Tetrahedron 66 (2010) 4730–4737

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric syntheses of a GPR40 receptor agonist via diastereoselective and enantioselective conjugate alkynylation

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ARTICLE INFO

Article history:
Received 1 March 2010
Received in revised form
2 April 2010
Accepted 2 April 2010
Available online 9 April 2010

Keywords:
GPR40
Conjugate addition
Diastereoselective
Enantioselective
Oxazepanedione
Cinchonidine
β-Alkynyl acid
Zincate

ABSTRACT

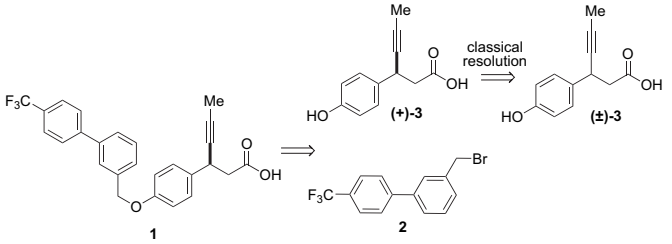
Two asymmetric methods to synthesize a potent GPR40 receptor agonist are reported. Both synthetic routes utilize readily available, inexpensive starting materials and reagents. The first route relies on a highly diastereoselective conjugate alkynylation of an ephedrine-derived oxazepanedione acceptor. The second route features the enantioselective alkynylation of a Meldrum's acid-derived acceptor mediated by a chiral zinc cinchonidine reagent.

1. Introduction

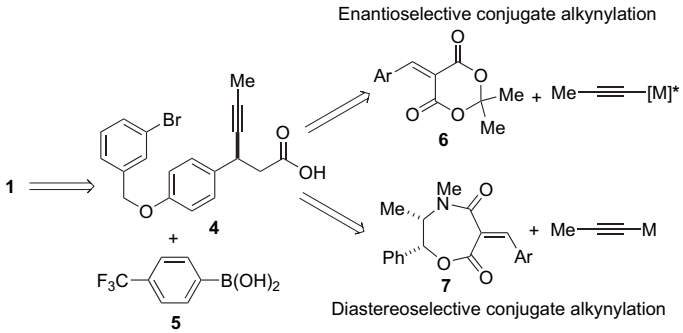
The recent recognition of the function of the G-protein coupled receptor GPR40[1] in modulating insulin secretion has provided insight into regulation of carbohydrate and lipid metabolism in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes, cardiovascular disease, and dyslipidemia.

Recent efforts at Amgen led to the discovery of the potent GPR40 receptor agonist **1**.[2] To supply toxicological and clinical studies, a scalable synthesis of **1** was developed. This convergent nine-step route relied on the synthesis and coupling of two key fragments, biaryl bromide **2** and the chiral β-alkynyl acid (+)-**3** (Scheme 1).[3] Due to the lack of suitable methods for asymmetric alkynylation on large-scale, (+)-**3** was initially prepared by racemic synthesis followed by resolution via diastereomeric salt formation. Although this process was suitable for kilogram-scale preparation of **1**, the use of classical resolution limited the theoretical yield to 50% (actual yield 35%) and an asymmetric route was desired.

We now report the development of two new asymmetric syntheses of **1** employing inexpensive raw materials and reagents (Scheme 2). The first route relies on the diastereoselective



Scheme 1. First generation synthetic route.



Scheme 2. Retrosynthetic analysis.

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doi:10.1016/j.tet.2010.04.019

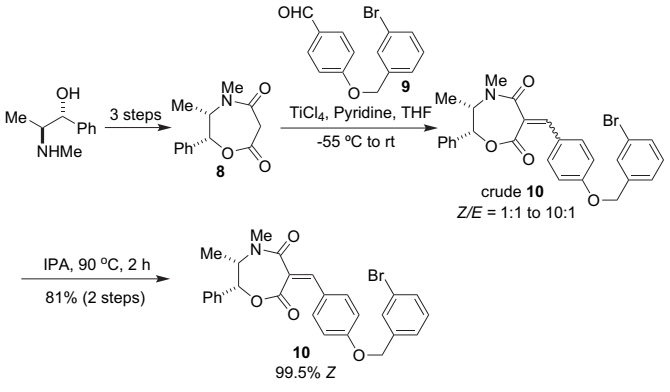
conjugate alkynylation of an ephedrine-derived oxazepanedione acceptor **7**. The second approach features a practical and highly enantioselective conjugate alkynylation of Meldrum's acid-derived acceptors **6** employing cinchonidine, an inexpensive and recyclable chiral mediator (<$100/kg).[4] Both of these strategies relied on the preparation and cross-coupling of the key chiral intermediate **4** with boronic acid **5**. β-Alkynyl acid **4** was considered attractive since the optical purity of scalemic material could be readily upgraded via crystallization of the corresponding α-methylbenzylamine salt.

2. Results and discussion

2.1. Diastereoselective conjugate alkynylation

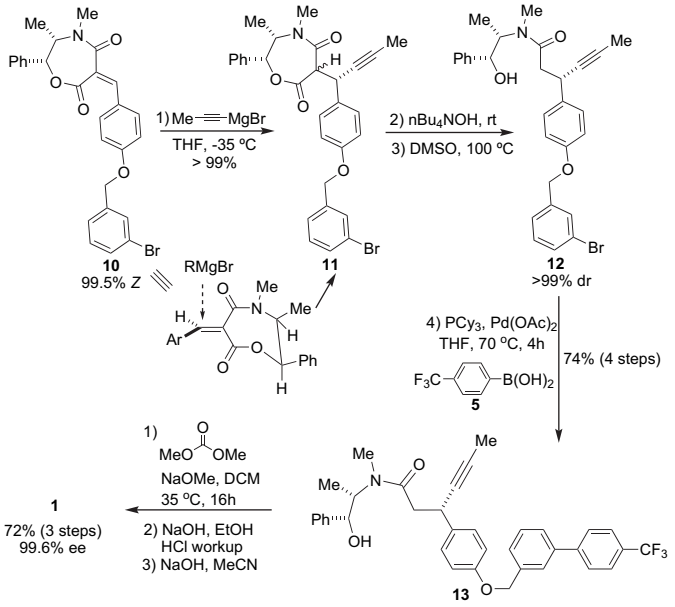
The oxazepanedione **8** was first introduced by Mukaiyama[5] as an effective chiral auxiliary for a number of asymmetric transformations.[6] Recently, Carreira and co-workers[7] reported the diastereoselective conjugate addition of in situ generated zinc alkynylides to chiral oxazepanedione acceptors to provide access to enantiomerically enriched β-alkynyl acids. However, in this case, the substrate scope was limited to aliphatic acceptors and additions to acceptors with aromatic residues did not proceed, presumably due to the weak nucleophilicity of the in situ prepared zinc alkynylide. Therefore, we speculated that a stronger nucleophile, such as an alkynyl Grignard reagent, could resolve this issue.

