). Although the yield was only 30%, due to the concomitant pinacol coupling of the substrate, the enantiomeric excess of **20f** was 90%. Therefore, we examined further synthetic studies using **20f**, with the objective of achieving a total synthesis.

Product **20f** was treated with *n*-butyllithium to afford the corresponding alkyne **20a**, which was converted into but-2-ynoate **21** (Scheme 8). The transition-metal-mediated [2+2+2] cycloaddition of **21** with acetylene under Mori's conditions[9] proceeded smoothly to afford the desired product **23** in high yield, probably via intermediate **22**. Subsequent removal of the *tert*-butyldimethylsilyl group and Dess–Martin oxidation afforded aldehyde **24**. Wittig

Table 1 Enantioselective Methallylation of Ynals or Ynal Equivalents[a]



Entry	Aldehyde		Product	Yield (%)[a]	ee (%)[b]
1	$TBSOCH_2$—≡—CHO	**19a**	**20a**	66	46
2	TMS—≡—CHO	**19b**	**20b**	52	50
3	$(OC)_3Co$—$Co(CO)_3$ (alkyne) $TBSOCH_2$—CHO	**19c**	**20c**	0	–
4	Br, CHO	**19d**	**20d**	0	–
5	CHO, Br, Br	**19e**	**20e**	0	–
6	CHO, TBSO, Cl	**19f**	**20f**	31	**90**[c]

[a] Reagents and conditions: methallyl chloride (2 equiv), $CrCl_2$ (10 mol%), ligand **12** (10 mol%), Mn (2 equiv), TMSCl (2 equiv), DIPEA (30 mol%).

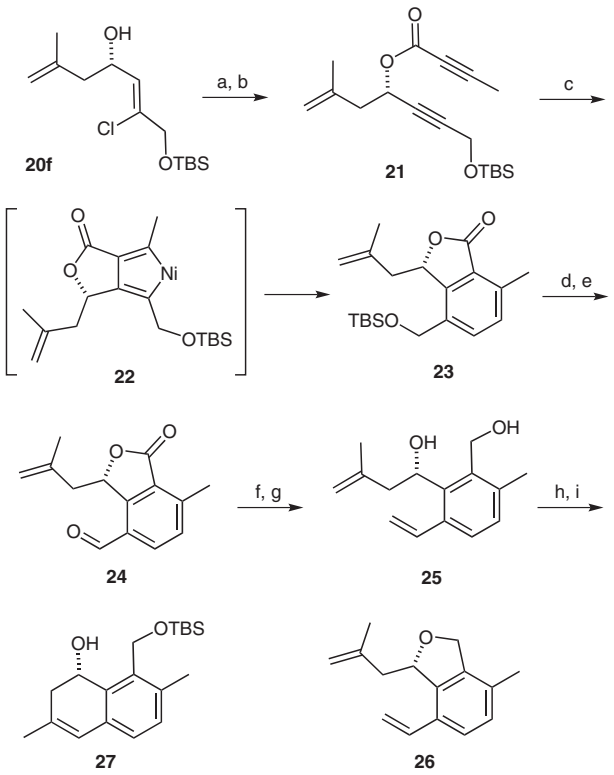
[b] The ee was determined by ^1H NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [(*R*)-MTPA ester].

[c] The ee was determined by HPLC [DAICEL CHIRALPAK OD-H, 0.46 cm × 25 cm; hexane–*i*-PrOH, 99:1; flow rate, 0.5 mL/min; t_R = 43.3 min (*S*), 53.2 min (*R*)].

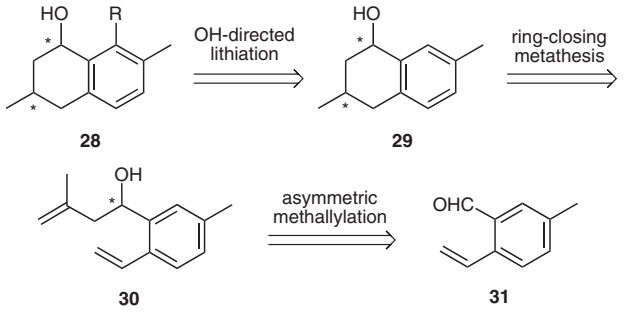
reaction of **24** and subsequent diisobutylaluminum hydride reduction afforded diol **25** and the tetrahydrofuran derivative **26** as a side product. The primary hydroxy group of **25** was selectively protected as a *tert*-butyldimethylsilyl ether, and the subsequent ring-closing metathesis with the Grubbs second-generation catalyst[10] successfully afforded the dihydronaphthol derivative **27**.

Although the optimization of the reaction conditions during the preparation of compound **27** would improve the overall yield, an alternative synthetic route to compound **27** was found to be more efficient. Consequently, the total synthesis via the synthetic route shown in Scheme 8 was not pursued.

An extensive investigation of the enantioselective methallylation of benzaldehyde derivatives with ligand **12** revealed that the reactions of 2,6-disubstituted benzaldehyde derivatives afforded the desired products, but in low enantiomeric excess. Thus, we found that the benzaldehyde derivative must have a hydrogen atom at the *ortho* position to afford the product in high enantioselectivity. We assumed that substituent R of compound **28** could be introduced by hydroxy-group-directed lithiation of compound **29** (Scheme 9), which was to be obtained by ring-closing metathesis of alcohol **30**. Alcohol **30** would



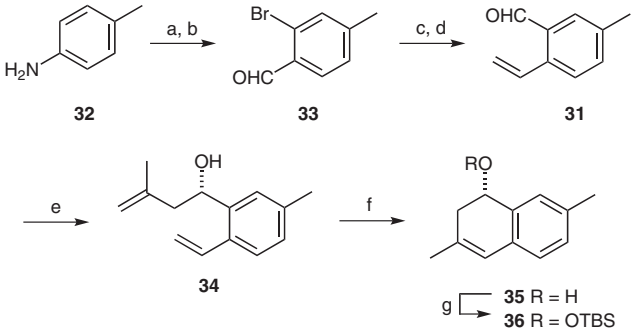
Scheme 8 *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C, 53%; (b) but-2-ynoic acid, DCC, DMAP, CH_2Cl_2, –25 to –10 °C, 100%; (c) acetylene, $Ni(acac)_2$ (20 mol%), DIBAL-H (40 mol%), Ph_3P (80 mol%), THF, hexane, 0 °C; (d) TBAF, THF, 0 °C, 90% (2 steps); (e) DMP, CH_2Cl_2, 0 °C, 88%; (f) Ph_3PMeBr, *t*-BuOK, THF, 0 °C, 91%; (g) DIBAL-H, CH_2Cl_2, hexane, –10 °C to r.t., 56%; (h) TBSCl, imidazole, CH_2Cl_2, quant; (i) [Ru(=CHPh)(IMes)(PCy_3)Cl_2] (10 mol%), toluene (0.02 M), 61%.



Scheme 9 Retrosynthetic analysis of compound **28**

be prepared by an enantioselective reaction of aldehyde **31** with ligand **12**.

Although aldehyde **33** was available commercially, it could be prepared by a two-step process from *p*-toluidine (**32**) (Scheme 10). Treatment of **32** with *N*-bromosuccinimide resulted in bromination at the *ortho* position, and the subsequent reaction with sodium nitrite under acidic conditions afforded a diazonium salt, which was subjected to the reaction reported by Rajagopal,[11] to afford aldehyde **33**. The Wittig reaction of aldehyde **33** afforded an *o*-bromostyrene,[12] and subsequent lithiation and formylation afforded aldehyde **31**.



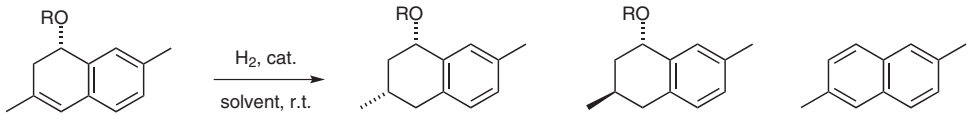
Scheme 10 *Reagents and conditions*: (a) NBS, $CHCl_3$, –50 °C, 94%; (b) $NaNO_2$, HCl, –10 °C, H_2C=NOH, NaOAc, $CuSO_4$, Na_2SO_3, HCl, reflux, 54%; (c) Ph_3PMeBr, *t*-BuOK, THF, 0 °C, 92%; (d) *n*-BuLi, THF, DMF, –78 °C, 96%; (e) methallyl chloride, $CrCl_2$ (5 mol%), **12** (6 mol%), Mn, TMSCl, DIPEA, THF, 93%; (f) [Ru(=CHPh)(IMes)(PCy_3)Cl_2] (3 mol%), toluene (0.03 M), 50 °C, 96%; (g) TBSCl, imidazole, CH_2Cl_2, 98%.

The enantioselective methallylation of aldehyde **31** with ligand **12** successfully afforded alcohol **34** in excellent yield and with excellent enantioselectivity (93%, 92% ee) (Scheme 10).[13] We used a Grubbs second-generation catalyst under high dilution conditions for the ring-closing metathesis of alcohol **34** to generate trisubstituted alkene **35** (96%). The protection of the hydroxy group of compound **35** by reaction with *tert*-butyldimethylsilyl chloride afforded *tert*-butyldimethylsilyl ether **36**.

