CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200700330

Chiral-Catalyst-Based Convergent Synthesis of HIV Protease Inhibitor GRL-06579A

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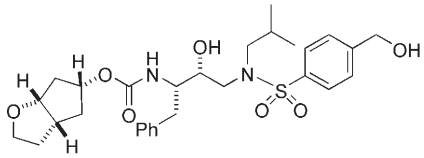
Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: Catalytic asymmetric synthesis of GRL-06579A (**1**), an HIV-1 protease inhibitor effective against multi-protease-inhibitor-resistant viruses, is described. A convergent strategy that utilizes heterobimetallic multifunctional catalysts developed in our group is a key feature of the synthesis. The chirality of the bicyclic tetrahydrofuran unit of **1** was introduced through Al–Li–bis(binaphthoxide) (ALB) catalyst-controlled Michael addition of dimethyl malonate to racemic 4-O-protected cyclopentenone. ALB afforded not only the *trans* adduct with up to 96% *ee* from a matched substrate through kinetic resolution, but also the *cis* adduct with 99% *ee* through a catalyst-controlled Michael addition to a mismatched substrate. The Michael addition to produce the unusual *cis* adduct is described in detail. The framework of the bicyclic tetrahydrofuran was constructed by an intramolecular oxy-Michael reaction. The amino alcohol unit was constructed by an La–Li_3–tris(binaphthoxide) (LLB)-catalyzed diastereoselective nitroaldol reaction of *N*-Boc aldehyde (Boc = *tert*-butoxycarbonyl) derived from L-phenylalanine. LLB promoted the nitroaldol reaction without racemization of the chiral aldehyde to give the nitroaldol adduct in 85% yield and with 93:7 diastereoselectivity and over 99% *ee*.

Keywords: asymmetric catalysis · asymmetric synthesis · HIV protease inhibitor · Michael addition · nitroaldol reaction

Introduction

Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV).[1] The AIDS epidemic is one of the most serious global social problems in the world. The current estimate is that over 40 million people worldwide are suffering from HIV/AIDS.[2] Although recent progress in exploring HIV-1 protease inhibitors has significantly contributed to improving AIDS chemotherapy in industrialized countries,[3] the rapid emergence of multi-drug-resistant strains of the virus is an important concern.[4] Rational drug development to retain full activity against a broad range of multi-drug-resistant viruses is highly desirable. On the basis of protein–ligand X-ray crystal analysis, Ghosh et al. developed a new generation of protease inhibitors with promising antiviral potency toward multi-drug-resistant viruses.[5] Their inhibitors are designed to make multiple hydrogen-bonding interactions with the active site of the HIV-1 protease. Because only small structural changes are induced at the active-site backbone in multiple mutations of the protease, a strategy targeting the protein backbone would provide a general prototype for the design of chemotherapeutic agents to combat drug resistance. GRL-06579A (**1**)[5b] is one of the most promising drug candidates in their studies, with superior activity against a wide range of multi-protease-inhibitor-resistant strains relative to other US Food and Drug Administration (FDA) approved inhibitors.



GRL-06579A (**1**)

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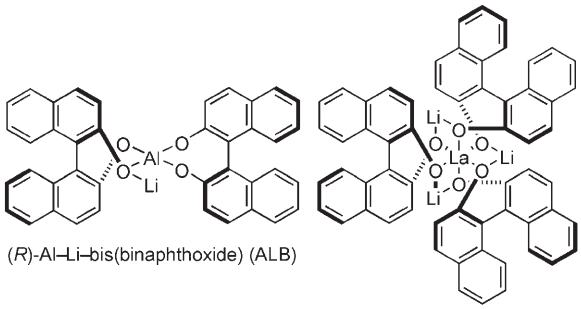
Other serious problems of AIDS chemotherapy include high therapeutic doses, expensive synthesis of protease inhibitors, and high treatment cost. The ability to supply sufficient quantities of HIV-1 protease inhibitors worldwide, including to affected individuals in developing nations, at an acceptable cost requires an efficient synthetic route.[6] The original synthesis of optically pure GRL-06579A (**1**) elegantly used the known chiral building blocks *cis*-4-cyclopentene-1,3-diol 1-acetate and an amino acid derived epoxide.[7,8] The starting materials are commercially available; however, they are relatively expensive, possibly because multistep syntheses are required.

Asymmetric catalysis is a potentially powerful method of providing optically active compounds from inexpensive prochiral substrates.[9] Since our first report of a heterobimetallic rare-earth–alkali-metal–binol catalyst in 1992,[10] our group has been working on bifunctional asymmetric catalysis to enable facile and efficient access to diverse functionalized chiral molecules.[11,12] We planned to apply our bifunctional asymmetric catalysts to the synthesis of an HIV-1 protease inhibitor. Herein, we report our efforts to synthesize GRL-06579A (**1**) by utilizing an Al–Li–bis(binaphthoxide) (ALB) complex[13] and an La–Li_3–tris(binaphthoxide) (LLB) complex.[14]

