Pergamon

Tetrahedron 58 (2002) 7403–7410

TETRAHEDRON

Practical enantioselective synthesis of a COX-2 specific inhibitor

Lushi Tan,[a,*] Cheng-yi Chen,[a] Weirong Chen,[a] Lisa Frey,[a] Anthony O. King,[a] Richard D. Tillyer,[a] Feng Xu,[a] Dalian Zhao,[a] Edward J. J. Grabowski,[a] Paul J. Reider,[a] Paul O'Shea,[b,*] Philippe Dagneau[b] and Xin Wang[b]

[a]*Department of Process Research, Merck and Co. Inc., P.O. Box 2000, Rahway, NJ 07065, USA*
[b]*Department of Process Research, Merck Frosst Centre for Therapeutic Research, P.O./C.P. 1005, Pointe Claire-Dorval, Que., Canada, H9R 4P8*

Received 20 May 2002; revised 9 July 2002; accepted 11 July 2002

Abstract—Two synthetic strategies to the COX-2 specific inhibitor **1** have been described that allowed its preparation in large quantities in 79% overall yield from (*S*)-2-hydroxy-2-methylbutyric acid. These studies have led to the identification of an efficient resolution of (±)-2-hydroxy-2-methylbutyric acid and a novel thionyl chloride aided formation of amide **11** from acid **6**.

1. Introduction

Cyclooxygenase (COX) is the first enzyme involved in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes from arachidonic acid. The major COX isozyme, COX-1, is expressed as a constitutive enzyme and is involved in homeostasis of the gastrointestinal (GI) tract (in addition to other functions).[1] Another COX isozyme is inducible, and commonly referred to as COX-2. It is expressed principally in inflammatory tissue.[2] Traditional nonsteroidal antiinflammatory drugs (NSAIDs) used for the treatment of inflammatory conditions act by inhibition of both COX-1 and COX-2 with little specificity, leading to serious side effects such as gastric lesions and renal toxicity.[3] The rationale that a specific COX-2 inhibitor will greatly improve the side-effect profile associated with the chronic use of traditional NSAIDs has led several groups to search for selective inhibitors of COX-2.[4] Recently, a series of highly substituted butenolides has been evaluated by Merck for their ability to inhibit the isozymes of cyclooxygenase, COX-1 and COX-2.[5] (*S*)-5-Ethyl-5-methyl-3-methylethoxy-4-(4-methylsulfonylphenyl)oxolen-2-one **1** was identified as a very potent and specific COX-2 inhibitor that may provide therapeutically useful alternatives to traditional NSAIDs with a great GI safety profile.

We envisioned that the compound may be assembled by either the introduction of an aryl group to a butenolide core containing compound (Scheme 1, A) or via the Dieckmann condensation to form the butenolide ring (Scheme 1, B). Both approaches require the use of optically pure (*S*)-2-hydroxy-2-methylbutyric acid **6** as the starting material. In this paper, a 2-step preparation of α-hydroxy ketone **5** from α-hydroxy acid **6**, an efficient resolution of racemic 2-hydroxy-2-methylbutyric acid, and details of two syntheses of **1** are disclosed.

2. Results and discussion

2.1. Resolution of (±)-2-hydroxy-2-methylbutyric acid

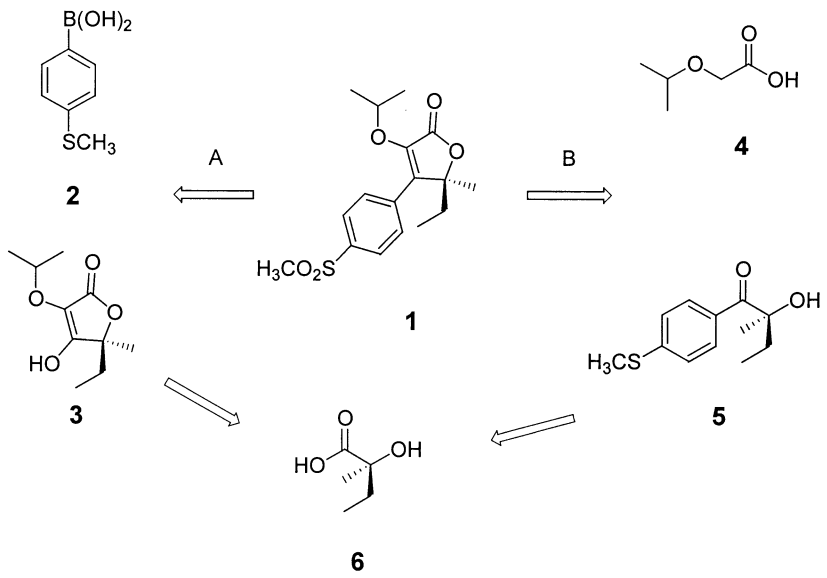
The resolution of (±)-2-hydroxy-2-methylbutyric acid using brucine has been reported.[6] The procedure however, requires many recrystallizations of the more soluble acid-brucine salt and is tedious and low yielding. After an extensive survey of other chiral amines, we found that commercially available (*R*)-(+)-1-(1-naphthyl)ethylamine[7] is efficient for the resolution of (±)-2-hydroxy-2-methylbutyric acid. Thus, formation of the salt in acetone followed by slow crystallization at 10°C gave the desired acid enantiomer **6** as the amine salt in 84% yield and 92% ee. The ee of the material was easily upgraded to >99% by a single recrystallization from acetone.[6b] The enantiomerically pure acid was then obtained by usual acid–base treatment and crystallization from heptane with an overall yield of 76% (salt formation, recrystallization, and salt break).