The stereoselective hydrogenation of compounds **35** and **36** was examined (Table 2). The hydrogenation of alkene **35** with Wilkinson's catalyst merely provided naphthalene derivative **39** (entry 1), whereas hydrogenation of **35** with Crabtree's catalyst[14] afforded *trans*-**37** as a single diastereomer. This stereoselectivity could be well explained by the directing effect of the hydroxy group. However, the reaction was accompanied by the formation of a certain amount of **39** (33%) (entry 2). This aromatization was believed to be due to the dehydration caused by Crabtree's catalyst, which could act as a Lewis acid. Consequently, the solvent effect on the hydrogenation was examined. As Crabtree's catalyst was almost insoluble in diethyl ether, the reaction in diethyl ether afforded no products (entry 3). The reaction in tetrahydrofuran improved the yield of **37** and suppressed the formation of **39** (entry 4). Conducting the reaction in a more basic solvent such as 1,2-dimethoxyethane successfully resulted in the formation of *trans*-**37** in high yield (94%), almost as a single diastereomer (entry 5, >100:1 dr).

The hydrogenation of **35** with rhodium/alumina afforded *cis*-**37**, but the diastereoselectivity was low (Table 2, entry 6, 1.6:1 dr). The use of platinum black as the catalyst slightly improved the *cis*/*trans* ratio (entry 7, 2.7:1 dr). Therefore, we examined the hydrogenation of *tert*-butyldimethylsilyl ether **36**, and found that the hydrogenation with the Adams catalyst afforded *cis*-**38** in a *cis*/*trans* ratio of 10:1 (entry 8). Finally, the hydrogenation with platinum black successfully afforded *cis*-**38** in 92% yield in a *cis*/*trans* ratio of 32:1 (entry 9).

Table 2 Stereoselective Hydrogenation of Compounds **35** and **36**



35 R = H
36 R = OTBS

cis-**37** R = H
cis-**38** R = OTBS

trans-**37** R = H
trans-**38** R = OTBS

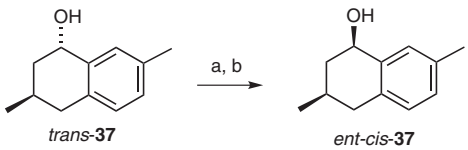
39

Entry	Substrate	Catalyst	Solvent	Yield (%)[a]	*cis*/*trans*[a]
1	**35**	$[RhCl(PPh_3)_3]$	CH_2Cl_2	91 (**39**)	–
2	**35**	$[Ir(cod)(PCy_3)py]PF_6$	CH_2Cl_2	59 (**37**), 33 (**39**)	1:>50
3	**35**	$[Ir(cod)(PCy_3)py]PF_6$	Et_2O	no reaction	–
4	**35**	$[Ir(cod)(PCy_3)py]PF_6$	THF	73 (**37**), 16 (**39**)	1:>100
5[b]	**35**	$[Ir(cod)(PCy_3)py]PF_6$	DME	94 (**37**), 3 (**39**)	1:>100
6[c]	**35**	Rh/Al_2O_3	EtOH	93 (**37**)	1.6:1
7[c]	**35**	Pt black	EtOH	98 (**37**)	2.7:1
8[c]	**36**	PtO_2	EtOH	45 (**38**)	10:1
9[c]	**36**	Pt black	EtOH	92 (**38**)[d]	32:1

[a] The ratio was determined by ^1H NMR analysis.
[b] The reaction was carried out at 0 °C.
[c] The reaction was carried out at 60 °C
[d] The TBS group was removed with TBAF to afford *cis*-**37** in 83% yield (2 steps from **36**).

The *tert*-butyldimethylsilyl group of *cis*-**38** was removed with tetrabutylammonium fluoride, thus affording *cis*-**37** (Table 2, entry 9). As the enantiomers of *cis*-**37** and *trans*-**37** would be synthesized starting from *ent*-**34**, which would be prepared by use of *ent*-ligand **12**, the synthetic route that afford all the isomers of compound **37** has been established.

Alternatively, *ent-cis*-**37** was prepared from *trans*-**37** by an oxidation–stereoselective reduction sequence (Scheme 11). Thus, Dess–Martin oxidation of *trans*-**37** and its subsequent reduction with sodium borohydride in the presence of cerium(III) chloride heptahydrate provided *ent-cis*-**37** in excellent yield and with excellent diastereoselectivity.

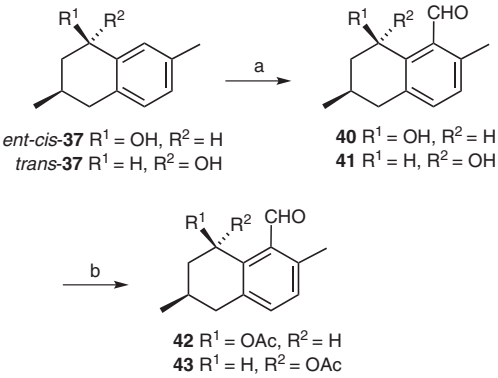


trans-**37** *ent-cis*-**37**

Scheme 11 *Reagents and conditions*: (a) DMP, CH_2Cl_2, 0 °C; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –78 °C, 100% (2 steps), >99% de.

The regioselective lithiation of *trans*-**37**[15] and its subsequent formylation were crucial in that these reactions afforded aldehyde **41** in 43% yield under optimized conditions (Scheme 12). A nonpolar solvent, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (which acted as an additive), and a large excess of the reagents were required to complete the reaction. The acetylation of alcohol **41** above 0 °C afforded acetate **43** in low yields, due to the formation of an unidentified byproduct; however, performing the acetylation at –78 °C improved the yield of **42** (94%, 74% conversion). Alcohol *ent-cis*-**37** was also converted into acetate **42** via aldehyde **40** by transformations identical to those in the method used to provide acetate **43**.

A comparison of the ^1H NMR spectra of acetates **42**, **43**, and naturally occurring **1** clearly indicated that the tetralin moiety of **1** had a *trans* relative configuration (Figure 3). Furthermore, alcohol **41** was satisfactorily transformed into a crystalline derivative **45** via three steps (Scheme 13), and the X-ray crystallographic analysis of **45** (Figure 4)[16] established its absolute structure, as shown in Scheme 13.



ent-cis-**37** R^1 = OH, R^2 = H
trans-**37** R^1 = H, R^2 = OH

40 R^1 = OH, R^2 = H
41 R^1 = H, R^2 = OH

42 R^1 = OAc, R^2 = H
43 R^1 = H, R^2 = OAc

Scheme 12 *Reagents and conditions*: (a) *s*-BuLi, TMEDA, hexane, –10 °C, then DMF, THF, –40 to –10 °C 43% (**41**); (b) Ac_2O, DMAP, THF, –78 °C, 13% (14% conversion) (**42**), 94% (75% conversion) (**43**).

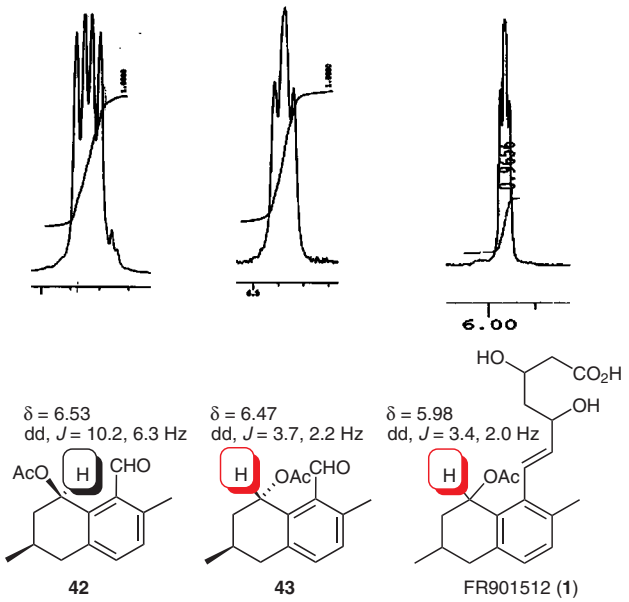
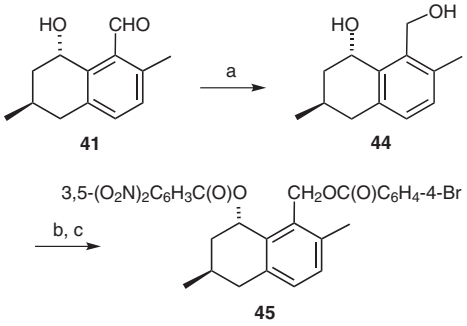


Figure 3 Comparison of ^{1}H NMR spectra of **42**, **43**, and **1**



Scheme 13 *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0 °C, 100%; (b) *p*-bromobenzoyl chloride, DIPEA, CH_2Cl_2, 10 °C; (c) 3,5-dinitrobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 75% (2 steps).