Oxazepanedione **8** was conveniently prepared in a three-step sequence from (−)-ephedrine and dimethylmalonate (Scheme 3).[8] Condensation of **8** with aldehyde **9** was performed in the presence 1.05 equiv of $TiCl_4$ and pyridine to provide a mixture of geometric isomers favoring the (*Z*)-alkylidene **10** in ratios of 1–10:1[6b] Assuming high facial selectivity in the conjugate addition step, control of *E*- versus *Z*-olefin geometry would be critical to obtaining a high optical purity of the final product. Although the isomers could be separated by chromatography, for operational ease we desired a chromatography-free process to **10**. With this goal in mind, additional experimentation revealed that a >95:5 *Z*/*E* ratio could be obtained for crude **10** when 5 equiv of $TiCl_4$ were used in the condensation reaction. After further process refinement, a crystallization driven thermal isomerization was developed, which took advantage of the solubility difference between the *Z*/*E*-isomers in isopropanol. For example, heating a 1:1 *Z*/*E*-mixture in isopropanol at 90 °C for 2 h, followed by cooling and filtration, provided **10** as a crystalline solid in 81% yield and 99.5:0.5 *Z*/*E* ratio.



Scheme 3. Preparation of chiral oxazepanedione acceptor.

The addition of propynylmagnesium bromide to acceptor **10** proceeded smoothly at −35 °C to room temperature, furnishing the adduct **11** in >99% yield as a mixture of diastereomers (3:1) due to non-selective enolate protonation at the Cα stereocenter (Scheme 4). The removal of the chiral auxiliary proved challenging, as commonly used strong acid and basic conditions caused significant decomposition.[9] Eventually cleavage of the auxiliary and transformation to the target **1** was accomplished using a mild multi-step sequence. Hydrolysis of the ester moiety of **11** with *n*-Bu_4NOH in ^{t}BuOH (rt, 6 h) led to an intermediate acid, which was decarboxylated in DMSO at 100 °C to furnish **12**. The high dr of **12** mirrored the *Z*/*E* ratio of the acceptor **10**, which attests to the excellent facial selectivity of the conjugate addition step. In agreement with literature, the stereochemistry of the adduct was consistent with the acceptor reacting through a boat-like conformation with attack of the Grignard reagent occurring from the convex face, *syn* to the substituents on the ring.[7a] Without purification, the crude acyclic amide **12** was coupled with boronic acid **5** using a Pd/PCy_3 catalyst[10] to afford **13** in 74% yield over four steps. Treatment of **13** with a mixture of sodium methoxide and dimethyl carbonate[11] resulted in net cleavage of the amide bond to provide the methyl ester of **1**. Following ester hydrolysis, **1** was isolated as the corresponding sodium salt in 72% yield for the three-step sequence.



Scheme 4. Synthesis of **1** via diastereoselective conjugate alkynylation.

Despite the superb stereoselectivity, this route was considered unattractive for long-term development due to the length of the overall sequence and difficulty to recover the chiral auxiliary.

2.2. Enantioselective conjugate alkynylation

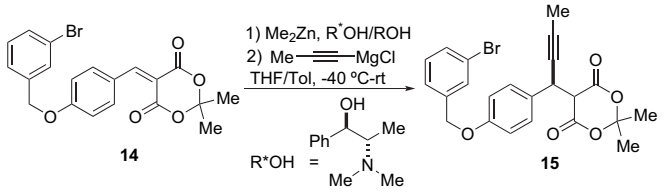
The enantioselective conjugate alkynylation of an ester-derived acceptor represents a particularly direct route to the target molecule **1**. Meldrum's acid-derived acceptors **6** are attractive substrates for such processes since they can be readily prepared by Knoevenagel condensation of Meldrum's acid[12] with aldehydes, and challenges associated with the control and influence of olefin geometry are absent. Furthermore, the conjugate addition products can be easily converted to the corresponding β-alkynyl acids in high yield.[13]

An article by Carreira and co-workers describing the first catalytic enantioselective conjugate additions to Meldrum's acid-derived acceptors employed phenylacetylene and a Cu/QUINAP derived catalyst[14] and a recent contribution from the Fillion group used a Rh/xylyl-MeOBiPHEP catalyst to promote TMS-acetylene additions.[15] However, despite considerable effort that has been devoted to

developing enantioselective conjugate alkynylation processes over the last decade,[16] a general and practical method remains elusive and few successful reports of aliphatic alkynes as nucleophiles have appeared. We recently reported a general, asymmetric alkynylation procedure for the preparation of β-alkynyl acids using a chiral zincate as the mediator.[4] Herein, our efforts leading to the discovery and development of this method, and application to the synthesis of **1** are described.

Following an extensive screen,[17] we identified that treatment of **14** with a Zn–alkynylide species, prepared by treatment of MeC≡CMgCl with a chiral zinc alkoxide reagent generated by the reaction of Me_2Zn with 2 equiv of (1*R*,2*S*)-*N*-methylephedrine, afforded **15** in 95% yield and 49% ee (Table 1, entry 2).[18] During preparation of the requisite zinc alkoxide, the ratio of Me_2Zn to aminoalcohol proved to be critical for the enantioselectivity: a 1:2 ratio was superior to 1:1 (entries 1 and 2), suggesting that a $Zn(OR^*)_2$ precursor is superior to $Zn(OR^*)(Me)$. Interestingly, through addition of the achiral additive trifluoroethanol, 1 equiv of chiral aminoalcohol was sufficient to ensure comparable enantioselectivity without diminishing the efficiency of the process (entry 3).[19]

Table 1
Zn-mediated asymmetric conjugate alkynylation



Entry	Conditions	% ee[a] (% Yield[b])
1	C_3H_3MgCl:Me_2Zn:R*OH=1:1:1	12 (94)
2	C_3H_3MgCl:Me_2Zn:R*OH=1:1:2	49 (95)
3	C_3H_3MgCl:Me_2Zn:R*OH:CF_3CH_2OH=1:1:1:1	51 (95)

[a] Determined by chiral HPLC.
[b] Assay yields determined by quantitative HPLC.