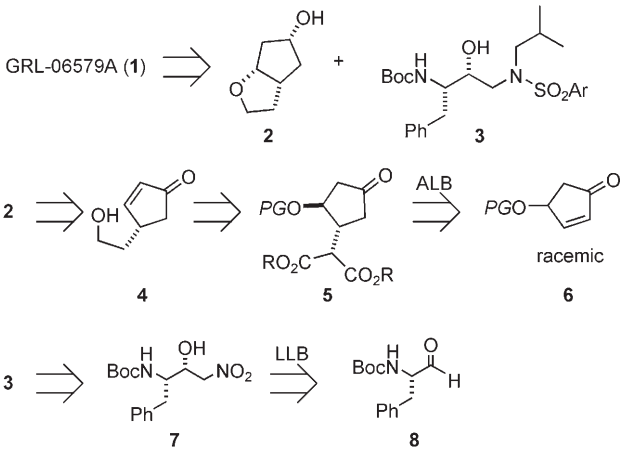


Abstract in Japanese:

多剤耐性ウイルスにも高い有効性を示す HIV-プロテアーゼ阻害剤 GRL-06579A の触媒的不斉合成を行った。二環性テトラヒドロフラン部のキラリティーは、Al-Li-bis(binaphthoxide) (ALB)触媒によるラセミ体の 4-TBSO-シクロペンテノンに対する触媒制御 Michael 付加反応にて導入した。速度論分割条件ではトランス付加体が最高 96% *ee* で得られ、さらに触媒制御で反応が進行することでシス付加体も 99% *ee* で得られた。分子内オキシ Michael 反応により二環性骨格を構築した。アミノアルコール部はアミノ酸由来の光学活性 *N*-Boc アルデヒドに対するジアステレオ選択的ニトロアルドール反応により構築した。La-Li_3-tris(binaphthoxide) (LLB)触媒を用いることで基質のラセミ化を伴うことなく、93：7 の立体選択性、>99% *ee* にて生成物を得た。

Results and Discussion

One structural characteristic of GRL-06579A (**1**) is the bicyclic tetrahydrofuran unit. As shown in Scheme 1, we planned to synthesize the bicyclic tetrahydrofuran fragment **2**



Scheme 1. Retrosynthetic analysis of GRL-06579A (**1**). Boc = *tert*-butoxycarbonyl, *PG* = protecting group.

and the amino alcohol fragment **3** by using our heterobimetallic catalysts, and then combine the two fragments by following the procedure of Ghosh et al.[5b] The framework of the bicyclic tetrahydrofuran could be constructed by an intramolecular oxy-Michael reaction (intramolecular hydroalkoxylation) from **4**, followed by stereoselective reduction. We planned to construct chirality in **4** by using a catalytic kinetic resolution[15] through a Michael reaction of racemic enone **6** with a malonate promoted by (*R*)-ALB. Because optically active 4-O-protected cyclopentenone is extremely expensive,[16] we used a racemic enone **6** that can be synthesized in two steps from inexpensive furfuryl alcohol.[17] The amino alcohol unit is a common building block in protease inhibitors.[6] The unit **3** could be synthesized from nitro alcohol **7**, which is readily available through an LLB-catalyzed diastereoselective nitroaldol reaction of the known chiral aldehyde **8** derived from L-phenylalanine with nitromethane.

Initial optimization studies of the Michael reaction of racemic 4-O-protected cyclopentenones and malonates are summarized in Table 1. Among a couple of effective catalysts for the Michael reaction of cyclic enones with malonates, ALB was selected on the basis of the results of the initial catalyst screening. The previously reported optimized conditions for 2-cyclohexen-1-one, ALB/KO*t*Bu (0.9 mol equiv to ALB) mixed with 4-Å molecular sieves,[18] gave promising results. Other chiral rare-earth-metal catalysts, such as a La(O*i*Pr)$_3$–linked-BINOL complex,[19] gave less satisfactory results in terms of reactivity and selectivity. In Table 1, the reaction conditions for kinetic resolution were optimized by using 0.5 molar equivalents of malonate **9** and 5 mol% of ALB.[20] The ratio of enone **6** to desired *trans*-**5**

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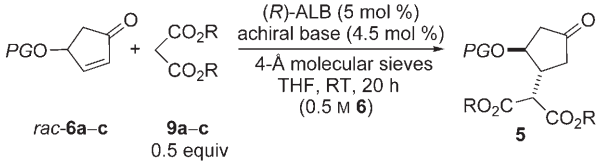
Table 1. Optimization of kinetic resolution of enone **6** catalyzed by (*R*)-ALB.