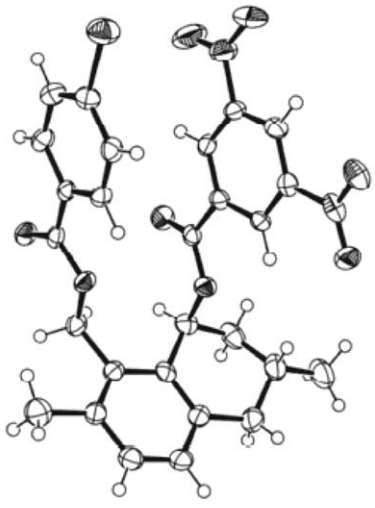
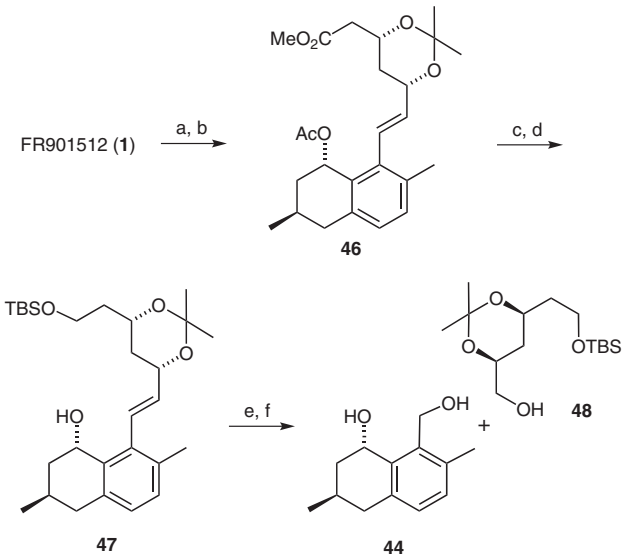
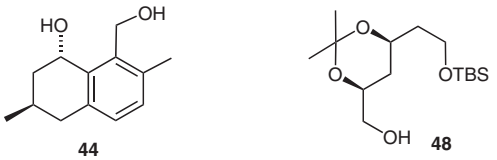


Figure 4 X-ray crystal structure of **45**

At the same time, we succeeded in preparing **44** and **48** from naturally occurring **1** (Scheme 14). The methyl ester formation of **1**, and its subsequent reaction with 2,2-dimethoxypropane under acidic conditions afforded acetonide **46**. The reduction of ester **46** with lithium borohydride and selective *tert*-butyldimethylsilyl ether formation afforded **47**. The reaction of **47** with osmium tetroxide and sodium periodate cleanly afforded the corresponding aldehydes; subsequent reduction with sodium borohydride afforded **44** and **48**. Diol **44** thus prepared was spectroscopically identical to the synthetic **44** (Scheme 13) in all respects; the absolute structure of **48** was determined by its comparison with known *ent*-**48**[17] (Figure 5). As a result, we could elucidate the entire absolute structure of FR901512 (**1**), as shown in Figure 1.



Scheme 14 *Reagents and conditions*: (a) MeI, K_2CO_3, acetone, reflux; (b) 2,2-dimethoxypropane, CSA, CH_2Cl_2, 0 °C; (c) $LiBH_4$, MeOH, THF; (d) TBSCl, imidazole, CH_2Cl_2, 86% (4 steps); (e) OsO_4, $NaIO_4$, Et_2O/H_2O, 50 °C; (f) $NaBH_4$, MeOH, 0 °C, 85% (**44**, 2 steps), 72% (**48**, 2 steps).

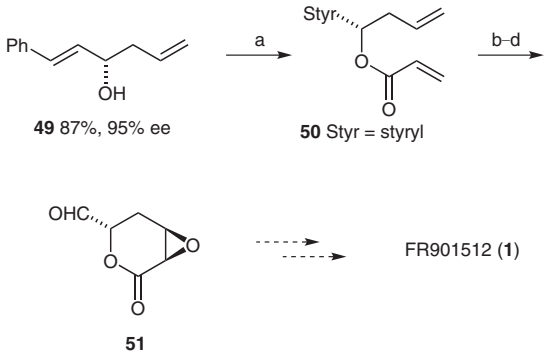


synthetic:
$[\alpha]_D^{29}$ –42.9 (*c* 0.68, $CHCl_3$)
authentic:
$[\alpha]_D^{29}$ –42.5 (*c* 0.68, $CHCl_3$)

authentic:
$[\alpha]_D^{23}$ –12.1 (*c* 0.90, $CHCl_3$)
Lit. (for *ent*-**48**)[17]:
$[\alpha]_D^{20}$ +10.2 (*c* 0.40, $CHCl_3$)

Figure 5 Specific rotation of **44** and **48**

To achieve the total synthesis of **1**, we attempted to assemble the side-chain moiety of **1**, which could be prepared via the enantioselective allylation of cinnamaldehyde with ligand **12** (Scheme 15). Homoallylic alcohol **49**, which was obtained by the enantioselective allylation of cinnamaldehyde with ligand **12**,[4] was converted into acrylate **50**, which was subjected to ring-closing metathesis with a Grubbs first-generation catalyst, followed by stereoselective epoxidation and ozonolysis to afford aldehyde **51**. However, all the attempts to assemble



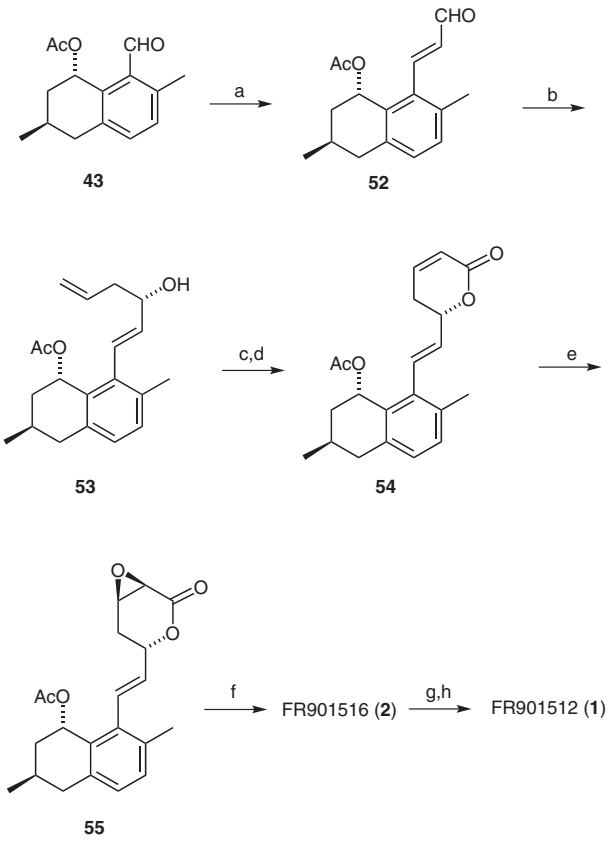
Scheme 15 *Reagents and conditions*: (a) $CH_2CHCOCl$, DIPEA, CH_2Cl_2, 0 °C to r.t., 82%; (b) [Ru(=CHPh)$(PCy_3)_2Cl_2$] (10 mol%), CH_2Cl_2 (0.05 M), reflux, 54%; (c) H_2O_2, NaOH, *i*-PrOH, r.t., 58%; (d) O_3, CH_2Cl_2, –78 °C, then Me_2S, 73%.

the side chain moiety using **51** and its derivative with the tetralin moiety failed.

After several attempts, we found that the Horner–Wadsworth–Emmons reaction of aldehyde **43** afforded the desired product. Consequently, we carried out further synthetic studies beginning from **43** via the stepwise construction of the side-chain moiety (Scheme 16). The reaction of aldehyde **43** with Nagata's reagent[18] provided aldehyde **52** in excellent yield (88%). Although a reactive benzylic acetate was incorporated in aldehyde **52**, the enantioselective allylation of **52** with ligand **12** afforded **53** in excellent yield and with excellent stereoselectivity (99%, 90% de). As no stereoselectivity was observed in the Nozaki–Hiyama allylation of aldehyde **52** in the absence of ligand **12**, this stereoselective allylation must be a chiral-reagent-controlled reaction.

The acrylate derived from **53** was subjected to ring-closing metathesis with a Grubbs second-generation catalyst; however, a complex mixture was formed. Fortunately, the reaction with a Grubbs first-generation catalyst[19] afforded **54** in 100% yield (Scheme 16). The chemoselective and diastereoselective epoxidation of **54** was well achieved with *tert*-butyl hydroperoxide (TBHP) and Triton B in toluene, affording **55** as the sole product.[20] This stereoselectivity could be explained by the axial attack of the *tert*-butyl hydroperoxide ion. Epoxide **55** was reacted with diphenyldiselenide, sodium borohydride, and acetic acid in tetrahydrofuran–ethanol,[21] affording **2** in 100% yield with complete regioselectivity. The methanolysis of **2** and the subsequent cleavage of the resultant methyl ester furnished **1**.

The synthesized **1** and **2** were spectroscopically identical to natural FR901512 and FR901516, respectively (Figure 6). Although the specific rotation of **2** measured in methanol was unreproducible,[22] the specific rotation of synthetic **2** measured using chloroform as solvent {$[\alpha]_D^{24}$ –58 (*c* 0.45, $CHCl_3$)} was in good agreement with the specific rotation of naturally occurring **2** {$[\alpha]_D^{23}$ –61 (*c* 0.50, $CHCl_3$)}; this confirmed the absolute structure of synthetic **2**.