Encouraged by these preliminary results, a systematic study was performed to optimize the reaction parameters. We envisioned that both the enantioselectivity and yield could be further improved by tuning the structure of the chiral zincate[20] by altering the chiral ligand, achiral additive, and counterion (Fig. 1).

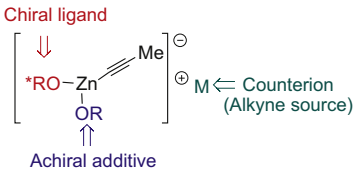
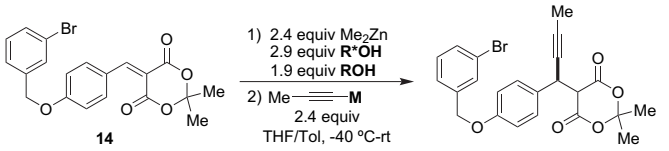


Figure 1. Zincate design parameters.

A marked counterion effect was observed (Table 2, entries 2–4) and the use of MeC≡CMgCl proved superior to MgBr or Li counterions. As expected, the selection of chiral aminoalcohol had a dramatic effect on the enantioselectivity of the process. Our initial success with *N*-methylephedrine prompted us to focus our attention on related ligands and further screening (Fig. 2) indicated that cinchonidine was the most selective ligand (90% ee and 95% yield). Notably, the opposite enantiomer of the product was obtained with similar asymmetric induction by using the pseudoenantiomer cinchonine. Another interesting observation was that the product chirality was completely dictated by the alcohol chiral center of the ligand.

A large selectivity disparity was observed by using different achiral additives (Table 2, entries 1 and 2), which prompted an in depth investigation. Compared to trifluoroethanol, a variety of

Table 2
Counterion effect on asymmetric conjugate alkynylation



Entry	M	R*OH	ROH	%ee[a] (% Yield[b])
1	MgBr	(1*R*,2*S*)-*N*-methylephedrine	MeOH	29 (96)
2	MgBr	(1*R*,2*S*)-*N*-methylephedrine	CF_3CH_2OH	44 (95)
3	MgCl	(1*R*,2*S*)-*N*-methylephedrine	CF_3CH_2OH	54 (96)
4	Li	(1*R*,2*S*)-*N*-methylephedrine	CF_3CH_2OH	0 (7)

[a] Determined by chiral HPLC.
[b] Assay yields determined by quantitative HPLC.

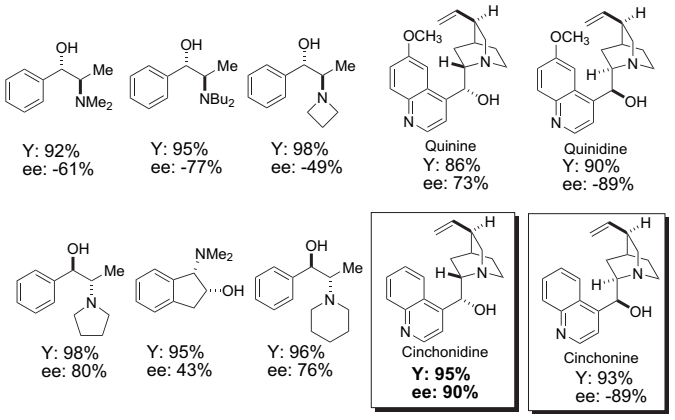


Figure 2. Survey of chiral ligands.

alcohols and carboxylic acids (Fig. 3) also offered comparable enantioselectivity and yield. Ultimately, trifluoroethanol was selected for further optimization studies due to its low cost and easy removal by distillation.[21]

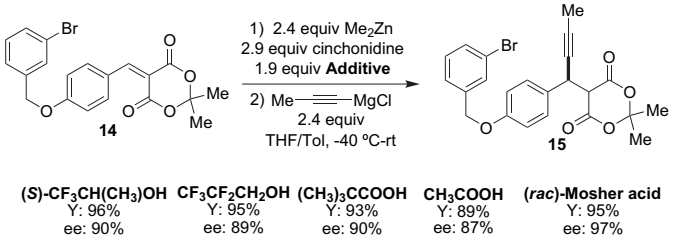
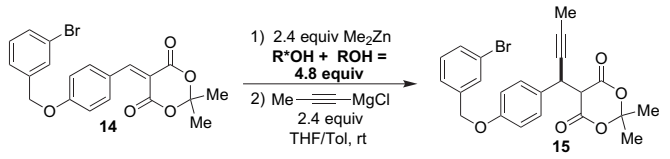


Figure 3. Additive effect on asymmetric conjugate alkynylation.

Throughout the course of the reaction, the observed enantioselectivity did not significantly change with time, and it was also not strongly dependent on the reaction temperature. Reactions at 0 °C and 30 °C gave 92% ee and 88% ee, respectively. However, no reaction was detected below −30 °C and full conversion was generally reached at room temperature. The optimal ratio of chiral to achiral alcohol was determined to be 1.5:1 (Table 3). A slight increase in enantioselectivity was observed when the ratio of chiral to achiral alcohol increased, but the reaction rate and yield diminished.[22] Reactions were slower in the absence of trifluoroethanol. For instance, the reaction in entry 2, reached 100% conversion in 4 h at room temperature. However, the use of zincate derived from 2 equiv of cinchonidine relative to Zn (with no achiral additive) furnished the product in 94% ee but required 24 h to reach 95% conversion (entry 4). Interestingly, addition of a coordinating solvent, such as NMP (entry 5) led to much lower enantioselectivity, presumably due to the disruption of the chiral zincate structure.