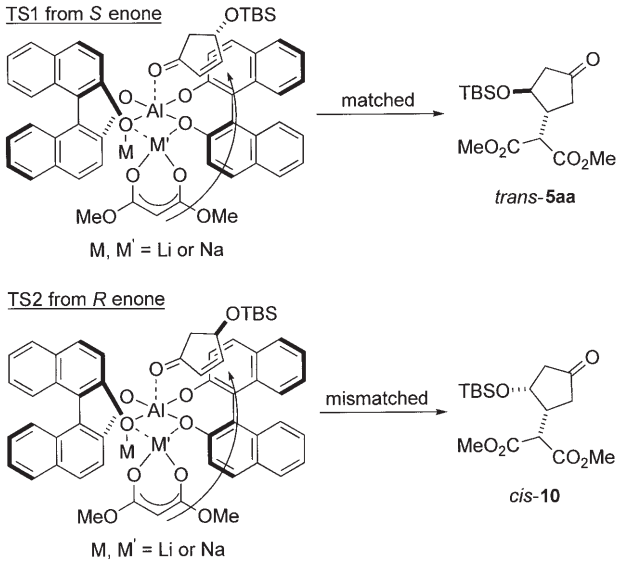
Entry	*PG*	R	Achiral base	Product	**5**[a] [%]	*ee*[b] [%]
1	*t*BuMe$_2$Si (**6a**)	Me (**9a**)	KO*t*Bu	**5aa**	49	93
2	*t*BuMe$_2$Si (**6a**)	Et (**9b**)	KO*t*Bu	**5ab**	48	78
3	*t*BuMe$_2$Si (**6a**)	Bn (**9c**)	KO*t*Bu	**5ac**	24	95
4	*t*BuMe$_2$Si (**6a**)	Me (**9a**)	none	**5aa**	14	96
5	*t*BuMe$_2$Si (**6a**)	Me (**9a**)	NaO*t*Bu	**5aa**	48	95
6	acetyl (**6b**)	Me (**9a**)	NaO*t*Bu	**5ba**	0[c]	–[c]
7	CH_3OCH_2(**6c**)	Me (**9a**)	NaO*t*Bu	**5ca**	40	94
8[d]	*t*BuMe$_2$Si (**6a**)	Me (**9a**)	NaO*t*Bu	**5aa**	48	96

[a] Conversion determined by ^{1}H NMR spectroscopic analysis. [b] Determined by chiral HPLC. [c] The β-eliminated adduct was obtained in 35% yield and with 89% *ee*. [d] Reaction was run with 1.2 M **6**.

was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Among the malonates examined (Table 1, entries 1–3), dimethyl malonate (**9a**) had the best reactivity and selectivity. With dimethyl malonate (**9a**), both the conversion and enantioselectivity of *trans*-**5aa** were good after 24 h (Table 1, entry 1: 49% yield, 93% *ee*). Diethyl malonate (**9b**) showed good reactivity, but the selectivity was modest (Table 1, entry 2: 48% yield, 78% *ee*). With dibenzyl malonate (**9c**), *trans*-**5ac** was obtained with high enantioselectivity (95% *ee*); however, the reactivity was poor, the desired *trans*-**5ac** being obtained in only 24% yield after 24 h (Table 1, entry 3). The addition of an achiral base effectively enhanced the reactivity (Table 1, entry 1: with KO*t*Bu vs. entry 4: without achiral base). In the absence of an achiral base, the reactivity decreased significantly (Table 1, entry 4: 14% yield, 96% *ee*). This trend was similar to that observed in reactions of achiral cyclic enones and malonates.[18,21] Comparison of the selectivity factor in Table 1, entries 1 and 5 indicates that NaO*t*Bu gave slightly better results than KO*t*Bu (Table 1, entry 5: 48% yield, 95% *ee*). Thus, further optimizations were performed with NaO*t*Bu. The high selectivity obtained in Table 1, entries 1 and 5 suggests that the racemic pathway catalyzed by the achiral base alone is negligible. We assumed that a catalytic amount of achiral base would coordinate to the chiral ALB catalyst, thereby enhancing the rate-determining enolate-formation step. Among the cyclopentenone derivatives investigated, **6a**, which has a 4-*t*BuMe$_2$SiO group, gave the best reactivity and selectivity. In the case of the Ac-protected substrate **6b**, β elimination of the AcO group occurred under the reaction conditions (Table 1, entry 6). The β-eliminated Michael adduct was obtained in 35% yield and 89% *ee*; however, the β-eliminated adduct was not suitable for the synthesis of fragment **2**. The results of **6c** with CH_3OCH_2- ether are comparable to those of **6a** (Table 1, entry 7: 40% yield, 94% *ee*), but **6c** was not selected because it is volatile. Therefore, **6a** was chosen for the synthesis of GRL-06579A (**1**). Under the optimized reaction conditions (enone **6a**, 5 mol% ALB, 4.5 mol% NaO*t*Bu, 0.5 equiv malonate **9a**), the kinetic resolution of enone **6a** proceeded without any problems under more-concentrated conditions (1.2 M; Table 1, entry 8). The desired *trans*-**5aa** was obtained in 48% yield (determined by NMR spectroscopy) and 96% *ee*.

At this stage, we found that not only *trans*-**5aa** but also sterically hindered *cis*-**10** formed as a minor adduct under the ALB-catalyzed reaction conditions. Although the yield of *cis*-**10** was poor (4% yield by NMR spectroscopy), the enantioselectivity of *cis*-**10** was excellent (99% *ee*). The relative configuration of **10** was confirmed by an NOE experiment. The absolute configuration of *cis*-**10** was confirmed after β elimination of the *t*BuMe$_2$SiO group by comparing the HPLC retention time with that of the same β-eliminated Michael adduct from *trans*-**5aa**. We became interested in the unusual minor adduct *cis*-**10**, because the formation of *cis*-**10** with high enantiomeric excess implies that ALB promotes the Michael reaction through a catalyst-controlled stereochemical course rather than in a substrate-controlled manner. Plausible transition-state models to afford *trans*-**5aa** from *S* enone **6a** (TS1) and *cis*-**10** from *R* enone **6a** (TS2) are shown in Scheme 2. We speculated that ALB would recognize the enantioface of enone, thus promoting unusual *cis* addition from *R* enone **6a** through TS2 in spite of severe steric hindrance at the 4-position (Scheme 2). As *cis*-**10** is also a suitable intermediate for the synthesis of GRL-06579A (**1**), we decided to optimize the reaction con-