Scheme 16 *Reagents and conditions*: (a) $(EtO)_2P(O)CH_2CH{=}NCy$, KHMDS, THF, –78 to –30 °C, then aq oxalic acid, 88%; (b) allyl bromide, $CrCl_2$ (15 mol%), **12** (16 mol%), Mn, DIPEA, TMSCl, THF, 3 °C, 99%, 90% de; (c) acryloyl chloride, DIPEA, CH_2Cl_2, 10 °C, 94%; (d) [Ru(=CHPh)$(PCy_3)_2Cl_2$] (10 mol%), CH_2Cl_2 (0.005 M), reflux, 100%; (e) TBHP, Triton B, toluene, 0 °C, 70%; (f) $(PhSe)_2$, $NaBH_4$, AcOH, THF–EtOH, 0 °C, 100%; (g) MeOH, toluene, r.t.; (h) TMSOK, THF, 0 °C, 95% (2 steps).

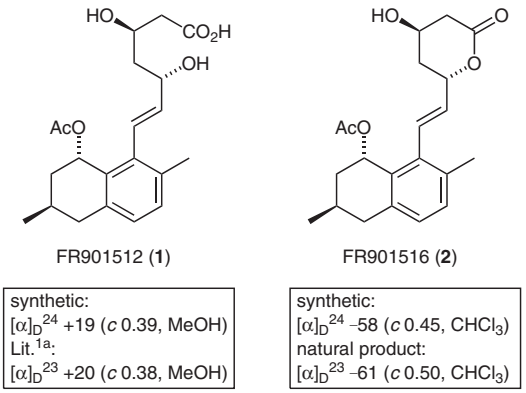


Figure 6 Comparison of the specific rotations of synthetic **1** and **2** with those of naturally occurring **1** and **2**

Conclusion

The structure elucidation and enantioselective total syntheses of FR901512 (**1**) and FR901516 (**2**) were carried out. FR901512 (**1**) was prepared in 15 steps from commercially available 2-bromo-4-methylbenzaldehyde in 16.3% overall yield (89% average yield). This study vali-

dated the applicability and reliability of the catalytic asymmetric Nozaki–Hiyama reactions that were developed by us. These reactions enabled the concise, efficient, and protecting-group-free enantioselective total syntheses of these new statins.

Chiral HPLC analysis was performed on JASCO PU-980 and UV-970 instruments. Melting points were recorded on a Yanako micro melting point apparatus and are uncorrected. Optical rotations were measured using a 2-mL cell with 1 dm path length on a JASCO DIP-1000 instrument. IR spectra were recorded on a JASCO FT/IR-8300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 or a Bruker AVANCE-600 spectrometer. ^{1}H and ^{13}C chemical shifts are reported relative to TMS, with the solvent resonances as internal standards. Mass spectra and elemental analyses were carried out at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with anhyd, freshly distilled solvents under anhyd conditions, unless otherwise noted. All reactions were monitored by TLC carried out on 0.25-mm E. Merck silica gel plates (60F-254) using UV light for visualizing and phosphomolybdic acid and heat for development. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative TLC (PTLC) separations were carried out on self-made 0.3-mm E. Merck silica gel plates (60F-254). THF was distilled from Na/benzophenone ketyl. Toluene was distilled from Na. CH_2Cl_2, benzene, and DMF were distilled from CaH_2. $CrCl_2$ (99.99%) and Mn (powder, 99.99%) were purchased from Aldrich, and all other reagents were purchased from Aldrich, TCI, or Kanto Chemical Co. Ltd.

2-Bromo-4-methyl-1-vinylbenzene

To a suspension of Ph_3PMeBr (25.2 g, 70.5 mmol) in THF (100 mL) was added a soln of *t*-BuOK (7.90 g, 70.4 mmol) in THF (100 mL) at 0 °C. The mixture was stirred for 1 h at the same temperature, and to the yellow suspension was added 2-bromo-4-methylbenzaldehyde (8.77 g, 44.1 mmol) in THF (50 mL). After the mixture had stirred at 0 °C for an additional 15 min, sat. aq NH_4Cl (100 mL) was added and the resultant mixture was extracted with Et_2O (3 × 100 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane); this afforded 2-bromo-4-methyl-1-vinylbenzene.

Colorless oil; yield: 8.00 g (92%).

IR (neat): 2922, 1605, 910 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.8 Hz, 1 H), 7.38 (br, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 7.02 (dd, *J* = 17.3, 11.0 Hz, 1 H), 5.65 (d, *J* = 17.3 Hz, 1 H), 5.30 (d, *J* = 11.0 Hz, 1 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.3, 135.5, 134.5, 133.2, 128.3, 126.4, 123.4, 115.7, 20.7.

HRMS (EI): *m*/*z* [M]$^+$ calcd for C_9H_9Br: 195.9888; found: 195.9888.

5-Methyl-2-vinylbenzaldehyde (31)

To a soln of 2-bromo-4-methyl-1-vinylbenzene (1.03 g, 5.20 mmol) in THF (20 mL) was added 1.60 M *n*-BuLi in hexane (3.58 mL, 5.73 mmol) at –78 °C. The reaction mixture was stirred at the same temperature for 1 h, and to the yellow suspension DMF (0.48 mL, 6.22 mmol) was added dropwise. After the mixture had stirred at –78 °C for an additional 20 min, sat. aq NH_4Cl (20 mL) was added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 50:1 to 20:1); this afforded **31**.

Colorless oil; yield: 0.723 g (96%).

IR (neat): 2926, 2856, 1691, 1610 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.3 (s, 1 H), 7.63 (br, 1 H), 7.49 (dd, *J* = 17.3, 11.0 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 5.67 (d, *J* = 17.3 Hz, 1 H), 5.47 (d, *J* = 11.0 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5, 137.9, 137.8, 134.6, 133.0, 132.6, 131.4, 127.3, 118.6, 20.9.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}O$: 146.0732; found: 146.0733.

(*S*)-3-Methyl-1-(5-methyl-2-vinylphenyl)but-3-en-1-ol (34)

To a mixture of Mn (0.784 g, 14.3 mmol), ligand **12** (215 mg, 0.396 mmol), and $CrCl_2$ (46.1 mg, 0.375 mmol) was added anhyd THF (70 mL) to form a brown suspension. After the mixture had stirred for 1 h, DIPEA (0.370 mL, 2.12 mmol) and methallyl chloride (1.40 mL, 14.2 mmol) were added and the mixture was stirred for 30 min. A soln of **31** (1.04 g, 7.08 mmol) in THF (5 mL) and TMSCl (1.80 mL, 14.2 mmol) were added successively to the suspension. The resulting mixture was stirred vigorously at r.t. for 24 h. The reaction was quenched with sat. aq $NaHCO_3$ (100 mL) and the mixture was extracted with Et_2O (5 × 70 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–Et_2O, 12:1 to 4:1); this afforded **34**.

Colorless oil; yield: 1.32 g (93%); 92% ee {determined by HPLC [254 nm; DAICEL CHIRALCEL OD-H, 0.46 cm × 25 cm; hexane–*i*-PrOH, 9:1; flow rate, 0.4 mL/min; t_R = 15.1 min (*S*), 16.4 min (*R*)]}; $[\alpha]_D^{27}$ –46.1 (*c* 0.90, $CHCl_3$).

IR (neat): 3410, 3074, 2918, 1649 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 1 H), 7.36 (d, *J* = 7.8 Hz, 1 H), 7.07 (d, *J* = 7.8 Hz, 1 H), 6.99 (dd, *J* = 17.3, 11.0 Hz, 1 H), 5.59 (dd, *J* = 17.3, 1.2 Hz, 1 H), 5.28 (dd, *J* = 11.0, 1.2 Hz, 1 H), 5.12 (ddd, *J* = 10.3, 2.7, 2.2 Hz, 1 H), 4.95 (s, 1 H), 4.90 (s, 1 H), 2.41 (dd, *J* = 14.2, 2.7 Hz, 1 H), 2.36 (s, 3 H), 2.32 (dd, *J* = 14.2, 10.3 Hz, 1 H), 2.09 (d, *J* = 2.2 Hz, 1 H), 1.83 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 140.8, 137.7, 133.7, 132.4, 128.1, 126.0, 125.7, 115.6, 113.8, 67.7, 47.4, 22.2, 21.2.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}ONa$: 225.1255; found: 225.1256.

(*S*)-3,7-Dimethyl-1,2-dihydronaphthalen-1-ol (35)

To a soln of **34** (1.58 g, 7.79 mmol) in toluene (250 mL, 0.03 M) was added [Ru(=CHPh)(IMes)(PCy_3)Cl_2] (0.207 g, 0.244 mmol) in toluene (10 mL) at 50 °C. The resulting mixture was stirred at the same temperature for 30 min and the solvent was removed in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 20:1 to 6:1); this afforded **35**.

White solid; yield: 1.30 g (96%); mp 73 °C; $[\alpha]_D^{25}$ –96.6 (*c* 0.75, $CHCl_3$).