2.2. The Suzuki coupling route (A)

This route involves a Suzuki coupling reaction[8] between **9**, the corresponding triflate of hydroxy lactone **3**, and the commercially available boronic acid **2** as a key step (Scheme 2). Hydroxy lactone **3** was prepared in three

Keywords: COX-2 inhibitor; resolution; Suzuki coupling; hydroxy ketone.
* Corresponding authors. Tel.: +1-732-594-1013; fax: +1-732-594-5170; e-mail: lushi_tan@merck.com

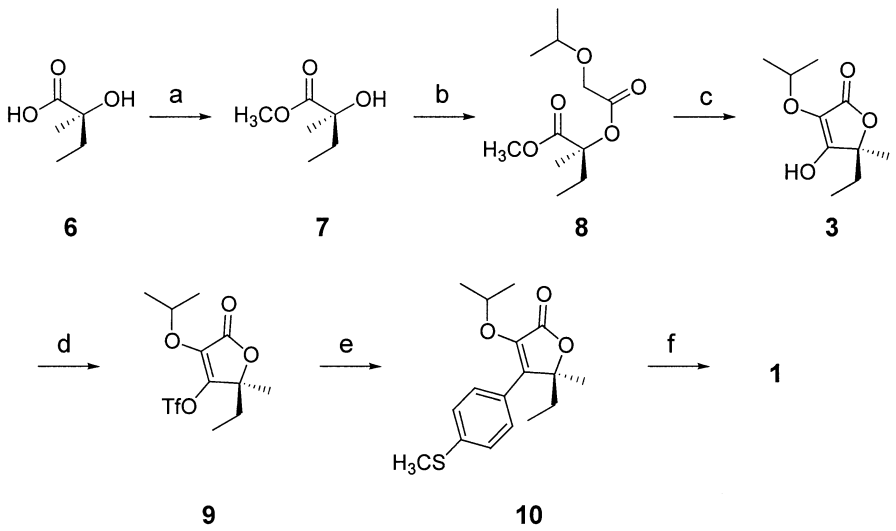
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00826-8



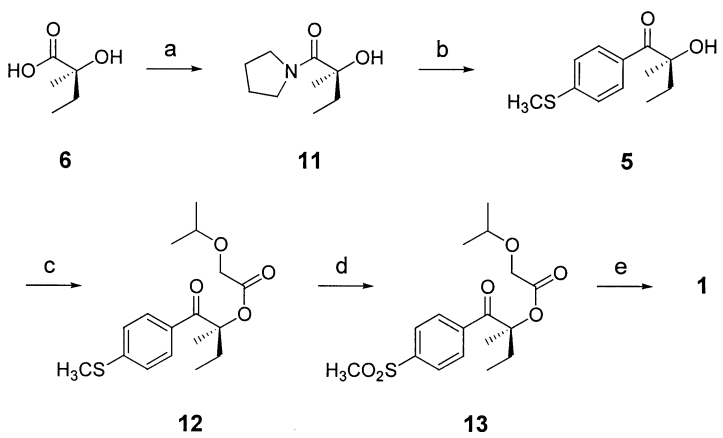
Scheme 1.

steps from optically pure acid **6**. Heating a solution of **6** in methanol with catalytic amount of concentrated sulfuric acid resulted in the formation of the methyl ester **7**. Most of the methanol was removed by atmospheric distillation after the reaction. The remaining methanol residue was removed by a brine wash after diluted with toluene. The toluene solution of **7**, after dried with anhydrous $MgSO_4$, was ready to use in the next step reaction. The coupling reaction of **7** using isopropoxyacetic acid **4**[9] was carried out in toluene with DCC, triethylamine, and catalytic amount of DMAP. The resulting diester **8** was obtained in 82% overall yield from **6**. The ring closure of **8** was promoted by lithium bis(trimethylsilyl)amide (LiHMDS) at −78°C in THF, which gave **3** in 91% isolated yield. Hydroxy lactone **3** was easily purified by crystallization from toluene/heptane (5:95). A variety of reaction conditions[10] were attempted for the cross couplings of either the corresponding tosylate or phosphate of **3** with boronic acid **2**. However, no trace amount of **10** was observed, presumably due to the steric hindrance of the lactone moiety. These results led us to work on the more reactive triflate. Thus, treating **3** with triflic anhydride and pyridine in 1,2-dichloroethane smoothly converted it into the triflate **9**. The reaction of triflate **9** with **2** using $PdCl_2(PPh_3)_2$ as catalyst and Na_2CO_3 as base provided product **10** in 69% isolated yield.[11] Major side reactions include hydrolysis of **9** to hydroxy lactone **3**, and formation of the biaryl from self coupling of boronic acid **2**. A wide variety of bases, solvents, and catalysts were screened in order to improve the reaction. Optimal conditions involved carrying the reaction in DME with 2 M aqueous Cs_2CO_3 as base (2.2 equiv.) and $Pd(PPh_3)_4$ (5 mol%) as catalyst. Under these conditions, **10** was obtained in 80% isolated yield. Finally, oxidation of **10** using oxone in acetone/water afforded **1** in 94% yield.

The Suzuki coupling route led to the synthesis of **1** in 6 steps and 56% overall yield from optically pure acid **6**. This strategy constitutes a very good method for the construction of a variety of arylsubstitued butenolides because of the ready availability of many aryl boronic acids.



Scheme 2. *Conditions*: (a) CH_3OH, H_2SO_4 (cat); (b) **4**, DCC, NEt_3, DMAP (cat) (82% from **6**); (c) THF, LiHMDS (91%); (d) Tf_2O, pyridine, CH_2ClCH_2Cl; (e) **2**, $Pd(PPh_3)_4$, Cs_2CO_3(aq), DME (69% from **3**); (f) oxone, acetone/H_2O (94%).