Table 3
Ratio of chiral to achiral alcohols

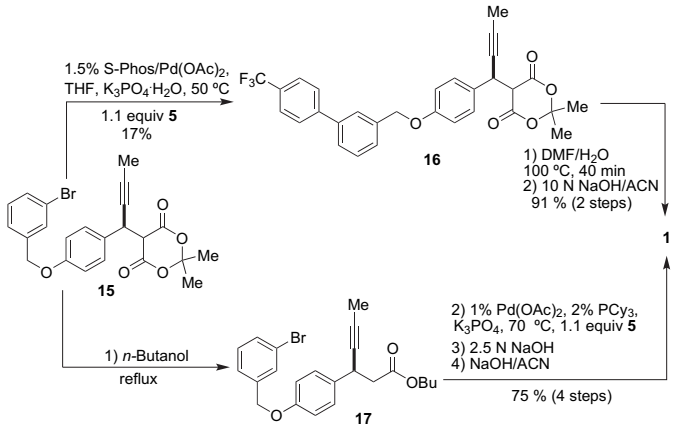


Entry	Cinchonidine/CF_3CH_2OH	%ee[a] (% Yield[b])	Note
1	1:1	76 (98)	Complete in 2 h, rt
2	1.5:1	90 (96)	Complete in 4 h, rt
3	2:1	92 (95)	Complete in 16 h, rt
4	No CF_3CH_2OH	94 (92)	95% Conv. 24 h, rt
5	1.5:1+5 equiv NMP	56 (97)	Complete in 4 h, rt

[a] Determined by chiral HPLC.
[b] Assay yields determined by quantitative HPLC.

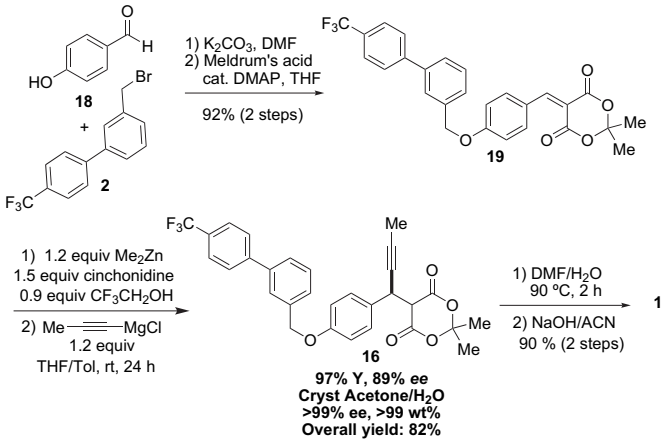
Under the optimized conditions shown in Figure 3 with trifluoroethanol as the additive, the product **15** was isolated in 85% yield and >99% ee after a single crystallization from acetone/water. Notably, cinchonidine could be recovered from the aqueous layer in 95% yield by simple pH adjustment and filtration.

With the adduct **15** in hand, strategies for the transformation to the target **1** were explored (Scheme 5). Our initial plan was to perform a cross-coupling reaction with **16**, followed by decarboxylation and sodium salt formation. Unfortunately, a variety of Suzuki–Miyaura coupling conditions were investigated, but the best isolated yield of **16** was only 17% using *S*-Phos/$Pd(OAc)_2$ as the catalyst.[23] Alternatively, an efficient telescoped sequence was developed to achieve our goal. Thus, heating a solution of **15** in *n*-BuOH at reflux gave rise to the *n*-butyl ester **17** in 98% yield. The cross-coupling reaction of **17** with boronic acid **5** proceeded smoothly in the presence of catalytic Pd/PCy_3, leading to the corresponding butyl ester of **1**, which was not isolated but rather directly hydrolyzed by adding aqueous NaOH to the mixture. After work-up and a final sodium salt formation step in acetonitrile/water, pure **1** was isolated in 75% yield over four steps. Notably, the whole sequence (**15**→**1**) could be performed in a single solvent (*n*-BuOH) without the need for distillative solvent switches or purification of intermediates.



Scheme 5. Conversion of the adduct **15** to **1**.

The broad substrate scope of the enantioselective conjugate alkynylation process[4] encouraged us to attempt a more concise synthetic route. As shown in Scheme 6, a fully elaborated olefin acceptor was prepared from **2**, **18**, and Meldrum's acid in 92% yield. The olefin **19** was subjected to our chiral zincate mediated alkynylation procedure affording **16** in 97% assay yield and 89% ee. Crystallization from acetone/water provided optically pure (>99% ee) **16** in 82% overall yield. Sequential decarboxylation and sodium salt formation concluded the five-step synthesis of **1**.



Scheme 6. Second generation synthesis of **1**.

3. Conclusion

In summary, two asymmetric methods to synthesize the potent GPR40 receptor agonist **1** have been developed. Both synthetic routes made use of readily available inexpensive starting materials and reagents. The first route relies on the highly diastereoselective conjugate alkynylation of an ephedrine-derived oxazepanedione acceptor. The second approach involved a highly enantioselective conjugate alkynylation of Meldrum's acid-derived acceptors employing the inexpensive and recyclable chiral mediator cinchonidine. Overall, the first generation synthesis of **1** (nine steps, 35% yield), was replaced by this efficient, second generation asymmetric process (five steps, 65% yield), which was suitable for long-term application.

4. Experimental section

4.1. General information

Reactions were carried out under an atmosphere of dry nitrogen. All reagents were purchased from suppliers and used as received unless noted otherwise. Anhydrous solvents were purchased from Aldrich in Sure/Seal™ bottles. Propynylmagnesium chloride was freshly prepared by reaction of a solution of propyne in THF with *n*-butylmagnesium chloride (2.0 M in THF) at 0 °C followed by stirring at rt for 16 h. The final concentration was adjusted to 0.5–0.7 M by diluting with THF. The concentration of organometallic reagents was titrated by the method reported by Knochel and coworkers.[24]

The racemates of **15** or **16** were prepared by the reaction of propynylmagnesium bromide (2.0 equiv) with **14** or **19** at room temperature.