IR (KBr): 3280, 3163, 2920, 1651, 1612 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (br, 1 H), 7.06 (d, *J* = 7.8 Hz, 1 H), 6.96 (d, *J* = 7.8 Hz, 1 H), 6.27 (s, 1 H), 4.74 (ddd, *J* = 7.1, 5.3, 4.8 Hz, 1 H), 2.53 (dd, *J* = 17.3, 5.3 Hz, 1 H), 2.47 (dd, *J* = 17.3, 4.8 Hz, 1 H), 2.34 (s, 3 H), 1.94 (s, 3 H), 1.65 (d, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3, 134.8, 133.8, 130.9, 128.9, 127.5, 125.7, 121.7, 68.4, 38.0, 23.6, 21.2.

HRMS–FAB: *m*/*z* [M + H] calcd for $C_{12}H_{15}O$: 175.1123; found: 175.1117.

(*S*)-1-(*tert*-Butyldimethylsiloxy)-3,7-dimethyl-1,2-dihydronaphthalene (36)

Imidazole (27.9 mg, 0.410 mmol) and TBSCl (60.8 mg, 0.403 mmol) were added successively to a soln of **35** (44.0 mg, 0.253 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 24 h, and then hexane (10 mL) was added. The solvent was removed to 10% of its volume and silica gel was charged with the resulting suspension. Purification by flash column chromatography (hexane–EtOAc, 100:1) gave **36**.

Colorless oil; yield: 71.6 mg (98%); $[\alpha]_D^{25}$ –17.2 (*c* 0.81, $CHCl_3$).

IR (neat): 2954, 2927, 2856, 1255 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (br, 1 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 6.89 (d, *J* = 7.8 Hz, 1 H), 6.19 (s, 1 H), 4.93 (dd, *J* = 11.5, 6.8 Hz, 1 H), 2.38 (dd, *J* = 16.2, 11.5 Hz, 1 H), 2.35 (s, 3 H), 2.28 (dd, *J* = 16.2, 6.8 Hz, 1 H), 1.91 (s, 3 H), 0.98 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 136.0, 134.5, 131.5, 127.6, 125.3, 125.0, 122.4, 69.7, 39.0, 25.9, 23.4, 21.5, 18.3, –4.5, –4.8.

HRMS–FAB: *m*/*z* $[M - H]^+$ calcd for $C_{18}H_{27}OSi$: 287.1831; found: 287.1829.

(1*S*,3*S*)-3,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (*cis*-37)

Pt black (5.4 mg, 0.028 mmol) was added to a soln of **36** (53.8 mg, 0.186 mmol) in absolute EtOH (8 mL), and the mixture was stirred under a H_2 atmosphere at 60 °C. After 18 h, the catalyst was removed by filtration, and the solvent was evaporated to afford crude *cis*-**38**. The well-dried crude *cis*-**38** was dissolved in THF (3 mL), and to the soln was added 1.0 M TBAF in THF (0.240 mL, 0.24 mmol) at 0 °C. After 1 h, sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–CH_2Cl_2–EtOAc, 8:2:1); this afforded *cis*-**37** with its diastereomer.

Yield: 27.1 mg (83%); 32:1 dr.

IR (KBr): 3320, 2947, 2868, 1498, 1450 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (br, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 4.80 (m, 1 H), 2.75 (dd, *J* = 16.1, 3.9 Hz, 1 H), 2.41 (dd, *J* = 16.1, 11.7 Hz, 1 H), 2.33 (s, 3 H), 2.23 (dddd, *J* = 12.2, 5.9, 2.7, 2.2 Hz, 1 H), 1.92 (m, 1 H), 1.65 (m, 1 H), 1.34 (ddd, *J* = 12.2, 12.0, 11.7 Hz, 1 H), 1.08 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 135.7, 133.6, 128.4, 128.0, 127.0, 69.8, 42.5, 38.0, 28.4, 22.1, 21.1.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{16}ONa$: 199.1099; found: 199.1098.

(1*S*,3*R*)-3,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (*trans*-37)

A soln of **35** (1.30 g, 7.46 mmol) in DME (40 mL) was stirred with $[Ir(cod)(PCy_3)py]PF_6$ (0.251 mg, 0.311 mmol) under a H_2 atmosphere at 0 °C for 12 h, and then the solvent was removed in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 10:1); this afforded alcohol *trans*-**37**.

White solid; yield: 1.23 g (94%); >50:1 dr; mp 62 °C; $[\alpha]_D^{24}$ –21.0 (*c* 0.75, $CHCl_3$).

IR (KBr): 3304, 2939, 1506, 1456 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (br, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 4.79 (ddd, *J* = 5.4, 3.3, 2.4 Hz, 1 H), 2.82 (dd, *J* = 16.4, 4.2 Hz, 1 H), 2.32 (s, 3 H), 2.29 (dd, *J* = 16.4, 11.5 Hz, 1 H), 2.15 (m, 1 H), 2.03 (ddd, *J* = 13.9, 4.2, 2.4 Hz, 1 H), 1.63 (d, *J* = 5.4 Hz, 1 H), 1.55 (m, 1 H), 1.09 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 135.7, 134.1, 130.0, 128.9, 128.8, 68.2, 39.9, 37.7, 23.8, 21.8, 20.9.

HRMS $[M + Na]^+$ calcd for $C_{12}H_{16}ONa$: 199.1099; found: 199.1098.

(6*R*,8*S*)-8-Hydroxy-2,6-dimethyl-5,6,7,8-tetrahydronaphthalene-1-carbaldehyde (41)

To a soln of *trans*-**37** (1.20 g, 6.80 mmol) and TMEDA (3.05 mL, 20.2 mmol) in hexane (60 mL) was added a fresh 1.01 M soln of *s*-BuLi in hexane and cyclohexane (54.0 mL, 54.5 mmol) at –10 °C. The reaction mixture was stirred at the same temperature for 7 h, and then a soln of DMF (5.27 mL, 68.1 mmol) in THF (10 mL) was added dropwise to the orange suspension at –40 °C. After stirring of the mixture at 0 °C for an additional 20 min, sat. aq NH_4Cl (40 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 20:1 to 10:1); this afforded **41**.

Pale yellow solid; yield: 589 mg (43%); mp 48 °C; $[\alpha]_D^{23}$ +31.8 (*c* 0.56, $CHCl_3$).

IR (KBr): 3295, 2956, 2926, 1676, 1458 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.6 (s, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H), 7.12 (d, *J* = 7.8 Hz, 1 H), 4.89 (m, 1 H), 4.28 (d, *J* = 2.9 Hz, 1 H), 2.88 (dd, *J* = 16.1, 2.7 Hz, 1 H), 2.62 (s, 3 H), 2.33 (dd, *J* = 16.1, 12.0 Hz, 1 H), 2.24 (m, 1 H), 2.15 (ddd, *J* = 13.7, 4.2, 2.2 Hz, 1 H), 1.43 (ddd, *J* = 13.7, 12.9, 3.9 Hz, 1 H), 1.09 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.7, 140.2, 139.1, 136.4, 135.2, 133.2, 130.8, 64.2, 39.2, 38.7, 22.9, 21.8, 19.3.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{16}O_2Na$: 227.1048; found: 227.1055.

(1*S*,3*R*)-8-Formyl-3,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl Acetate (43)

To a soln of DMAP (98.9 mg, 0.810 mmol) in THF (4 mL) was added Ac_2O (0.072 mL, 0.76 mmol) at –78 °C. The resulting white suspension was stirred for 1 h and a soln of well-dried **41** (110 mg, 0.539 mmol) in THF (3 mL) was added dropwise. After the mixture had stirred at the same temperature for 3 h, pH 7 buffer soln (10 mL) was added at –78 °C and the mixture was extracted with Et_2O (4 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 15:1 to 6:1); this afforded **43** and recovered starting material **41** (28.8 mg, 26%).

Yield (**43**): 92.1 mg (70%, 94% brsm); mp 89 °C; $[\alpha]_D^{30}$ –51.6 (*c* 0.60, $CHCl_3$).

IR (KBr): 2924, 1724, 1684, 1240 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.5 (s, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 6.47 (dd, *J* = 3.7, 2.2 Hz, 1 H), 2.91 (dd, *J* = 16.6, 4.4 Hz, 1 H), 2.57 (s, 3 H), 2.39 (dd, *J* = 16.6, 12.0 Hz, 1 H), 2.22 (ddd, *J* = 14.6, 4.4, 2.2 Hz, 1 H), 2.07 (m, 1 H), 2.03 (s, 3 H), 1.54 (ddd, *J* = 14.6, 12.7, 3.7 Hz, 1 H), 1.08 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 169.9, 139.2, 137.0, 134.4, 134.0, 132.7, 132.2, 66.8, 38.2, 37.0, 23.5, 21.6, 21.2, 20.4.

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{18}O_3Na$: 269.1154; found: 269.1144.