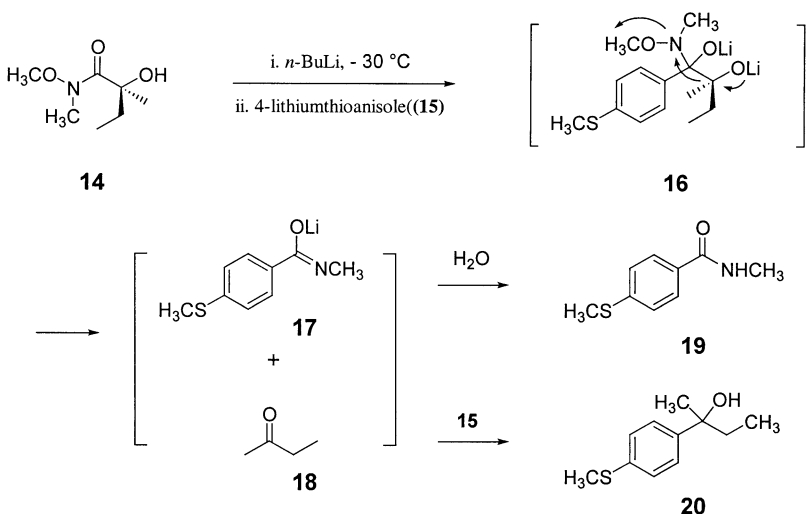
Scheme 3. *Conditions*: (a) $SOCl_2$, pyrrolidine, −5°C (97%); (b) (i) *n*-BuLi, −30°C, (ii) 4-lithiumthioanisole, −30 to 0°C (94%); (c) **4**, NEt_3, DMAP (cat), $(CH_3)_3COCl$ (100%); (d) H_2O_2, Na_2WO_4 (cat), toluene/CH_3OH, 50°C (95%); (e) DBU, $CF_3CO_2CH(CH_3)_2$, CH_3CN, reflux (91%).

2.3. The hydroxy ketone route (B)

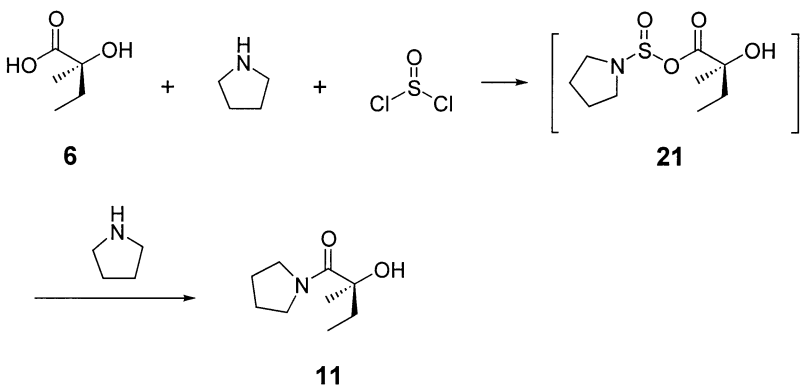
Although the Suzuki coupling route allowed for the construction of **1** in a reasonable overall yield, there are a few concerns upon scale up using this process, particularly, the low temperature required for the cyclization reaction of diester **8** and the use of the triflate for the Suzuki coupling reaction. Thus, an alternative route for the construction of **1** was developed and is outlined in Scheme 3. It relies on the efficient preparation of a key intermediate, the hydroxy ketone **5**. The butenolide structure was established by the coupling of **5** with isopropoxyacetic acid **4** and the subsequent base promoted ring closure.

Early attempts for the preparation of hydroxy ketone **5** focused on the Friedel–Crafts acylation of thioanisole using the derivatives of acid **6** such as acid chloride, anhydride, and acyl imidazole but none of these reactions worked. Another strategy was to convert **6** into its cyclic carbonate or acetonide followed by the addition of aryllithium.[12] This method was eventually abandoned due to the formation of substantial over addition product. The problem of over addition for the preparation of ketones from carboxylic acid derivatives could typically be circumvented by the use of *N*-methyl-*N*-methoxy amides (Weinreb amides).[13] However, the reaction of the alkoxide of Weinreb amide **14** with 4-lithiumthioanisole **15** resulted in the formation of more than 20% each of amide **19** and tertiary alcohol **20** (Scheme 4). This may be due to the steric hindrance presented in the tetrahedral intermediate **16** that caused its fragmentation to give **17** and **18**. Protonation of **17** would give amide **19** and the reaction of ketone **18** with lithium reagent **15** would produce alcohol **20**. Although the protection of the hydroxy group in Weinreb amide **14** with triethylsilyl (TES) group prevented the fragmentation completely, a more practical solution for the preparation of hydroxy ketone **5** from the optically pure acid **6** was through the formation of pyrrolidinyl amide **11** and the subsequent arylation.

Initial attempts to convert acid **6** into pyrrolidinyl amide **11** employed the corresponding acyl imidazole of acid **6** as an intermediate. Although 89–95% yield was obtained, the cost of CDI and the instability of the acyl imidazole were major concerns upon scale up. An investigation to a scalable process was thus initiated and it was discovered that thionyl chloride could be used as an alternative to CDI. The reaction



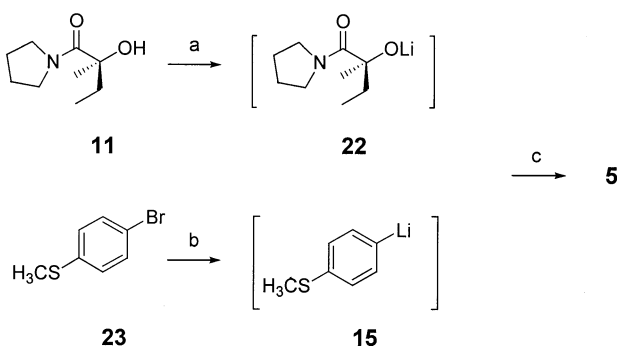
Scheme 4.