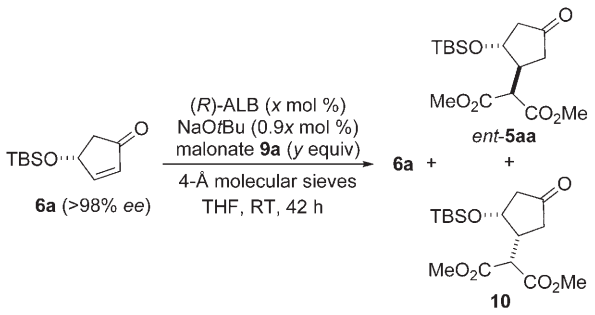


Scheme 2. Postulated transition-state models to afford *trans*-**5aa** from *S* enone **6a** and *cis*-**10** from *R* enone **6a**. TBS = *tert*-butyldimethylsilyl.

ditions further to improve the total yield of the *trans*- and *cis*-adducts.

To evaluate the ability of ALB to promote the *cis*-Michael reaction from a mismatched substrate, we first investigated the Michael reaction by using optically active *R* enone **6a** (>98% *ee*) and (*R*)-ALB (Table 2). The *cis*-addition of

Table 2. Catalyst-controlled asymmetric *cis*-Michael reaction of chiral enone **6a**.



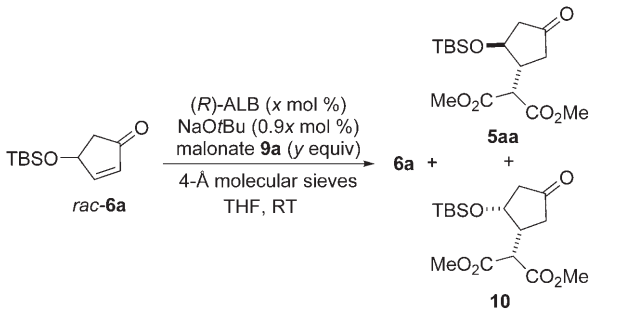
Entry	ALB [mol%]	Malonate [equiv]	**6a**/*ent*-**5aa**/**10**[a]	*ee* of **6a**[b] [%]	*ee* of *ent*-**5aa**[b] [%]	*ee* of **10**[b] [%]
1	10	1.0	34:14:52	99	90	99
2	10	1.5	29:19:52	99	92	99
3	10	2.0	27:21:52	99	91	99
4	10	3.0	25:28:46	99	94	99
5	20	1.0	29:12:59	99	89	99
6	30	1.0	23:14:63	99	86	99

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [b] Determined by chiral HPLC.

1 equivalent of dimethyl malonate (**9a**) was promoted by 10 mol% of (*R*)-ALB, and *cis*-**10** was obtained in 52% yield and with 99% *ee*, together with 14% of *trans-ent*-**5aa** (90% *ee*) (Table 2, entry 1). The lower enantiomeric excess of *trans-ent*-**5aa** was due to a minor contamination of the starting material with *S* enone **6a**. To improve the yield of the desired *cis*-**10**, the amount of malonate **9a** used was increased (Table 2, entries 2–4). The yield of *cis*-**10**, however, did not improve. Instead, there was an increase in the yield of *trans-ent*-**5aa**, which was produced through substrate control. Although detailed mechanistic studies are required to clarify the precise reasons, we speculate that *cis*-**10** might deactivate the ALB catalyst to suppress the catalyst-controlled *cis*-addition pathway. Higher catalyst loading slightly improved the yield of *cis*-**10**, but the results were still not satisfactory (Table 2, entry 5: 59% yield with 20 mol% ALB; entry 6: 63% yield with 30 mol% ALB).

On the basis of the results shown in Tables 1 and 2, we investigated the Michael reaction with racemic enone **6a** and 1 equivalent of dimethyl malonate (Table 3, entries 2–6). As expected, the yield of *cis*-**10** improved to 11% after 24 h, and its enantiomeric excess was high (99% *ee*) (Table 3, entry 1 vs. 2). The enantiomeric excess of *trans*-**5aa**, however, decreased significantly (86% *ee*) because of a competitive substrate-controlled reaction from mismatched *R* enone **6a** to afford a minor enantiomer of *trans*-**5aa**. When the

Table 3. Catalytic asymmetric Michael reaction: trials to maximize total yield of *trans*-**5aa** and *cis*-**10**.