(1*R*,3*R*)-3,7-Dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (*ent-cis*-37)

To a soln of *trans*-**37** (14.2 mg, 0.0806 mmol) in CH_2Cl_2 (2 mL) was added DMP (64.7 mg, 0.153 mmol) at 0 °C. After the mixture had stirred at the same temperature for 1 h, the soln was diluted with Et_2O (10 mL), and sat. aq $NaHCO_3$ (10 mL) and sat. aq $Na_2S_2O_3$ (5

mL) were added. The mixture was extracted with Et_2O (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude ketone and $CeCl_3·7H_2O$ (60.0 mg, 0.161 mmol) were dissolved in MeOH (6 mL). The soln was cooled to –78 °C and $NaBH_4$ (10.1 mg, 0.267 mmol) was added. The resultant mixture was stirred at the same temperature for 1 h. The reaction was quenched with sat. aq NH_4Cl (10 mL) and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 6:1); this afforded *ent-cis*-**37**.

White solid; yield: 14.2 mg (100%); >50:1 dr; mp 100 °C; $[\alpha]_D^{24}$ –148 (*c* 0.21, $CHCl_3$).

IR (KBr): 3320, 2947, 2868, 1498, 1450 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (br, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 4.80 (m, 1 H), 2.75 (dd, *J* = 16.1, 3.9 Hz, 1 H), 2.41 (dd, *J* = 16.1, 11.7 Hz, 1 H), 2.33 (s, 3 H), 2.23 (dddd, *J* = 12.2, 5.9, 2.7, 2.2 Hz, 1 H), 1.92 (m, 1 H), 1.65 (m, 1 H), 1.34 (ddd, *J* = 12.2, 12.0, 11.7 Hz, 1 H), 1.08 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.2, 135.7, 133.6, 128.4, 128.0, 127.0, 69.8, 42.5, 38.0, 28.4, 22.1, 21.1.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}ONa$: 199.1099; found: 199.1098.

(1*R*,3*R*)-8-Formyl-3,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl Acetate (42)

Acetate **42** was prepared from *ent-cis*-**37** via **40** according to the same procedure as that used for the synthesis of **43** from *trans*-**37**.

Yield: 13% (14% conversion); $[\alpha]_D^{23}$ –166 (*c* 0.15, $CHCl_3$).

IR (KBr): 2926, 1740, 1699, 1230 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.3 (s, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.12 (d, *J* = 8.0 Hz, 1 H), 6.40 (dd, *J* = 8.1, 7.5 Hz, 1 H), 2.77 (ddd, *J* = 16.0, 4.1, 1.7 Hz, 1 H), 2.57–2.47 (m, 2 H), 2.50 (s, 3 H), 2.02 (s, 3 H), 1.94 (m, 1 H), 1.40 (ddd, *J* = 12.7, 12.0, 8.8 Hz, 1 H), 1.09 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 193.6, 170.2, 137.4, 136.9, 135.6, 133.6, 132.8, 131.4, 69.5, 38.1, 37.4, 27.4, 21.5, 21.0, 20.0.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{18}O_3Na$: 269.1154; found: 269.1161.

(1*S*,3*R*)-8-(Hydroxymethyl)-3,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (44)

To a soln of **41** (70.3 mg, 0.344 mmol) in MeOH (5 mL) was added $NaBH_4$ (16.3 mg, 0.431 mmol) at 0 °C. After the mixture had stirred for 15 min, sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–CH_2Cl_2–EtOAc, 2:2:1); this afforded diol **44**.

White solid; yield: 71.0 mg (100%).

Recrystallization from EtOAc afforded optically pure **44**; mp 115.2 °C; $[\alpha]_D^{29}$ –42.9 (*c* 0.68, $CHCl_3$).

IR (KBr): 3310, 2906, 1439, 1321 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 7.8 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 5.16 (dd, *J* = 3.6, 2.7 Hz, 1 H), 4.82 (s, 2 H), 2.85 (ddd, *J* = 16.3, 3.9, 1.5 Hz, 1 H), 2.41 (s, 3 H), 2.34 (dd, *J* = 16.3, 12.0 Hz, 1 H), 2.17–2.07 (m, 2 H), 1.56 (ddd, *J* = 13.9, 13.0, 3.6 Hz, 1 H), 1.09 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 136.6, 135.5, 135.0, 130.3, 129.2, 65.5, 58.6, 40.4, 38.8, 23.1, 21.8, 19.5.

HRMS–FAB: *m*/*z* calcd for $C_{13}H_{18}O_2Na$ [M + Na]$^+$: 229.1204; found: 229.1204.

(1*S*,3*R*)-8-(4-Bromobenzoyloxymethyl)-3,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl 3,5-Dinitrobenzoate (45)

DIPEA (0.025 mL, 0.14 mmol) and *p*-bromobenzoyl chloride (27.7 mg, 0.126 mmol) were added successively to a soln of **44** (13.8 mg, 0.0669 mmol) in CH_2Cl_2 (1 mL) at 10 °C. After the mixture had stirred at r.t. for 12 h, the reaction mixture was filtered through a short pad of silica gel, eluted with CH_2Cl_2, and concentrated. Et_3N (0.015 mL, 0.11 mmol), DMAP (2.0 mg, 0.016 mmol), and 3,5-dinitrobenzoyl chloride (22.4 mg, 0.0972 mmol) were added to a soln of the residue in CH_2Cl_2 (2 mL), and the mixture was stirred for 8 h. The reaction was quenched with sat. aq NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2); this afforded **45**. (A single crystal for X-ray crystallography was prepared by recrystallization from hexane–CH_2Cl_2.)

White solid; yield: 29.3 mg (75%, 2 steps from **41**); mp 188 °C; $[\alpha]_D^{24}$ –18.5 (*c* 0.72, $CHCl_3$).

IR (KBr): 3113, 2960, 2920, 1720, 1539, 1344, 1277 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.94 (t, *J* = 2.1 Hz, 1 H), 8.85 (d, *J* = 2.1 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 7.8 Hz, 1 H), 6.69 (dd, *J* = 3.4, 2.4 Hz, 1 H), 5.35 (d, *J* = 12.4 Hz, 1 H), 5.22 (d, *J* = 12.4 Hz, 1 H), 3.04 (dd, *J* = 16.6, 3.9 Hz, 1 H), 2.48 (dd, *J* = 16.6, 12.0 Hz, 1 H), 2.41 (s, 3 H), 2.26 (ddd, *J* = 14.6, 3.9, 2.0 Hz, 1 H), 2.16 (m, 1 H), 1.72 (ddd, *J* = 14.6, 13.7, 3.4 Hz, 1 H), 1.10 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 161.3, 148.2, 137.5, 137.1, 133.8, 132.7, 131.9, 131.6, 131.4, 130.6, 130.5, 129.2, 128.3, 128.2, 121.8, 70.5, 61.2, 38.4, 37.8, 23.9, 21.6, 19.4.

HRMS–FAB: *m*/*z* calcd for $C_{27}H_{23}BrN_2O_8Na$ [M + Na]$^+$: 605.0535; found: 605.0557.

(*E*)-8-(2-{6-[2-(*tert*-Butyldimethylsiloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}vinyl)-3,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-ol (47)

A mixture of FR901512 (**1**) (authentic sample, 42.1 mg, 0.112 mmol), MeI (0.070 mL, 1.1 mmol), and K_2CO_3 (95.1 mg, 0.688 mmol) in acetone (7 mL) was refluxed for 3 h. The precipitate was removed by filtration and sat. aq NH_4Cl (10 mL) was added to the filtrate. The mixture was extracted with EtOAc (4 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. To a soln of the residue in CH_2Cl_2 (5 mL) were added 2,2-dimethoxypropane (0.060 mL, 0.49 mmol) and CSA (2.1 mg, 0.0090 mmol) at 0 °C. After the mixture had stirred for 15 min, Et_3N (0.005 mL, 0.036 mmol) was added, and the solvent was removed in vacuo. To a soln of the residue in THF (4 mL) were added $LiBH_4$ (20.7 mg, 0.950 mmol) and MeOH (0.100 mL, 2.47 mmol). After stirring of the mixture for 24 h, sat. aq NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (4 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. Imidazole (20.3 mg, 0.298 mmol) and TBSCl (33.9 mg, 0.225 mmol) were added successively to a soln of the crude diol in CH_2Cl_2 (5 mL). After the mixture had stirred for 2 h, sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 8:1); this afforded **47**.

Colorless oil; yield: 46.2 mg (86%, 4 steps from **1**); $[\alpha]_D^{26}$ +15.3 (*c* 2.0, $CHCl_3$).

IR (neat): 3435, 2951, 2927, 2856, 1379, 1254, 1095, 962, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 7.8 Hz, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.79 (d, *J* = 16.3 Hz, 1 H), 5.80 (dd, *J* = 16.3, 6.1 Hz, 1 H), 4.96 (m, 1 H), 4.59 (m, 1 H), 4.14 (m, 1 H), 3.75 (ddd, *J* = 10.2, 7.7, 5.5 Hz, 1 H), 3.68 (ddd, *J* = 10.2, 5.4, 5.1 Hz, 1 H), 2.83 (dd, *J* = 15.9, 3.7 Hz, 1 H), 2.30 (dd, *J* = 15.9, 11.7 Hz, 1 H), 2.28 (s, 3 H), 2.06 (m, 1 H), 2.03 (ddd, *J* = 13.7, 4.1, 2.0 Hz, 1 H), 1.82 (m, 1 H), 1.71–1.65 (m, 2 H), 1.52 (s, 3 H), 1.48–1.38 (m, 2 H), 1.44 (s, 3 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2, 136.8, 135.4, 134.5, 133.7, 129.8, 127.8, 127.0, 98.7, 70.3, 65.4, 65.2, 58.8, 40.0, 39.4, 38.4, 37.6, 30.2, 25.9, 23.2, 22.0, 20.7, 19.9, 18.3, –5.4.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{46}O_4SiNa$: 497.3063; found: 497.3056.