Scheme 5.

was carried out by the addition of pyrrolidine (4.0 equiv.) to a mixture of thionyl chloride (1.2 equiv.) and acid **6** (1.0 equiv.) in THF/toluene (1:1) at ≤ -5°C which gave the desired product in 93–97% yield. Some aspects of this reaction are very interesting; firstly, the order of the reagent addition was important; pyrrolidine must be added as the last reagent. Addition of thionyl chloride to a solution of acid **6** and pyrrolidine led to the formation of inactive bis-pyrrolininosulfinamide and resulted in low conversion. Secondly, there was no reaction observed by ^{1}H NMR when acid **6** was mixed with thionyl chloride in deuterated THF. A possible pathway is depicted in Scheme 5, where intermediate **21**[14] was generated from the reaction of thionyl chloride with pyrrolidine and acid **6**. Interaction of **21** with another pyrrolidine molecule would give the desired amide **11**.

The arylation to convert pyrrolidinyl amide **11** to hydroxy ketone **5** was run as a two pot process (Scheme 6) which involves: (i) deprotonation of hydroxy amide **11** with *n*-BuLi at −30°C to give the corresponding lithium alkoxide **22**; (ii) generation of the 4-lithiumthioanisole **15** by reaction of 4-bromothioanisole **23** with *n*-BuLi at −30°C; and (iii) addition of the alkoxide solution to the slurry of 4-lithiumthioanisole **15**, warming to 0°C and quenching into aqueous HCl. The arylation proceeds at approximately −30°C, but requires warming to 0°C for complete conversion. After quench and concentration, the product was obtained in 93–97% yield and very low level of over addition product (<1%) was observed. The reaction of the O-protected α-hydroxy pyrrolidinyl amides with lithium reagents was reported to give α-hydroxy ketone at −78°C,[15]



Scheme 6. (a) *n*-BuLi, tol/THF, 6:1, −30°C; (b) *n*-BuLi, tol/THF, 6:1, −30°C; (c) **22** to **15**, warm to 0°C.

however over addition was reported at levels as high as 10%. The result here indicates that the α-alkoxide group is important for stabilizing the tetrahedral intermediate such as **16** by chelation in a way similar to the N–OMe group in the Weinreb amides.

The preparation of hydroxy ketone **5** from hydroxy acid **6** via pyrrolidinyl amide **11** provided an efficient 2-step preparation of α-hydroxy ketone from α-hydroxy acid and allowed the synthesis of **5** in 94% overall yield.

With key intermediate hydroxy ketone **5** in hand, we next sought its conversion to the final product **1**. Initial attempts focused on the oxidation–coupling–cyclization sequence. This strategy was proved to be troublesome mainly because the oxidation of **5** with either oxone or hydrogen peroxide resulted in the partial cleavage of the C–C bond, generating the corresponding carboxylic acid. To solve this problem, hydroxy ketone **5** was first coupled with isopropoxyacetic acid **4**. The resulting ketoester sulfide **12** was much more stable to the C–C bond cleavage and was then smoothly oxidized to the desired ketoester sulfone **13** (Scheme 3).

The coupling reaction of hydroxy ketone **5** with isopropoxy-acetic acid **4** was initially carried out at 30–35°C using 1.5 equiv. each of **4**, DABCO, and EDC in toluene. Quenching the reaction mixture with 1 M HCl after 2 h gave the ketoester sulfide **12** in quantitative isolated yield. The cost of EDC and the environmental impact of the large amount of DABCO and the by-product from EDC were major concerns of this process. Other methods including, using the corresponding acid chloride of **4** as the coupling reagent were not successful due to low conversion and impure product. It was later found that pivaloyl chloride served as an effective coupling reagent for the esterification of **4**. Presumably, it forms a mixed anhydride with isopropoxyacetic acid **4** in situ which reacts with hydroxy ketone **5** in the presence of DMAP and triethylamine to give the desired product **12**.[16] Experimentally, the reaction was carried out by the addition of pivaloyl chloride (1.5 equiv.) to a mixture of hydroxy ketone **5** (1.0 equiv.), triethyl amine (2.5 equiv.), **4** (1.2 equiv.), and DMAP (0.3 equiv.) in toluene. It normally takes 3–4 h to obtain ≥99% conversion at ambient temperature. After quench (with water), ketoester sulfide **12** was isolated as a toluene solution in quantitative yield and no trace amount of the pivalic ester was detected either by ^{1}H NMR or HPLC assay. The

product was oxidized subsequently with 30% aqueous hydrogen peroxide (3.0 equiv.) in toluene with methanol as a co-solvent and Na_2WO_4 (3.5 mol%) as a catalyst.[17] The resulting ketoester sulfone **13** was isolated in 95% yield by crystallization from toluene/heptane (1:3).