^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.27). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (hertz) and integration. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with proton decoupling. Analytical thin layer chromatography (TLC) was performed using JT Baker silica gel plates precoated with a fluorescent indicator. Standard flash chromatography was performed on a Biotage MPLC system. Melting points are uncorrected. Optical rotations were recorded in cells with 1 dm path length. Enantiomeric excess was determined by HPLC or SFC analysis. All columns are 250×4.6 mm. Mass spectra analyses and high-resolution mass spectral analyses were measured by means of fast-atom bombardment (FAB) or electrospray ionization (ESI).

4.2. (2*R*,3*S*)-3,4-Dimethyl-2-phenyl-1,4-oxazepane-5,7-dione 8

Compound **8** was prepared according to literature procedure: (−)-(1*R*,2*S*)-ephedrine was treated with dimethylmalonate at 80 °C for 16 h[25] and the resulting mixture was hydrolyzed with LiOH to yield the free acid.[26] Cyclization was performed with *N*-methyl-2-chloropyridinium tosylate (2-chloropyridine and methyltosylate were stirred neat at 60 °C for 16 h) as reported.[5]

4.3. 4-(3-Bromobenzyloxy)benzaldehyde 9

A mixture of 4-hydroxybenzaldehyde (2.5 g, 20.47 mmol, 1.0 equiv), K_2CO_3 (3.68 g, 26.61 mmol, 1.3 equiv), and DMF (9 mL) was aged at rt for 5 min, and 3-bromobenzyl bromide (5.63 g, 22.52 mmol, 1.1 equiv) was charged in one portion. The resulting mixture was aged at 60 °C for 19 h. After cooling to rt, water (27 mL) was added to dissolve the K_2CO_3, and the solution was extracted with isopropyl acetate (2×27 mL). The combined organic layers were washed with water (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was crystallized from 20% isopropyl acetate in heptane to afford the product as white solids (4.7 g, 79%). Mp 65–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.11 (s, 2H), 7.07 (d, J=8.8 Hz, 2H), 7.24–7.31 (m, 1H), 7.35 (d, J=7.6 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.60 (s, 1H), 7.85 (d, J=8.8 Hz, 2H), 9.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 190.7, 163.3, 138.2, 132.0, 131.3, 130.3, 130.2, 125.8, 122.8, 115.1, 69.2. HRMS (m/z): $[M+H]^+$ calcd for $C_{14}H_{11}BrO_2$, 290.99424; found, 291.00065.

4.4. (2*R*,3*S*,*Z*)-6-(4-(3-Bromobenzyloxy)benzylidene)-3,4-dimethyl-2-phenyl-1,4-oxazepane-5,7-dione 10

To a solution of **8** (1.03 g, 4.41 mmol, 1.0 equiv), **9** (1.41 g, 4.85 mmol, 1.1 equiv), and pyridine (892 μL, 11.05 mmol, 2.5 equiv) in THF (22 mL) at −55 °C was added $TiCl_4$ (508 μL, 4.63 mol, 1.05 equiv) dropwise. The pale yellow solution became dark brown immediately. The suspension was stirred for 16 h, warming to rt. HPLC analysis indicated a 1:1 mixture of diastereomers. The suspension was filtered through a pad of Celite and the filtrate was concentrated. The yellow oil was dissolved in CH_2Cl_2 (20 mL), washed consecutively with an aqueous solution of HCl (0.1 N, 10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Isopropanol (10 mL) was added to the resulting oil, and the mixture was aged at 90 °C for 4.5 h. The suspension was cooled and filtered to afford the product as a white solid (1.81 g, 81%). HPLC analysis indicated the *E*/*Z* ratio of the product was 0.5:99.5 (230 nm). Mp 188–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.26 (d, J=6.5 Hz, 3H), 3.11 (s, 3H), 3.66 (q, J=6.7 Hz, 1H), 5.03 (s, 2H), 6.15 (s, 1H), 6.90 (d, J=8.6 Hz, 2H), 7.20–7.26 (m, 1H), 7.28–7.34 (m, 1H), 7.37 (t, J=7.04 Hz, 1H), 7.41–7.52 (m, 7H), 7.55 (s, 1H), 7.88 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.3, 162.0, 160.4, 145.9, 138.6, 136.0, 132.1, 131.2, 130.2, 128.8, 128.6, 126.0, 125.9, 125.8, 124.4, 122.7, 78.5, 75.1, 69.1, 63.9, 35.8, 11.6. HRMS (m/z): $[M+H]^+$ calcd for $C_{27}H_{24}BrNO_4$, 506.08887; found, 506.09561.

4.5. (2*R*,3*S*)-6-((*S*)-1-(4-(3-Bromobenzyloxy)phenyl)but-2-ynyl)-3,4-dimethyl-2-phenyl-1,4-oxazepane-5,7-dione 11

To a suspension of **10** (1.0 g, 1.97 mmol, 1.0 equiv) in THF (15 mL) at −45 °C was charged a solution of 1-propynylmagnesium bromide in THF (0.5 M, 5.94 mL, 2.96 mmol, 1.5 equiv) dropwise. The reaction temperature was maintained below −35 °C during the addition. The reaction was aged for 16 h while warming to rt. HPLC analysis of the yellow solution indicated starting material was consumed. To the reaction mixture was added an aqueous solution of saturated ammonium chloride (10 mL) and water (10 mL), and the mixture was extracted with CH_2Cl_2 (1×20 mL, then 2×10 mL). The combined organic layers were washed with a solution of water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the product as a foam (1.08 g, quantitative). The product was used directly in the next step without purification.

4.6. (*S*)-3-(4-(3-Bromobenzyloxy)phenyl)-*N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylhex-4-ynamide 12

To a slurry of **11** (875 mg, 1.60 mmol, 1.0 equiv) in *tert*-butanol (15 mL) at rt was added a solution of *n*-Bu_4NOH (40% in water, 5.19 mL, 8.0 mmol, 5.0 equiv). The pale yellow solution turned orange immediately. The reaction was aged at rt for 16 h, quenched with an aqueous solution of saturated ammonium chloride (20 mL), and extracted with CH_2Cl_2 (20 mL, then 2×15 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting foam was dissolved in DMSO (7.5 mL) and heated at 100 °C for 4.5 h. After the reaction was cooled to rt, CH_2Cl_2 (20 mL) and water (20 mL) were added. The organic layer was separated and washed with water (2×20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford an orange oil. The crude product was used directly in the next step without purification.