(4*S*,6*S*)-{6-[2-(*tert*-Butyldimethylsiloxy)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl}methanol (48)

A 0.039 M soln of OsO_4 in *t*-BuOH (0.20 mL, 0.0078 mmol) and $NaIO_4$ (49.1 mg, 0.230 mmol) were added to a soln of **47** (39.0 mg, 0.0821 mmol) in Et_2O/H_2O (6 mL/2 mL). The reaction mixture was stirred at 50 °C for 2 h. Sat. aq Na_2SO_3 (5 mL) was added to the soln and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. To a soln of the residue in MeOH (3 mL) was added $NaBH_4$ (12.0 mg, 0.317 mmol) at 0 °C. After the mixture had stirred for 5 min, sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (5 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 10:1 to 2:1); this afforded **44** and **48**.

44: Yield: 14.3 mg (85%); $[\alpha]_D^{29}$ –42.5 (*c* 0.68, $CHCl_3$).

48: Yield: 18.0 mg (72%); $[\alpha]_D^{23}$ –12.1 (*c* 0.90, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ +10.2 (*c* 0.40, $CHCl_3$) for *ent*-**48**].

(1*S*,3*R*)-3,7-Dimethyl-8-[(*E*)-3-oxoprop-1-enyl]-1,2,3,4-tetrahydronaphthalen-1-yl Acetate (52)

A 0.5 M soln of KHMDS in toluene (1.7 mL, 0.85 mmol) was added dropwise to a soln of $(EtO)_2P(O)CH_2CH{=}NCy$ (313 mg, 1.20 mmol) in THF (10 mL) at 0 °C. The resulting yellow soln was stirred at the same temperature for 15 min and then a soln of **43** (175 mg, 0.710 mmol) in THF (2 mL) was added at –78 °C. The reaction mixture was warmed to –30 °C over 4 h, and then 1% aq oxalic acid (0.5 mL) was added under vigorous stirring. The mixture was extracted with Et_2O (3 × 15 mL), dried (Na_2SO_4), and concentrated to 10% of its volume. The soln was filtered through a short pad of silica gel and concentrated. The residue was purified by flash column chromatography (hexane–EtOAc, 20:1 to 12:1); this afforded **52**.

White solid; yield: 169 mg (88%); mp 93 °C; $[\alpha]_D^{23}$ –233 (*c* 0.88, $CHCl_3$).

IR (KBr): 2950, 2923, 1732, 1686, 1228 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.66 (d, *J* = 7.8 Hz, 1 H), 7.57 (d, *J* = 16.3 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 6.30 (dd, *J* = 16.3, 7.8 Hz, 1 H), 6.07 (dd, *J* = 3.4, 2.4 Hz, 1 H), 2.90 (dd, *J* = 16.6, 4.1 Hz, 1 H), 2.37 (m, 1 H), 2.32 (s, 3 H), 2.11–2.03 (m, 2 H), 1.98 (s, 3 H), 1.53 (ddd, *J* = 14.6, 13.2, 3.4 Hz, 1 H), 1.08 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 170.0, 151.0, 136.4, 135.7, 134.6, 133.7, 131.5, 131.1, 130.0, 67.8, 38.1, 37.5, 23.7, 21.6, 21.1, 20.8.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_3Na$: 295.1310; found: 295.1300.

(1*S*,3*R*)-8-[(*S*,*E*)-3-Hydroxyhexa-1,5-dienyl]-3,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl Acetate (53)

To a mixture of Mn (71.0 mg, 1.29 mmol), ligand **12** (56.3 mg, 0.104 mmol), and $CrCl_2$ (11.7 mg, 0.0952 mmol) was added anhyd THF (4 mL) to form a brown suspension. After the mixture had stirred for 1 h, DIPEA (0.055 mL, 0.316 mmol) and allyl bromide (0.115 mL, 1.33 mmol) were added, and the mixture was stirred for 20 min. Compound **52** (175 mg, 0.643 mmol) in THF (3 mL) and TMSCl (0.165 mL, 1.30 mmol) were added successively to the suspension at 3 °C. The resulting mixture was stirred vigorously at the same temperature for 12 h. The reaction was quenched with sat. aq $NaHCO_3$ (0.5 mL), filtered through Celite, and evaporated. The crude product was dissolved in THF (5 mL) and the stirred mixture was treated with 0.02 M HCl (0.05 mL). After the desilylation was complete, sat. aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with Et_2O (4 × 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 10:1); this afforded **53** with its inseparable minor diastereomer.

Yield: 200 mg (99%); 90% de.

IR (KBr): 3440, 2951, 1714, 1639, 1242 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (**53**) = 7.11 (d, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.37 (d, *J* = 16.3 Hz, 1 H), 6.27 (dd, *J* = 3.4, 2.0 Hz, 1 H), 5.87 (dddd, *J* = 17.3, 10.2, 7.3, 7.1 Hz, 1 H), 5.67 (dd, *J* = 16.3, 6.8 Hz, 1 H), 5.18–5.10 (m, 2 H), 4.24 (m, 1 H), 2.86 (ddd, *J* = 16.3, 4.3, 1.1 Hz, 1 H), 2.59 (d, *J* = 2.7 Hz, 1 H), 2.47–2.31 (m, 3 H), 2.21 (s, 3 H), 2.09–1.96 (m, 2 H), 2.03 (s, 3 H), 1.52 (ddd, *J* = 14.4, 12.7, 3.4 Hz, 1 H), 1.06 (d, *J* = 6.3 Hz, 3 H); δ (*epi*-**53**) = 6.47 (d, *J* = 16.3 Hz, 1 H), 6.13 (dd, *J* = 3.4, 2.0 Hz, 1 H), 5.63 (dd, *J* = 16.3, 6.8 Hz, 1 H), 4.31 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 138.3, 137.6, 135.9, 134.3, 133.7, 131.1, 130.1, 127.8, 127.5, 117.7, 72.2, 68.1, 41.2, 38.3, 37.9, 24.0, 21.7, 21.5, 20.3.

HRMS–FAB: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}O_3Na$: 337.1780; found: 337.1773.

(*S*,*E*)-1-[(6*R*,8*S*)-8-Acetoxy-2,6-dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl]hexa-1,5-dien-3-yl Acrylate

DIPEA (0.145 mL, 0.832 mmol) and acryloyl chloride (0.065 mL, 0.800 mmol) were added successively to a soln of **53** (161.8 mg, 0.515 mmol) in CH_2Cl_2 (7 mL) at 10 °C. After the mixture had stirred at the same temperature for 4 h, sat. aq NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 15:1); this afforded the acrylate title compound.

White solid; yield: 178.3 mg (94%); mp 49 °C; $[\alpha]_D^{23}$ –103 (*c* 0.28, $CHCl_3$).

IR (KBr): 2951, 1732, 1238, 1188 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 7.8 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.52 (d, *J* = 16.3 Hz, 1 H), 6.44 (dd, *J* = 17.3, 1.5 Hz, 1 H), 6.18 (dd, *J* = 17.3, 10.2 Hz, 1 H), 5.99 (dd, *J* = 3.5, 2.2 Hz, 1 H), 5.85 (dd, *J* = 10.2, 1.5 Hz, 1 H), 5.82 (dddd, *J* = 17.3, 10.2, 7.1, 6.9 Hz, 1 H), 5.68 (dd, *J* = 16.3, 6.3 Hz, 1 H), 5.55 (ddd, *J* = 12.9, 6.3, 1.0 Hz, 1 H), 5.15 (m, 1 H), 5.10 (m, 1 H), 2.87 (ddd, *J* = 16.6, 4.4, 1.5 Hz, 1 H), 2.53–2.49 (m, 2 H), 2.33 (dd, *J* = 16.6, 11.8 Hz, 1 H), 2.22 (s, 3 H), 2.12 (ddd, *J* = 14.4, 4.4, 2.2 Hz, 1 H), 2.02 (m, 1 H), 1.99 (s, 3 H), 1.46 (ddd, *J* = 14.4, 12.9, 3.5 Hz, 1 H), 1.05 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 165.4, 137.6, 135.9, 133.9, 133.2, 132.8, 131.0, 130.6, 130.4, 128.9, 128.7, 128.0, 118.1, 73.2, 68.5, 38.8, 38.3, 37.3, 23.8, 21.8, 21.3, 20.6.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{28}O_4Na$: 391.1885; found: 391.1872.