A wide range of bases, solvents, and temperatures were examined for the conversion of ketoester sulfone **13** to the final product **1**. Potassium *tert*-butoxide and DBU were identified to be effective bases. Although the reaction was instantaneous at 0°C in DMF with potassium *tert*-butoxide as the base, DBU was eventually chosen for the reaction due to the instability of the product in the presence of excess potassium *tert*-butoxide. The reaction was carried out in refluxing acetonitrile and isopropyl trifluoroacetate (1.2 equiv.) was used as a dehydrating agent to prevent the hydrolysis of the ester.[18] The reaction was quenched after 10–13 h by the addition of aqueous 1N HCl (1 equiv.) at 0–5°C. This serves to neutralize the DBU and to effect product crystallization. The crystallization was completed by the addition of water to a final solvent ratio of 30% acetonitrile/water. The product was isolated by filtration and was further purified by recrystallization from acetone/water (3:7) to give **1** in 91% overall yield.

The route via hydroxyketone **5** led to the synthesis of **1** in 5 steps and 79% overall yield from optically pure acid **6**. This synthesis is highly practical, cost effective, and scalable.

3. Summary

We have described two synthetic strategies to the COX-2 specific inhibitor **1** that allowed its preparation in large quantities in 79% overall yield from (*S*)-2-hydroxy-2-methylbutyric acid. These studies have led to the identification of an efficient resolution of (±)-2-hydroxy-2-methylbutyric acid and a novel thionyl chloride aided formation of amide **11** from acid **6**. Compared to traditional amide formation reactions the conditions discussed here are much milder.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H, ^{13}C NMR spectra were collected at 400 and 100 MHz, respectively. All reactions were run under nitrogen and all reagents were plant grade unless otherwise noted. Combustion analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. High resolution mass spectra were obtained by the Biomedical Mass Spectrometry Unit of McGill, Montreal, Canada.

4.1.1. (*S*)-2-Hydroxy-2-methylbutyric acid 6. Under nitrogen, a 22 L round bottom flask equipped with mechanical stirrer and thermocouple was charged with (±)-2-hydroxy-2-methylbutyric acid (2.5 kg) and acetone (12.7 L). (*R*)-(+)-1-(1-naphthyl)ethylamine (3.6 kg) was added over 20 min. The solution was heated to reflux and aged for 2 h. The batch was then cooled to 0–5°C over 16 h. The precipitate was isolated by filtration, washed with acetone (0–5°C, 2×1.6 L) and dried under reduced pressure to afford 2.6 kg of the salt (84% yield, >92.5% ee). The salt was dissolved in acetone (36.4 L) at 55°C and the solution was concentrated by atmospheric distillation to remove 24.7 L of acetone. The resulting suspension was cooled to 0–5°C over 3–5 h. The solid was isolated by filtration, washed with acetone (0°C, 2×2 L) and dried under reduced pressure to afford 2.4 kg of the salt (92% yield, 77% overall yield for two steps, >99% ee). The salt was dissolved in 10N NaOH (1.7 L) and extracted with toluene (9.6 L). The toluene solution was concentrated to give 1.36 kg (95%) of (*R*)-(+)-1-(1-naphthyl)ethylamine which can be directly used for the next cycle resolution. The pH of the aqueous solution was adjusted to 1 with 12N HCl (1.7 L) at <30°C and extracted with ethyl acetate (2×9.6 L). The combined ethyl acetate extracts were concentrated, flushed with heptane (60 L) to a final volume of 20–25 L and crystallized at 0–5°C. The product was isolated by filtration, washed with heptane (0°C, 4 L) and dried to afford 953 g of *(S)-(+)-2-hydroxy-2-methylbutyric acid* **6** (98% yield, overall yield for three steps 76%, >99% ee determined by chiral HPLC: column, CHIRALPACK AD; eluent, 0.1% TFA in 96:4 v/v hexane/isopropanol; temperature, 35°C): mp 74–75°C. $[\alpha]_D^{25}=+9.1°$ (c=1.6, $CHCl_3$), cf. Lit:[19] mp 75–76°C; $[\alpha]_D^{25}=+9.0°$.

4.1.2. (*S*) Methyl 2-methyl-2-[2-(methylethoxy)acetyloxy]-butanoate 8. To a solution of acid **6** (50 g, 0.42 mol) in methanol (150 mL) was added 1 mL of concentrated sulfuric acid. The solution was refluxed overnight and then concentrated by distillation to a volume of ~80 mL. To the residue was added toluene (500 mL). The solution was washed with brine (50 mL), dried over anhydrous $MgSO_4$, and filtered. To the filtrate at room temperature was sequentially added DMAP (0.77 g, 6.3 mmol), triethlamine (146 mL, 1.05 mol), and DCC (130 g, 0.63 mol). After 10 min a solution of isoproproxyacetic acid (74.3 g, 0.63 mol) in toluene (100 mL) was added at room temperature in one portion. The resulting slurry was heated at 30–35°C for 2–3 h, cooled to 10°C, and quenched with 1 M HCl (1.1 L). The two layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (1 L), water (1 L), and concentrated. Chromatography of the residue over silica gel (hexane/ethyl acetate, 95:5, v/v) provided 80 g (82% from **6**) of **8** as an oil: IR (neat): $[\alpha]_D^{25}=+2.54°$ (c=1.15, CH_3OH). IR (neat). 1743, 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.11 (d, J=7 Hz, 1H), 4.09 (d, J=7 Hz, 1H), 3.73 (s, 3H), 3.70 (qq, J=6 and 6 Hz, 1H), 1.97 (dq, J=7.6 and 15 Hz, 1H), 1.84 (dq, J=7.5 and 15 Hz, 1H), 1.59 (s, 3H), 1.21 (d, J=6 Hz, 3H), 1.20 (d, J=6 Hz, 3H), and 0.92 (dd, J=7.5 and 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 169.9, 81.6, 72.5, 65.5, 52.2, 31.2, 21.7, 21.6, 20.8, and 7.5. HRMS Calcd for $C_{11}H_{21}O_5$ ($M+H^+$): 233.1389. Found: 233.1389.