4.7. (*S*)-*N*-((1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-3-(4-((4′-(trifluoromethyl)biphenyl-3-yl)methoxy)phenyl)hex-4-ynamide 13

A 75 mL Schlenk tube with a septum was charged with $Pd(OAc)_2$ (7.2 mg, 0.032 mmol, 0.02 equiv), PCy_3 (17.9 mg, 0.064 mmol, 0.04 equiv), 4-(trifluoromethyl)phenylboronic acid (456 mg, 2.4 mmol, 1.5 equiv), and $K_3PO_4 \cdot H_2O$ (737 mg, 3.2 mmol, 2.0 equiv, finely ground with mortar and pestle). The reaction vessel was purged with N_2 for 10 min, and a solution of **12** (1.60 mmol from last step) in THF (200 ppm water, degassed by bubbling with N_2 for 10 min, 8 mL) was added. The septum was replaced with a screw-cap and the reaction was heated in a 70 °C oil bath for 4 h. HPLC analysis indicated reaction was complete. After cooling to rt, the suspension was filtered through a pad of Celite, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 2–100% ethyl acetate in hexanes gradient) to afford the product as a yellow oil (0.69 g, 74% over four steps from **10**). $[\alpha]_D^{25}$ +5.7 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, δ): (a mixture of rotamers was observed) 0.98 (d, J=6.5 Hz, 3H, minor rotamer), 1.11 (d, J=7.2 Hz, 3H), 1.76 (d, J=2.2 Hz, 3H, minor), 1.80 (d, J=2.2 Hz, 3H) 2.57 (s, 3H), 2.52–2.63 (m, 2H, minor), 2.57 (s, 3H, minor), 2.65–2.76 (m, 2H), 3.35 (d, J=3.1 Hz, 1H, minor), 3.73–3.85 (m, 1H, minor), 3.96–4.04 (m, 1H, minor), 4.10–4.21 (m, 2H), 4.45–4.57 (m, 1H), 4.77 (t, J=3.4 Hz, 1H), 5.06 (s, 2H, minor), 5.08 (s, 2H), 6.89 (d, J=8.6 Hz, 2H, minor), 6.94 (d, J=8.6 Hz, 2H), 7.16–7.70 (m, 15H). ^{19}F NMR (377 MHz, $CDCl_3$, δ): −62.73 (major rotamer), −62.26 (minor rotamer). ^{13}C NMR (100 MHz, $CDCl_3$, δ): (a mixture of rotamers was observed) 3.5, 3.6, 11.9, 14.2, 28.2, 32.9, 33.5, 41.6, 42.7, 57.5, 58.1, 69.7, 75.7, 76.8, 77.7, 78.2, 80.2, 80.6, 114.7, 114.8, 120.1, 122.8, 125.5 (q, 4.0 Hz), 125.9, 126.1, 126.7, 127.0, 127.1, 127.2, 127.8, 128.2 (q, 53.7 Hz), 128.3, 128.4, 129.3 (q, 30.3 Hz), 34.1, 134.2, 134.4, 137.8, 137.8, 139.9, 141.6, 141.9, 144.2, 157.4, 157.5, 170.4. HRMS (m/z): $[M+H]^+$ calcd for $C_{36}H_{34}F_3NO_3$, 586.24908; found, 586.25648.

4.8. Conversion of the adduct 13 to 1

To a solution of **13** (320 mg, 0.55 mmol, 1.0 equiv) in CH_2Cl_2 (6.4 mL) was added dimethyl carbonate (345 μL, 4.1 mmol, 7.5 equiv) and a solution of sodium methoxide (25% in methanol, 1.18 mL, 5.46 mmol, 10 equiv). The resulting solution was heated at 35 °C for 16 h. After cooling to rt, the reaction was acidified with an aqueous solution of HCl (1 N, 10 mL) and extracted with CH_2Cl_2 (3×10 mL).

The combined organic layers were washed with a solution of brine (10 mL) and water (10 mL), dried over $MgSO_4$, and concentrated to afford the methyl ester as a yellow oil. Ethanol (2 mL) and an aqueous solution of NaOH (2.5 N, 320 μL, 0.87 mmol, 2 equiv) were added. After stirring at rt for 16 h, the ethanol was evaporated, isopropyl acetate (5 mL) and an aqueous solution of HCl (1 N, 5 mL) were added. The separated aqueous layer was extracted with isopropyl acetate (3×2 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude acid product as a brown oil. Acetonitrile (7 mL) was added to dissolve the oil, and an aqueous solution of sodium hydroxide (5 N, 100 μL, 0.55 mmol, 1.0 equiv) was added dropwise. The resulting slurry was aged at rt for 16 h and filtered to afford product **1** as an off-white solid (182 mg, 72%).