(1*S*,3*R*)-3,7-Dimethyl-8-{(*E*)-2-[(*S*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]vinyl}-1,2,3,4-tetrahydronaphthalen-1-yl Acetate (54)

A soln of [Ru(=CHPh)$(PCy_3)_2Cl_2$] (36.0 mg, 0.0437 mmol) in CH_2Cl_2 (5 mL) was added to a refluxing soln of (*S*,*E*)-1-[(6*R*,8*S*)-8-acetoxy-2,6-dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl]hexa-1,5-dien-3-yl acrylate (161 mg, 0.438 mmol) in CH_2Cl_2 (90 mL, 0.005 M). The resulting mixture was stirred at the same temperature for 7 h and the solvent was removed in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 6:1 to 3:1); this afforded **54**.

White solid; yield: 149 mg (100%); mp 108 °C; $[\alpha]_D^{22}$ –142 (*c* 0.27, $CHCl_3$).

IR (KBr): 2951, 1724, 1635, 1240 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 7.8 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 6.93 (ddd, *J* = 9.8, 4.4, 3.9 Hz, 1 H), 6.64 (d, *J* = 16.3 Hz, 1 H), 6.08 (ddd, *J* = 9.8, 2.0, 1.7 Hz, 1 H), 5.99 (dd, *J* = 3.4, 2.2 Hz, 1 H), 5.76 (dd, *J* = 16.3, 5.6 Hz, 1 H), 5.08 (m, 1 H), 2.89 (ddd, *J* = 16.6, 4.6, 1.5 Hz, 1 H), 2.57–2.51 (m, 2 H), 2.34 (dd, *J* = 16.6, 11.8 Hz, 1 H), 2.27 (s, 3 H), 2.12–2.03 (m, 2 H), 2.02 (s, 3 H), 1.48 (ddd, *J* = 14.6, 13.2, 3.4 Hz, 1 H), 1.06 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 164.0, 144.9, 137.1, 136.0, 134.0, 131.9, 131.0, 130.5, 129.8, 128.3, 121.5, 77.6, 68.5, 38.1, 37.4, 29.2, 23.8, 21.8, 21.5, 20.5.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{24}O_4Na$: 363.1572; found: 363.1571.

(1*S*,3*R*)-3,7-Dimethyl-8-{(*E*)-2-[(1*R*,3*S*,6*R*)-5-oxo-4,7-dioxabicyclo[4.1.0]heptan-3-yl]vinyl}-1,2,3,4-tetrahydronaphthalen-1-yl Acetate (55)

To a soln of **54** (7.0 mg, 0.021 mmol) and a 4.13 M soln of TBHP in toluene (0.010 mL, 0.041 mmol) in toluene (2 mL) was added a 40% soln of Triton B in MeOH (0.003 mL, 0.007 mmol) at 0 °C. The pale yellow soln was stirred at the same temperature for 30 min. Sat. aq NH_4Cl (5 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 6:1); this afforded **55**.

White solid; yield: 5.2 mg (70%); mp 112 °C; $[\alpha]_D^{21}$ –20.0 (*c* 0.64, $CHCl_3$).

IR (KBr): 2924, 1747, 1714, 1250 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 7.8 Hz, 1 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 6.59 (d, *J* = 16.3 Hz, 1 H), 5.97 (dd, *J* = 3.2, 2.0 Hz, 1 H), 5.60 (dd, *J* = 16.3, 5.6 Hz, 1 H), 5.14 (m, 1 H), 3.74 (dd, *J* = 4.1, 3.2 Hz, 1 H), 3.63 (d, *J* = 4.1 Hz, 1 H), 2.89 (dd, *J* = 16.4, 3.2 Hz, 1 H), 2.52 (ddd, *J* = 14.9, 3.2, 2.9 Hz, 1 H), 2.34 (dd, *J* = 16.4, 11.8 Hz, 1 H), 2.23 (s, 3 H), 2.17 (dd, *J* = 14.9, 12.0 Hz, 1 H), 2.09–2.00 (m, 2 H), 2.02 (s, 3 H), 1.47 (ddd, *J* = 14.6, 13.2, 3.2 Hz, 1 H), 1.06 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 167.2, 137.1, 136.0, 133.9, 131.1, 131.0, 130.4, 129.6, 128.3, 73.3, 68.4, 52.1, 49.2, 38.1, 37.4, 29.3, 23.8, 21.8, 21.5, 20.4.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{24}O_5Na$: 379.1521; found: 379.1535.

FR901516 (2)

To a soln of $(PhSe)_2$ (156 mg, 0.500 mmol) in EtOH (5 mL) was added $NaBH_4$ (38.0 mg, 1.00 mmol) at 0 °C. After the mixture had stirred for 15 min, AcOH (0.075 mL, 1.3 mmol) was added to the reaction mixture at r.t. (this provided the PhSeH soln).[3] The PhSeH soln (0.6 mL) was added to a soln of epoxide **55** (13.5 mg, 0.0379 mmol) in THF–EtOH (1 mL/0.5 mL) at 0 °C. The resulting mixture was stirred at the same temperature for 1 h. Sat. aq NaCl (5 mL) was added and the mixture was extracted with EtOAc (5 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (hexane–EtOAc, 1:1 to 1:2); this afforded FR901516 (**2**).

White solid; yield: 13.7 mg (100%); mp 167 °C (Lit.[1a] 167–168 °C); $[\alpha]_D^{24}$ –58 (*c* 0.45, $CHCl_3$).

IR (KBr): 3408, 2951, 1724, 1716, 1371, 1241, 953 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 7.8 Hz, 1 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 6.59 (d, *J* = 16.3 Hz, 1 H), 5.98 (dd, *J* = 3.4, 2.0 Hz, 1 H), 5.68 (dd, *J* = 16.3, 5.1 Hz, 1 H), 5.36 (m, 1 H), 4.45 (m, 1 H), 2.88 (dd, *J* = 16.1, 3.4 Hz, 1 H), 2.85 (dd, *J* = 17.8, 4.9 Hz, 1 H), 2.67 (ddd, *J* = 17.8, 3.9, 1.5 Hz, 1 H), 2.34 (dd, *J* = 16.1, 11.7 Hz, 1 H), 2.26 (s, 3 H), 2.15–1.95 (m, 4 H), 2.11 (m, 1 H), 2.01 (s, 3 H), 1.48 (ddd, *J* = 14.6, 13.2, 3.4 Hz, 1 H), 1.06 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 169.8, 137.5, 135.9, 133.9, 132.8, 131.0, 130.4, 128.5, 128.1, 75.3, 68.6, 62.7, 38.7, 38.2, 37.5, 35.5, 23.8, 21.8, 21.4, 20.4.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{26}O_5Na$: 381.1678; found: 381.1675.

FR901512 (1)

To a soln of FR901516 (**2**) (8.0 mg, 0.022 mmol) in toluene (1 mL) was added MeOH (1 mL). The mixture was stirred at r.t. for 24 h and the solvent was removed in vacuo. The residue was dissolved in THF (2 mL), and a 90% soln of TMSOK (8.0 mg, 0.056 mmol) in THF (1 mL) was added to the soln at 0 °C. After the mixture had stirred for 15 min, sat. aq NH_4Cl (5 mL) was added and the mixture was extracted with EtOAc (5 × 10 mL). The combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography ($CHCl_3$–MeOH–AcOH, 200:20:1); this afforded FR901512 (**1**).

White solid; yield: 7.9 mg (95%, 2 steps from **2**); mp 134 °C; $[\alpha]_D^{24}$ +19 (*c* 0.39, MeOH) (Lit.[1a] $[\alpha]_D^{20}$ +20 (*c* 0.68, MeOH)).

IR (KBr): 3317, 2951, 1705, 1672, 1373, 1271, 1254, 1086, 974 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (d, *J* = 7.8 Hz, 1 H), 6.98 (d, *J* = 7.8 Hz, 1 H), 6.40 (d, *J* = 16.3 Hz, 1 H), 6.29 (dd, *J* = 3.6, 2.0 Hz, 1 H), 5.64 (dd, *J* = 16.3, 7.2 Hz, 1 H), 4.49 (m, 1 H), 4.37 (m, 1 H), 2.86 (dd, *J* = 16.1, 3.4 Hz, 1 H), 2.63 (dd, *J* = 16.2, 4.5 Hz, 1 H), 2.59 (dd, *J* = 16.2, 7.2 Hz, 1 H), 2.35 (dd, *J* = 16.1, 12.4 Hz, 1 H), 2.19 (s, 3 H), 2.04 (s, 3 H), 2.01 (m, 1 H), 1.96 (ddd, *J* = 14.4, 3.7, 2.0 Hz, 1 H), 1.85 (ddd, *J* = 14.4, 10.0, 9.5 Hz, 1 H), 1.75 (ddd, *J* = 14.4, 3.0, 2.4 Hz, 1 H), 1.52 (ddd, *J* = 14.4, 12.9, 3.6 Hz, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 171.5, 137.7, 136.6, 136.0, 133.6, 130.9, 130.1, 128.3, 128.1, 73.4, 68.2, 68.2, 41.6, 41.2, 38.2, 38.0, 24.0, 21.7, 21.6, 20.2.

HRMS–FAB: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{28}O_6Na$: 399.1784; found: 399.1787.

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