4.1.3. (*S*)-5-Ethyl-4-hydroxy-5-methyl-3-(methylethoxy)-oxolen-2-one 3. To a solution of the diester **8** (23.2 g, 0.10 mol) in THF (580 mL) was added LiHMDS (20.7 g, 0.12 mol) at −78°C. The reaction was quenched with 6 M HCl (23.3 mL) at −78°C after 2 h. The mixture was diluted with toluene (580 mL) and the two layers were separated.

The organic layer was washed with 1N HCl and brine and concentrated to ~35 mL. Hexane (200 mL) was added and the solid was collected by filtration to 18.4 g (91%) of **3** as a white solid: mp 35–37°C. $[\alpha]_D^{25}=+0.9°$ (c=0.56, CH_3OH). IR (neat): 1750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.54 (bs, 1H), 4.54 (qq, J=6 and 6 Hz, 1H), 1.85 (m, 2H), 1.50 (s, 3H), 1.25 (d, J=6 Hz, 3H), 1.24 (d, J=6 Hz, 3H), and 0.84 (dd, J=7.5 and 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 165.4, 118.5, 82.4, 73.8, 29.5, 23.3, 22.0(3), 22.0(0), and 7.3. HRMS Calcd for $C_{10}H_{17}O_4$ ($M+H^+$): 201.1127. Found: 201.1127.

4.1.4. (*S*)-5-Ethyl-5-methyl-3-methylethoxy-4-(4-methylthiophenyl)oxolen-2-one 10. To a solution of **3** (4.0 g, 20 mmol) in CH_2ClCH_2Cl (40 mL) at 0°C was added pyridine (2.1 mL, 26 mmol) and then Tf_2O (4.1 mL, 26 mmol). The mixture was aged for 2 h at 0°C. Saturated NH_4Cl (20 mL) was added. The two layers were separated. The organic layer was washed with brine (20 mL) and concentrated to dryness. To the residue was added 4-(methylthio)phenyl boronic acid **2** (5.0 g, 30 mmol), 2 M aqueous Cs_2CO_3 (22 mL, 44 mmol), $Pd(PPh_3)_4$ (1.2 g, 1 mmol) in ethylene glycol dimethyl ether (DME, 91 mL) at room temperature. The mixture was degassed 3 times by vacuum/N_2 purge and then refluxed at 80°C for 18 h. The mixture was diluted with ethyl acetate (90 mL) and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2×90 mL). The combined organic solutions were washed with brine (90 mL) and concentrated. Chromatography of the residue over silica gel (hexane/ethyl acetate, 90:10) gave 4.9 g (80%) of **10** as an oil. $[\alpha]_D^{25}=-22.5°$ (c=0.47, CH_3OH). IR (neat): 1756 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.4 Hz, 2H), 5.08 (qt, J=6.1 Hz, 1H), 2.49 (s, 3H), 2.02 (q, J=7.3 Hz, 2H), 1.92 (q, J=7.3 Hz, 2H), 1.60 (s, 3H), 1.25 (d, J=6.2 Hz, 3H), 1.23 (d, J=6.2 Hz, 3H), and 0.77 (t, J=7.3 Hz, 3H,). ^{13}C NMR ($CDCl_3$): 168.0, 142.2, 140.5, 139.3, 128.3, 126.7, 125.8, 85.9, 73.4, 31.6, 26.0, 22.6, 15.1, and 7.6. HRMS Calcd for $C_{17}H_{23}SO_3$ ($M+H^+$): 307.1368. Found: 307.1368.

4.1.5. (*S*)-2-Hydroxy-2-methyl-1-pyrrolidinyl butan-1-one 11. To a solution of thionyl chloride (1.81 kg, 15.2 mol) in a mixture of THF (12 L) and toluene (12 L) was added **6** (1.5 kg, 12.7 mol) portionwise at −15 to −10°C. Neat pyrrolidine (3.61 kg, 50.8 mol) was then added dropwise over 2.5 h, keeping the temperature below −5°C. The mixture was aged at −5°C for 20 min and the reaction was quenched by addition of saturated aqueous sodium chloride (750 mL) followed by water (2.63 L). The layers were separated and the aqueous was back extracted with toluene (7.5 L). The combined organic solutions were washed with a mixture of 3:1 (v/v) brine and 2N sodium hydroxide (4.5 L), dried by azeotropic distillation, and used as a toluene solution directly for the next step reaction. Assay of the solution indicated 2.09 kg of amide **11** (96%). An analytical sample was obtained by concentration and chromatography separation (hexane/ethyl acetate, 4:1, v/v) over silica gel: $[\alpha]_D^{25}=+0.6°$ (c=1.02, CH_3OH). IR (neat): 1703, 1595, 1571 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.55 (m, 4H), 1.96 (m, 2H), 1.85 (m, 2H), 1.75 (m, 2H), 1.41 (s, 3H), and 0.84 (dd, J=7.5 Hz and 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 74.3, 48.0, 47.5, 31.7, 27.0, 25.2, 23.2, and 7.9. HRMS Calcd for $C_9H_{18}NO_2$ ($M+H^+$): 172.1338. Found: 172.1338.