4.9. General procedure for enantioselective conjugate alkynylation optimization (Tables 2 and 3 and Figs. 2 and 3)

Reactions were typically carried out using 1 mmol substrate **14**. Chiral aminoalcohol (2.9 mmol, 2.9 equiv) and additive (1.9 mmol, 1.9 equiv) were slurried in dry THF (typically contain 30–150 ppm water, 3.5 mL) and then the mixture was cooled to 0 °C. Diethylzinc (2.4 mL, 1.0 M in toluene, 2.4 mmol, 2.4 equiv) was added dropwise via a syringe over 5 min while the temperature was maintained below 20 °C. The mixture was aged at 20 °C for 1 h to provide a colorless clear solution. The mixture was cooled to 0 °C and a solution of chloromagnesium acetylide (4.8 mL, 0.5 M in THF, 2.4 mmol, 2.4 equiv) was added dropwise via a syringe over 2 min while the temperature was maintained below 20 °C. The mixture was aged at 20 °C for 1 h and the substrate **9** (1 mmol) was added as a solid. After stirring at 22 °C for 24 h, the mixture was cooled to 0 °C, 1.0 M aqueous HCl (10 mL) was added followed by ethyl acetate (20 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (1×20 mL). The combined organic extracts were washed with brine (1×20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 75% hexanes/acetone) to afford, after concentration of the appropriate fractions, the desired product **15** as a white crystalline. Mp 134–136 °C. Enantiomeric excess was determined by HPLC analysis [Chiralpak AS-RH, water/acetonitrile/ethanol/H_3PO_4 (40:30:30:0.05), 0.5 mL/min: t_R (major)=31.57 min, t_R (minor)=34.60 min]. $[\alpha]_D^{25}$ +30.7 (*c* 0.6, acetone). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.58 (s, 1H), 7.47–7.43 (m, 3H), 7.33 (d, *J*=8.0 Hz, 1H), 7.23 (d, *J*=8.0 Hz, 1H), 6.91 (d, *J*=8.0 Hz, 2H), 5.01 (s, 2H), 3.83 (d, *J*=4.0 Hz, 1H), 1.88 (d, *J*=4.0 Hz, 3H), 1.71 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 164.1, 163.4, 157.9, 139.3, 131.0, 130.3, 130.2, 129.9, 125.8, 122.7, 114.7, 105.2, 81.2, 76.1, 69.1, 53.0, 36.1, 28.4, 27.8, 3.8. HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{21}BrO_5$, 479.0470; found, 479.0481. IR (neat): 3003, 1921, 1784, 1746, 1510, 1292, 1177 cm^{-1}.

4.10. Procedure for conversion of the adduct 15 to (*S*)-3-[4-(4′-trifluoromethyl-biphenyl-3ylmethoxy)-phenyl]-hex-4-ynoic acid sodium salt (1)

Compound **15** (2.74 g, 6 mmol) was dissolved in *n*-BuOH (27.5 mL, typically 300–500 ppm water) and heated at reflux for 16 h. The reaction was monitored by HPLC to reach >99 A% conversion. To this solution at rt were added boronic acid **5** (1.4 g, 7.2 mmol, 1.2 equiv), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol, 0.01 equiv), PCy_3 (33.7 mg, 0.12 mmol, 0.02 equiv), and K_3PO_4 (2.55 g, 12 mmol, 2.0 equiv) sequentially. The reaction mixture was degassed three times (vacuum/nitrogen cycle) and stirred at 75 °C for 18 h to reach >99 A% conversion (by HPLC). To the resulting mixture was added 1 g of charcoal and the mixture was agitated for 1 h at 65 °C. The mixture was cooled to rt and filtered through a silica pad (10 g silica). The cake was washed with *n*-BuOH (2×5 mL). The combined *n*-BuOH solution was used for the next reaction directly without further purification.

NaOH (2.5 N, 4.8 mL, 12 mmol, 2 equiv) was slowly added to the above solution over 10 min at rt. The reaction mixture was stirred at rt for 16 h to reach >99 A% conversion (by HPLC). Ethyl acetate (60 mL) and 10% aqueous HCl solution were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3×20 mL) and the combined organic layers were dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the remaining residue (a thick yellow oil) was used in the next step without further purification.

To a stirred solution of the crude acid from the last step in dry acetonitrile (22 mL) at rt was added a 10 N aqueous NaOH solution (0.57 mL, 5.7 mmol, 0.95 equiv) dropwise over 15 min (a voluminous white ppt formed). The resulting mixture was stirred at rt overnight and filtered onto a fine sintered glass filter funnel. The product cake was dried in a vacuum oven at 70 °C overnight to afford **1** (2.1 g, 75%) as a white solid. Mp 139–142 °C. Enantiomeric excess was determined by HPLC analysis [Chiracel AD-RH 5 micron, 4.6×150 mm; solvents: A: water (0.1% TFA), B: 80:20 MeOH/ACN (0.1% TFA) Gradient t_R (major)=8.2 min, t_R (minor)=9.4 min]. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.90 (d, *J*=8.2 Hz, 2H), 7.82 (d, *J*=8.2 Hz, 2H), 7.81 (br s, 1H), 7.69 (dt, *J*=6.3, 1.9 Hz, 1H), 7.53 (t, *J*=6.3 Hz, 1H), 7.52 (d, *J*=6.3 Hz, 2H), 7.26 (d, *J*=8.6 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 5.15 (s, 2H), 4.01 (m, 1H), 2.33 (dd, *J*=14.7, 6.9 Hz, 1H), 2.18 (dd, *J*=14.7, 7.3 Hz, 1H), 1.74 (d, *J*=2.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, δ): 174.2, 156.6, 143.9, 138.7, 138.3, 136.1, 129.3, 128.3, 127.9 (q, $^2J_{C\text{-}F}$=31.7 Hz), 127.6, 127.5, 127.0 (q, $^1J_{C\text{-}F}$=271.9 Hz), 126.5, 126.2, 125.8 (q, $^3J_{C\text{-}F}$=3.8 Hz), 114.4, 83.3, 76.4, 69.0, 47.5, 33.9, 3.3. HRMS (*m*/*z*): $[MH]^+$ calcd for $C_{26}H_{20}F_3NaO_3$, 461.1335 found, 461.1326; IR (KBr pellet): 3590, 3064, 1640–1500, 1413, 1328, 1124, 1112, 1071, 789 cm^{-1}.

Time (min)	%B
0	50
4	90
14	90
15	50
18	50

4.11. 2,2-Dimethyl-5-(4-((4′-(trifluoromethyl)biphenyl-3-yl) methoxy)benzylidene)-1,3-dioxane-4,6-dione 19

4-Hydroxybenzaldehyde **18** (8.6 g, 70.0 mmol), **2** (24.3 g, 77.0 mmol), and K_2CO_3 (14.5 g, 105.0 mmol) were combined in a 2 L round bottom flask. DMF (220 mL) was added to the mixture of solids, and the heterogeneous mixture was stirred for 16 h before quenched by pouring the mixture into water (200 mL). The mixture was stirred for an additional 2 h to allow agglomeration to occur. The resulting precipitate was filtered and dried under vacuum at ambient temperature to give 4-((4′-(trifluoromethyl)biphenyl-3-yl) methoxy)benzaldehyde as a yellow solid (24.7 g). The material was used directly in the next reaction.