Entry	ALB [mol%]	Malonate [equiv]	*t* [h]	**6a**/**5aa**/**10**[a]	*ee* of **6a**[b] [%]	*ee* of **5aa**[b] [%]	*ee* of **10**[b] [%]
1	10	0.5	24	48:48:4	80	96	99
2	10	1.0	24	33:56:11	99	86	99
3[c]	10	1.0	24	39:53:8	96	92	99
4[c]	10	1.0	66	22:56:22	99	82	99
5	20	1.0	61	17:56:27	99	82	99
6[c]	20	1.0	61	19:56:25	99	83	99

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [b] Determined by chiral HPLC. [c] Malonate **8a** was added slowly over 6 h.

malonate was added slowly over 6 h, *trans*-**5aa** was obtained in 53% yield and with 92% *ee*, and *cis*-**10** was obtained in 8% yield and with 99% *ee* (Table 3, entry 3). Prolonging of the reaction time had negative effects on the enantioselectivity of *trans*-**5aa** (Table 3, entry 4). With 20 mol% of ALB, the yield of *cis*-**10** increased to 27% (Table 3, entry 5) and 25% (Table 3, entry 6: with slow addition), but there were no positive effects on the enantiomeric excess of *trans*-**5aa**. On the other hand, in all entries in Table 3, the enantiomeric excess of c*is*-**10** was 99% *ee*. The high enantiomeric excess indicates that *cis*-**10** was produced only from mismatched *R* enone **6** by a catalyst-controlled pathway. No *cis*-Michael reaction proceeded from matched *S* enone **6**.

The results shown in Table 3 indicate that it was difficult to obtain both *trans*-**5aa** and *cis*-**10** simultaneously in good yield and with good enantioselectivity due to the competitive substrate-controlled pathway from mismatched *R* enone **6a**, thus decreasing the enantiomeric excess of *trans*-**5aa**. Therefore, we turned our attention to the sequential kinetic resolution/catalyst-controlled Michael reaction (Scheme 3). Under the optimized reaction conditions for kinetic resolution in Table 1 (racemic enone **6a**, 5 mol% ALB, 4.5 mol% NaO*t*Bu, 0.5 equiv dimethyl malonate **9a**, 1.2 M), we performed the kinetic resolution of enone **6a** on the gram scale (Scheme 3). NMR spectroscopic analysis of the crude reaction mixture indicated the ratio of **6a**/*trans*-**5aa**/*cis*-**10** to be 48:48:4. After purification, the target *trans*-**5aa** was isolated in 44% yield and with 96% *ee*, and enone **6a** was recovered in 45% yield and with 80% *ee*. *cis*-**10** was also isolated in 3% yield and with 99% *ee*. The recovered **6a** with 80% *ee* was then used for the second catalyst-controlled Michael reaction with 1.0 equivalent of malonate **9a**, 10 mol% of (*R*)-

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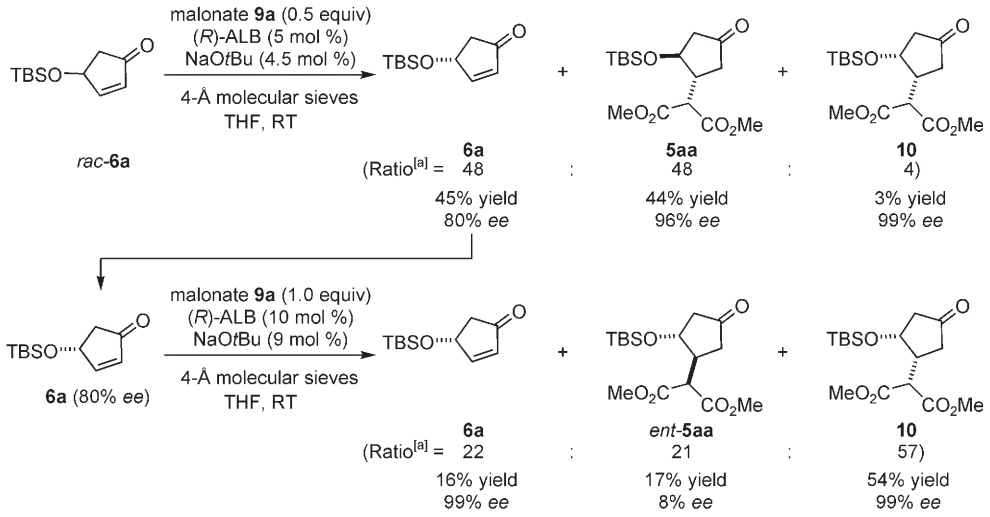
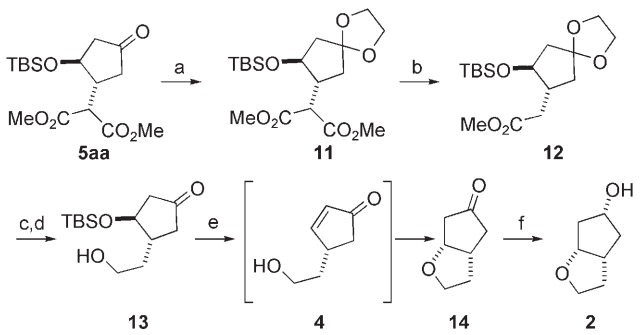


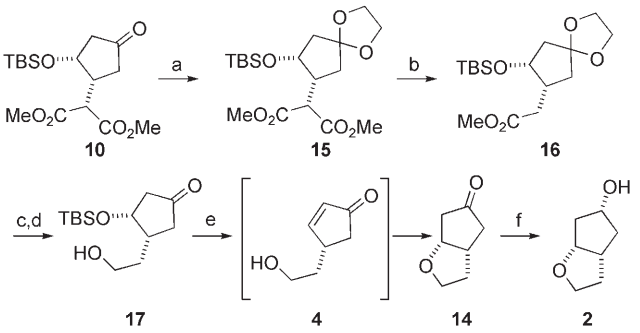
Scheme 3. Sequential kinetic resolution/catalyst-controlled Michael reaction of enone **6a** promoted by (*R*)-ALB. [a] Determined by NMR spectroscopy.