4.1.6. (*S*)-2-Hydroxy-2-methyl-1-(4-methylthiophenyl)-butan-1-one 5. To a solvent mixture of THF (4.04 L) and toluene (21.2 L) was added a solution of amide **11** in toluene (3 L, 2.1 kg assayed **11**, 12.3 mol) and triphenylmethane (10.1 g, 41 mmol). The solution was degassed by vacuum/N_2 purge. The mixture was cooled to −35 to −30°C and *n*-BuLi (1.6 M in hexane, 7.66 L, 12.3 mol) was added slowly over 2–4 h, keeping the temperature below −30°C. In another flask, 4-bromothioanisole (2.74 kg, 13.5 mol) was dissolved in a 6:1 (v/v) mixture of toluene/THF (28.2 L) and cooled to −35 to −30°C. The solution was also degassed thoroughly. *n*-BuLi (1.6 M in hexane, 8.05 L, 12.9 mol) was added slowly to the cold solution over 2 h to form a white slurry, keeping the temperature below −30°C. The amide-alkoxide solution was transferred into the aryllithium slurry over a 30 min period via cannula. The resulting solution was warmed to −15°C over 1 h and then to −5°C over 1 h period. The mixture was aged at −5°C until the reaction was complete as determined by HPLC assay. The reaction was quenched by cannulation into ice-cold aqueous 2N hydrochloric acid (25.4 L) with vigorous stirring. The layers were separated at room temperature and the organic layer was washed saturated sodium bicarbonate (9 L) and concentrated to 11 L. This affords 2.50 kg (95%) of hydroxyketo sulfide **5** as a toluene solution. An analytical sample was obtained by concentration and chromatography separation (hexane/ethyl acetate, 5:1) over silica gel. $[\alpha]_D^{25}=-15.2°$ (c=1.03, CH_3OH). IR (neat): 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (m, 2H), 7.27 (m, 2H), 4.30 (s, 1H), 2.52 (s, 3H), 2.00 (m, 2H), 1.59 (s, 3H), and 0.82 (dd, J=7.4 and 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4, 146.3, 130.0, 129.7, 124.8, 78.9, 34.3, 27.2, 14.6, and 7.9. Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19. Found: C, 64.15; H, 7.15.

4.1.7. (*S*)-1-Ethyl-1-methyl-2-(4-methylthiophenyl)-2-oxoethyl 2-(methylethoxy)acetate 12. *Procedure A*. Under nitrogen, to a solution of hydroxyketone sulfide **5** (67.3 g, 0.3 mol), isopropoxyacetic acid **4** (42.5 g, 0.36 mol), and DMAP (11.0 g, 90 mmol) in toluene (540 mL) was added triethyl amine (104.5 mL, 0.75 mol) at 10°C followed by pivaloyl chloride (55.4 mL, 0.45 mol). The reaction mixture was aged at room temperature for 3–4 h, quenched with water (350 mL), and stirred at ambient temperature for 1 h. The two layers were separated and the organic solution was used directly for the oxidation reaction. This afforded 97.3 g (100%) ketoester sulfide **12** as a toluene solution. An analytical sample was obtained by concentration and chromatography separation (hexane/ethyl acetate, 9:1) over silica gel. $[\alpha]_D^{25}=-23.9°$ (c=1.00, CH_3OH). ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (m, 2H), 7.20 (m, 2H), 3.99 (d, J=16 Hz, 1H), 3.98 (d, J=16 Hz, 1H), 3.45 (hept, J=6 Hz, 1H), 2.49 (s, 3H), 2.27 (dq, J=15 and 5 Hz, 1H), 2.04 (dq, J=15 and 5.0 Hz, 1H), 1.70 (s, 3H), 1.12 (d, J=5.0 Hz, 6H), and 0.97 (dd, J=7.5 and 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 169.8, 145.2, 130.9, 129.0, 124.8, 87.7, 72.5, 65.8, 30.8, 21.7, 21.6, 21.3, 14.7, and 7.6. Anal. Calcd for $C_{17}H_{24}O_4S$: C, 62.94; H, 7.46. Found: C, 63.02; H, 7.43.

Procedure B. To a solution of hydroxyl ketone **5** (20.0 g, 89.2 mmol) in toluene (180 mL) was added DMAP (1.63 g, 13.3 mmol), DABCO (15.5 g, 138 mmol), and EDC (25.6 g, 134 mmol) at room temperature sequentially. After 10 min a solution of isoproproxyacetic acid (15.8 g, 134 mmol) in toluene (20 mL) was added at room temperature in one portion. The resulting slurry was heated at 30–35°C for 2–3 h, cooled to 10°C, and quenched with 1 M HCl (223 mL). The two layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (110 mL) and water (110 mL) to give 28.9 g (100%) of ester sulfite **12** as a toluene solution. The isolated product had exactly the same physical and spectroscopic properties as those obtained from procedure A.