The crude aldehyde from the previous step, Meldrum's acid (12.1 g, 84.0 mmol), and DMAP (0.85 g, 7.0 mmol) were combined in THF (100 mL). The solution was stirred at room temperature for 24 h. The product was isolated by diluting the mixture with water (150 mL) and extracting with ethyl acetate (2×150 mL). The combined organic extracts were concentrated to dryness to yield a yellow solid. The yellow solid was purified by slurrying in acetone/water (1:2, 700 mL) at rt for 3 h. The mixture was filtered, the filter cake was dried under vacuum at ambient temperature to afford **19** (31.1 g, 92% yield over two steps) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.38 (s, 1H), 8.23 (d, *J*=8.0 Hz, 2H), 7.70 (s, 4H), 7.66 (s, 1H), 7.59 (d, *J*=8.0 Hz, 1H),

7.54–7.46 (m, 2H), 7.08 (d, J=8.0 Hz, 2H), 5.25 (s, 2H), 1.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 164.0, 163.6, 160.5, 157.7, 144.2, 140.4, 137.6, 136.7, 129.9 (q, $^1J_{C\text{-}F}$=220.0 Hz), 129.5, 127.5, 127.4, 127.3, 126.4, 125.8 (q, $^3J_{C\text{-}F}$=4.0 Hz), 125.4 (q, $^2J_{C\text{-}F}$=47.0 Hz), 115.2, 111.3, 104.2, 70.2, 27.6. HRMS (m/z): $[M]^+$ calcd for $C_{27}H_{21}F_3O_5$, 482.1341; found, 482.1349. IR (neat): 3003, 1921, 1784, 1746, 1510, 1292, 1177 cm^{-1}.

4.12. (*S*)-2,2-Dimethyl-5-(1-(4-((4′-(trifluoromethyl)biphenyl-3-yl)methoxy)phenyl)but-2-ynyl)-1,3-dioxane-4,6-dione 16

Cinchonidine (853.8 mg, 2.9 mmol, 1.45 equiv) and trifluoroethanol (140 μL, 1.9 mmol, 0.95 equiv) were slurried in dry THF (typically contain 30–150 ppm water, 3.5 mL) and then the mixture was cooled to 0 °C. Diethylzinc (2.4 mL, 1.0 M in toluene, 2.4 mmol, 1.2 equiv) was added dropwise via a syringe over 5 min while the temperature was maintained below 20 °C. The mixture was aged at 20 °C for 1 h to provide a colorless clear solution. The mixture was cooled to 0 °C and a solution of propynylmagnesium chloride (4.8 mL, 0.5 M in THF, 2.4 mmol, 1.2 equiv) was added dropwise via a syringe over 5 min while the temperature was maintained below 20 °C. The mixture was aged at 20 °C for 1 h and the substrate **19** (965 mg, 2 mmol, 1.0 equiv) was added as a solid. After stirring at 22 °C for 24 h, the mixture was cooled to 0 °C, 1.0 M aqueous HCl (25 mL) was added followed by ethyl acetate (60 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed with brine (2×20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was crystallized from acetone/water (3:1) to afford the desired product **16** (857 mg, 82% yield, >99 wt%, >99% ee) as a white crystalline solid. Mp 139–142 °C. Enantiomeric excess was determined by HPLC analysis [Chiralpak AS-RH, 4.6×150 mm, water (0.1% NH_4Ac)/MeCN (58:42), 0.8 mL/min: t_R (major)= 13.3 min, t_R (minor)=18.5 min]. $[\alpha]_D^{25}$ +29.3 (c 0.53, acetone). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.69 (s, 4H), 7.64 (s, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.50–7.43 (m, 4H), 6.95 (d, J=8.0 Hz, 2H), 5.12 (s, 2H), 4.85 (s, 1H), 3.83 (d, J=4.0 Hz, 1H), 1.88 (d, J=4.0 Hz, 3H), 1.71 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 164.1, 163.4, 158.2, 144.4, 140.2, 137.9, 130.2, 129.9, 129.5 (q, $^2J_{C\text{-}F}$=32.0 Hz), 129.3, 127.5, 127.2, 126.9, 126.3, 125.7 (q, $^3J_{C\text{-}F}$=4.0 Hz), 124.3 (q, $^1J_{C\text{-}F}$=274.0 Hz), 114.7, 105.2, 81.2, 76.1, 69.9, 53.0, 36.1, 28.4, 27.8, 3.8. HRMS (m/z): $[M+Na]^+$ calcd for $C_{30}H_{25}F_3O_5$, 545.1552; found, 545.1552. IR (neat): 3003, 2254, 1785, 1747, 1510, 1324, 1292, 1165 cm^{-1}.

4.13. Conversion of the adduct 16 to 1

Compound **16** (523 mg, 1.0 mmol) was dissolved in DMF (2.2 mL) and water (0.2 mL) and heated to 90 °C for 2 h. The reaction mixture was then cooled to rt, diluted with ethyl acetate (15 mL), and washed with brine (3×10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the free acid of **1** as colorless oil. The crude product was directly used in the next step.

To a stirred solution of the crude acid in dry acetonitrile (3.3 mL) at rt was added a 5 N aqueous NaOH solution (0.2 mL, 1.0 equiv) dropwise over 15 min (a voluminous white ppt formed). The resulting mixture was stirred at rt overnight and filtered onto a fine sintered glass filter funnel. The product cake was dried in a vacuum oven at 70 °C overnight to afford **1** (414 mg, 90%) as a white solid.

Acknowledgements

We are grateful to Dr. Tsang-Lin Hwang for NMR structural work. We thank Maosheng Chen, Bo Shen, and Judith Ostovic for the chiral HPLC analysis.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.019.

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22. (a) Other solvents (Me-THF, MTBE, DME, toluene) evaluated provided lower ee (<80%) and yield (<90%); (b) Me_2Zn and Et_2Zn were equally efficient; (c) Enantioselectivity was not dependent on the concentration (0.04–0.2 M); (d) The order of addition of reagents during preparation of the zincate (Et_2Zn/trifluoroethanol/cinchonidine) had no effect.
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