ALB, and 9 mol% of *t*BuONa. *cis*-**10** was isolated in 54% yield and with 99% *ee*. In the second reaction, *trans*-**5aa** was obtained in 17% yield and with low enantioselectivity (8% *ee*). After the second reaction, enone **6a** was recovered in 16% yield and with 99% *ee*. Through the two-step process, a total of 71% of racemic **6a** was converted into *trans*-**5aa** (44% yield, 96% *ee*) and *cis*-**10** (3% yield, 99% *ee* in the first run, 24% yield, 99% *ee* from racemic **6a** for the two runs), both of which are useful precursors for the bicyclic tetrahydrofuran **2**.

The *trans*-**5aa** and *cis*-**10** obtained were transformed into bicyclic tetrahydrofuran **2** (Schemes 4 and 5). Protection of the ketone moiety of **5aa** with 1,2-bis(trimethylsilyloxy)-ethane and $(CH_3)_3SiOTf$ at −78 °C gave acetal **11** in 80% yield.[22] Decarboxylation of **11** with LiCl and H_2O in DMSO at 140 °C produced **12** in 83% yield. Reduction of the ester unit of **12** with $LiAlH_4$ and deprotection of the acetal moiety with NaI and $CeCl_3{\cdot}7H_2O$[23] afforded **13**. Treatment of **13** with DBU produced a bicyclic tetrahydrofuran unit through β elimination of the *t*BuMe$_2$SiO group followed by an intramolecular oxy-Michael reaction in a one-pot manner. Because the bicyclic ketone **14** is volatile, it was subjected to the next step without purification. Stereoselective reduction of the ketone moiety of **14** from the convex face afforded bicyclic tetrahydrofuran alcohol **2** in 46% yield from **12** (4 steps). Conversion of *cis*-**10** into the same intermediate **2** was also performed with similar efficiency (Scheme 5). In the case of *cis*-**10**, the transformation of acetal **16** into **2** without purification of the intermediates **17** and **14** afforded tetrahydrofuran alcohol **2** in 42% yield from **16** (4 steps)

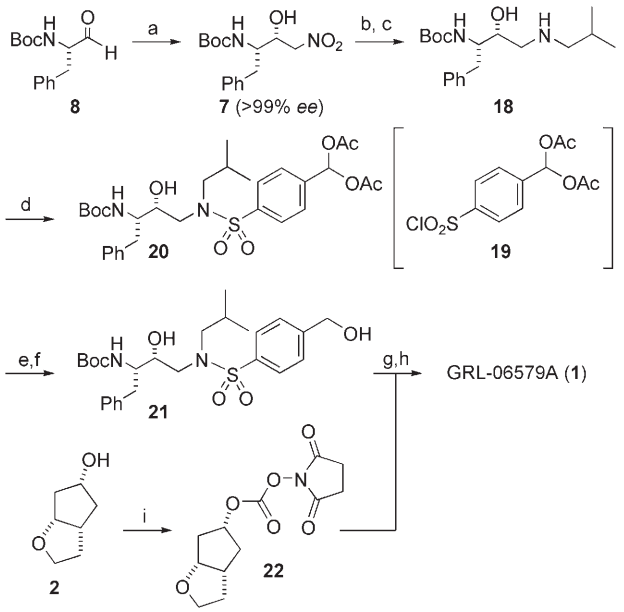


Scheme 4. Synthesis of optically active bicyclic compound **2** from **5aa**. Reagents and conditions: a) 1,2-Bis(trimethylsilyloxy)ethane, $(CH_3)_3SiOTf$, CH_2Cl_2, −78 °C, 8 h, 80%; b) LiCl, H_2O, DMSO, 140 °C, 15 h, 83%; c) $LiAlH_4$, THF, 0 °C, 5 min; d) NaI, $CeCl_3{\cdot}7H_2O$, CH_3CN, 60 °C, 2 h; e) DBU, CH_2Cl_2, 0 °C to room temperature, 5 h; f) $NaBH_4$, MeOH, 0 °C, 10 min (46%, 4 steps from **12**). DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMSO = dimethyl sulfoxide, Tf = trifluoromethanesulfonyl.



Scheme 5. Synthesis of optically active bicyclic compound **2** from **10**. Reagents and conditions: a) 1,2-Bis(trimethylsilyloxy)ethane, $(CH_3)_3SiOTf$, CH_2Cl_2, −78 °C, 8 h, then Et_3N, 78%; b) LiCl, H_2O, DMSO, 140 °C, 15 h, 83%; c) $LiAlH_4$, THF, 0 °C, 5 min; d) NaI, $CeCl_3{\cdot}7H_2O$, CH_3CN, 60 °C, 7 h; e) DBU, CH_2Cl_2, 0 °C to room temperature, 6 h; f) $NaBH_4$, MeOH, 0 °C, 10 min (42%, 4 steps from **16**).

The synthesis of the amino alcohol fragment and the coupling of the fragments are summarized in Scheme 6. Chiral *N*-Boc amino aldehyde **8**, prepared from L-phenylalanine by a known procedure,[24] was utilized as the starting material. A nitroaldol reaction of aldehyde **8** with nitromethane was



Scheme 6. Synthesis of GRL-06579A by a diastereoselective nitroaldol reaction. Reagents and conditions: a) (*R*)-LLB (5 mol%), nitromethane (10 equiv), THF, −40°C, 24 h, 85%, d.r. = 93:7, >99% *ee*; b) Pd/C (10 mol%), H_2, MeOH, room temperature, 21 h; c) $NaBH(OAc)_3$, isobutyraldehyde, room temperature, 4 h, 66% (2 steps); d) **19**, *i*Pr_2NEt, DMAP, THF, room temperature, 4 h, 68%; e) K_2CO_3, MeOH, room temperature, 1.5 h, quant.; f) $NaBH_4$, MeOH, 0°C, 15 min, 90%; g) 30% TFA in CH_2Cl_2, room temperature, 30 min; h) **22**, *i*Pr_2NEt, CH_3CN, room temperature, 12 h, 94% (2 steps); i) *N*,*N*′-disuccinimidyl carbonate, Et_3N, CH_3CN, room temperature, 24 h, 76%. DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

promoted by using 5 mol% of (*R*)-LLB at −40°C, and nitroaldol adduct **7** was obtained in 85% yield and with high diastereoselectivity (93:7) after 24 h. Although the *N*-Boc amino aldehyde **8** readily racemizes under basic conditions, chiral stationary phase HPLC analysis of **7** showed that the enantiomeric excess of **7** was over 99% *ee*. The result suggests that (*R*)-LLB chemoselectively deprotonated the α-proton of nitromethane rather than that of aldehyde **8**.[25,26] Conversion of the nitro group in **7** by Pd/C under H_2 atmosphere followed by reductive alkylation with isobutyraldehyde and $NaBH(OAc)_3$ gave secondary amine **18**, which was treated with *p*-(diacetoxymethyl)phenylsulfonyl chloride **19**[27] in the presence of diisopropylethylamine to give sulfonamide **20**. Further conversion into GRL-06579A was performed by following known procedures.[5b] After removal of the two acetate groups in **20** with K_2CO_3, reduction of the resulting aldehyde with $NaBH_4$ in methanol afforded amino alcohol fragment **21**. Finally, fragment **21** was treated with trifluoroacetic acid to remove the Boc group; the resulting amine was coupled with carbonate fragment **22**, prepared from **2** with *N*,*N*-disuccinimidyl carbonate and Et_3N, to afford GRL-06579A in 94% yield (2 steps from **21**).

Conclusions

We have achieved a convergent synthesis of GRL-06579A (**1**) through a catalytic kinetic resolution/catalyst-controlled asymmetric Michael reaction sequence of racemic 4-*t*Bu-Me_2SiO-cyclopentenone **6a** by using (*R*)-ALB and a catalytic diastereoselective nitroaldol reaction with (*R*)-LLB. The catalytic kinetic resolution of enone **6a** gave Michael adduct *trans*-**5aa** (44% yield, 96% *ee*), and enone **6a** was recovered in 44% yield (80% *ee*). The second catalyst-controlled asymmetric Michael reaction of recovered enone **6a** afforded *cis*-**10** in 54% yield and 99% *ee*. Diastereoselective nitroaldol reaction of chiral *N*-Boc aldehyde **8** proceeded without racemization to give nitroaldol adduct **7** in 85% yield (*syn*/*anti* = 93:7) and with over 99% *ee*. Further improvement of the catalyst-controlled *cis*-Michael addition is in progress.

Experimental Section

General

Spectral data and ^{13}C NMR spectra of all new compounds, detailed experimental procedures for chiral-catalyst preparation, catalytic asymmetric Michael reactions, and the nitroaldol reaction, and the synthesis of GRL-06579A (**1**) are available as the Supporting Information. $LiAlH_4$ for ALB preparation was purchased from Wako and freshly opened in a dry box. La(O*i*Pr)$_3$ for LLB preparation was purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (sales@kojundo.co.jp).

Syntheses

(*R*)-ALB in THF: A solution of (*R*)-binol (1.03 g, 3.60 mmol; binol = 1,1′-bi-2,2′-naphthol) in THF (8 mL + 2 × 2 mL for rinsing) was slowly added to a suspension of $LiAlH_4$ (powder, 68.3 mg, 1.80 mmol), which was freshly opened in a dry box just prior to use, in THF (8 mL) at 0°C by syringe. The resulting mixture was stirred at 0°C for 30 min, then at room temperature for 1 h. The mixture was then kept standing without stirring for 12 h, and the supernatant was used as a 0.1 M solution of (*R*)-ALB in THF. (Caution: The quality of $LiAlH_4$ is important for high enantioselectivity. $LiAlH_4$ powder should be used. Commercially available solutions of $LiAlH_4$ in THF are not suitable for ALB preparation.)

Procedure for kinetic resolution catalyzed by (*R*)-ALB: 4-Å molecular sieves (1.50 g) in a flask was flame-dried for 5 min under reduced pressure (0.7 kPa). (Caution: Activation of 4-Å molecular sieves is important to avoid decomposition of ALB and to achieve good selectivity. Activated 4-Å molecular sieves should be handled under Ar atmosphere). Upon cooling to room temperature, the flask was refilled with Ar, and dimethyl malonate (**9a**; 706 μL, 6.18 mmol), (*R*)-ALB (5 mol% with respect to **6a**, 6.20 mL, 0.1 M in THF, 0.62 mmol), and *t*BuONa (1.1 mL, 0.5 M in THF, 0.55 mmol) were added. The mixture was cooled to 0°C in an ice bath, and **6a** (2.62 g, 12.35 mmol, in 3.1 mL of THF) was added. (Compound **6a** was dried by azeotrope with toluene (3×) prior to use.) After the mixture was stirred for 5 min at 0°C, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. After the mixture was stirred for 20 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL), washed with brine (20 mL), and dried over Na_2SO_4. After evaporation under reduced pressure, the ratio of **6a**/*trans*-**5aa**/*cis*-**10** (48:48:4) was determined by ^1H NMR spectroscopic analysis of the crude residue. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane = 1:9) to afford **5aa** (1.89 g, 5.48 mmol, 44% yield, 96% *ee*) as a brown oil, **10** (115 mg, 0.334 mmol, 3% yield, 99% *ee*) as a brown oil, and recovered **6a** (1.19 g, 45% recovery, 80% *ee*) as a brown oil. **5aa** $[\alpha]_D^{26} = +71.8$ ($c = 2.51$, $CHCl_3$, 96% *ee*).

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Procedure for catalyst-controlled Michael reaction with (*R*)-ALB: A mixture of activated 4-Å molecular sieves (196 mg), **9a** (179.4 μL, 1.57 mmol), (*R*)-ALB (10 mol%, 1.57 mL, 0.1 M in THF, 0.157 mmol), and *t*BuONa (0.28 mL, 0.5 M in THF, 0.140 mmol) was cooled to 0 °C under Ar atmosphere. Compound **6a** (333.4 mg, 1.57 mmol, 80% *ee*, in 1.6 mL of THF) was added to the mixture. (Compound **6a** was dried by azeotrope with toluene (3×) prior to use.) After it was stirred for 5 min at 0 °C, the reaction mixture was allowed to warm to room temperature. After further stirring of the mixture for 65 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc (3×10 mL), washed with brine (10 mL), and dried over Na_2SO_4. After evaporation under reduced pressure, the ratio of **6a**/*trans*-**5aa**/*cis*-**10** (22:21:57) was determined by ^{1}H NMR spectroscopic analysis of the crude residue. The residue was purified by flash column chromatography (silica gel, EtOAc/hexane = 1:9) to give **5aa** (90.5 mg, 0.263 mmol, 17% yield, 8% *ee*) as a brown oil, **10** (280 mg, 0.814 mmol, 54% yield, 99% *ee*) as a brown oil, and recovered **6a** (54.6 mg, 16% recovery, 99% *ee*) as a brown oil.

(*R*)-LLB in THF: A solution of La(O*i*Pr)$_3$ (5 mL, 1.00 mmol, 0.20 M in THF) was added slowly to a stirred solution of (*R*)-binol (859 mg, 3.00 mmol) in THF (8 mL) at 0 °C. The solution was stirred for 30 min at room temperature, then solvent and *i*PrOH were removed slowly under reduced pressure, and the residue was dried for 1 h under vacuum. The residue was cooled at 0 °C, and THF (8 mL) was added. BuLi (1.88 mL, 3.00 mmol, 1.60 M in hexane) was added slowly to the solution. After the mixture was stirred for 1 h at room temperature, the solvent was removed slowly under reduced pressure, and the residue was dried for 3 h under vacuum. The residue was cooled at 0 °C, and THF (7.52 mL) was added. The mixture was stirred at room temperature for 1 h to afford (*R*)-LLB solution (0.133 M in THF).

Diastereoselective nitroaldol reaction catalyzed by (*R*)-LLB: Nitromethane (381 μL, 7.03 mmol) was added to a solution of **8** (175 mg, 0.703 mmol) in THF (2.8 mL) at −40 °C, and the mixture was stirred for 1 h at −40 °C. (*R*)-LLB (0.133 M in THF, 265 μL, 0.0352 mmol, 5 mol%) was added, and the mixture was stirred for 24 h at −40 °C. The reaction was quenched with saturated aqueous NH_4Cl (3 mL), and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2) to afford **7** (186 mg, 85%, *syn*/*anti* = 93:7, >99% *ee*) as a colorless solid. HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol = 20:1, 1.0 mL min^{-1}, detection at 254 nm): t_R = 19.6 min (major), 24.0 min (minor).

Acknowledgements

This work was supported by a Grant-in-Aid for Specially Promoted Research and a Grant-in-Aid for Encouragements for Young Scientists (B) (for Y.S.) from the JSPS and MEXT.

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Received: October 2, 2007
Published online: December 27, 2007