4.1.8. (*S*)-1-Ethyl-1-methyl-2-(4-methylsulfonylphenyl)-2-oxoethyl 2-(methylethoxy)acetate 13. A mixture of ketoester sulfide **12** (97.3 g, 0.3 mol), sodium tungstate dihydrate (13.8 g, 10.5 mmol) in toluene (800 mL) and methanol (195 mL) was heated to 50°C. The heat was removed and 30% aqueous hydrogen peroxide (92 mL, 0.9 mol) was added via an addition funnel, keeping the temperature at 50–55°C. The resulting two-phase reaction mixture was aged at 50°C for an additional 3.5 h. The reaction mixture was cooled to 10°C and quenched with 5% aqueous sodium sulfide solution (756 g). The layers were separated and the organic layer was washed with water (360 mL). The organic layer was concentrated to ~362 mL and heptane (786 mL) was added slowly over 1 h at room temperature. The resulting slurry was cooled to 0°C, aged for 30 min, and filtered. The solid was washed with cold (0°C) 15 v/v% toluene/heptane (300 mL) and heptane (300 mL) sequentially and dried under vacuum to give 101.6 g (95%) of **13** as a white solid: mp 63.5–64.5°C. $[\alpha]_D^{25}=-19.3°$ (c=1.00, CH_3OH). IR (KBr): 1741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (m, 2H), 7.97 (m, 2H), 3.97 (s, 2H), 3.44 (hept, J=6 Hz), 3.06 (s, 3H), 2.24 (dq, J=14.5 and 7.4 Hz, 1H), 2.03 (dq, J=14.5 and 7.4 Hz, 1H), 1.70 (s, 3H), 1.09 (d, J=6 Hz, 3H), 1.08 (d, J=6 Hz, 3H), and 0.98 (dd, J=7.4 and 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 170.1, 143.5, 139.4, 129.2, 127.5, 87.5, 72.8, 65.8, 44.3, 30.6, 21.7, 21.6, 21.2, and 7.6. Anal. Calcd for $C_{17}H_{24}O_6S$: C, 57.29; H, 6.79. Found: C, 57.20; H, 7.78.

4.1.9. (*S*)-5-Ethyl-5-methyl-3-methylethoxy-4-(4-methylsulfonylphenyl)oxolen-2-one 1. *Procedure A*. To a solution of **13** (17.8 g, 50 mmol) in degassed acetonitrile (90 mL) was added *i*-$PrOOCCF_3$ (8.4 mL, 60 mmol) and DBU (11.2 mL, 75 mmol). The reaction solution was heated to reflux under atmosphere of N_2 for 10–13 h and then cooled to 0–5°C. 1.0N HCl (49.2 mL) was added over 30 min followed by water (159 mL) over 1.5 h. The resulting slurry was aged at 0–5°C for 0.5 h and filtered. The wet cake was washed with 30% MeCN/water followed by 15% MeCN/water and dried under nitrogen to give 15.9 g (94%) of **1** as an off-white solid. The solid was dissolved in acetone (63.6 mL) at room temperature and water (148.4 mL) was added over 1.5 h. The resulting slurry was aged at 22°C for 0.5 h and filtered, washed with 30% acetone/water, and dried under nitrogen to give 15.6 g (98%) of purified **1** as a white solid, >99% ee (determined by chiral HPLC: column, CHIRALPACK AD; eluent, 95:5:0.1, v/v hexane/ethanol 200 proof/H_2O; temperature, 40°C): mp 107.5–108.5°C. $[\alpha]_D^{25}=-19.0°$ (c=1.02, CH_3OH). IR (KBr): 1745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (m, 2H), 7.85 (m, 2H), 5.30 (qq, J=7.4 and 7.4 Hz, 1H) 3.10 (s, 3H), 2.06 (dq, J=14.8 and 7.4 Hz, 1H), 1.93 (dq, J=14.7 and 7.3 Hz, 1H), 1.64 (s, 3H), 1.28 (d, J=6 Hz, 3H), 1.27 (d, J=6 Hz, 3H), and 0.82 (dd, J=7.4 and 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 141.5, 140.4, 139.3, 135.9, 128.7, 127.7, 85.9, 73.8, 44.4, 31.5, 25.9, 22.7, and 7.6. Anal. Calcd for $C_{17}H_{22}O_5S$: C, 60.34; H, 6.55. Found: C, 60.39; H, 6.43.

Procedure B. To a solution of **10** (0.50 g, 1.6 mmol) in acetone (30 mL) was added water (30 mL) and Oxone (2.0 g, 3.2 mmol) at room temperature. The reaction mixture was filtered after 3 h. The filtrate was extracted with ethyl acetate (3×30 mL). The combined ethyl acetate solutions were washed with brine (30 mL) and concentrated. Purification of crude product the same way as in procedure A gave 0.52 g (94%) of **1** as a white solid. The material had exactly the same physical and spectroscopic properties as those obtained from procedure A.

References

1. For a review see: Griswold, D. E.; Adams, J. L. *Med. Res. Rev.* **1996**, *16*, 181.
2. (a) Xie, W.; Chipman, J. G.; Robertson, D. L.; Erickson, R. L.; Simmons, D. L. *Proc. Natl Acad. Sci. USA* **1991**, *88*, 2692. (b) Kujubu, D. A.; Fletcher, B. S.; Varnum, B. C.; Lim, R. W.; Herschman, H. R. *J. Biol. Chem.* **1991**, *226*, 2692. (c) Masferrer, J. L.; Seibert, K.; Zweifel, B.; Neddleham, P. *Proc. Natl Acad. Sci. USA* **1992**, *89*, 3917. (d) Hla, T.; Neilson, K. *Proc. Natl Acad. Sci. USA* **1992**, *89*, 7384.
3. Vane, J. R.; Mitchell, J. A.; Appleton, I.; Tomlinson, A.; Bishop-Bailey, D.; Croxtall, J.; Willoughby, D. A. *Proc. Natl Acad. Sci. USA* **1994**, *91*, 2046.
4. Friesen, R. W.; Brideau, C.; Chan, C. C.; Charleson, S.; Deschênes, D.; Dubé, D.; Ethier, D.; Fortin, R.; Gauthier, J. Y.; Girard, Y.; Gordon, R.; Greig, G. M.; Riendeau, D.; Savoie, C.; Wang, Z.; Wong, E.; Visco, D.; Xu, J. L.; Young, R. N. *Bioorg. Med. Lett.* **1998**, *8*, 2777.
5. Belley, M. Y.; Leblanc, J. Y.; Gauthier, E.; Grimm, M.; Therien, C. B.; Prasit, P.; Lau, C. K.; Roy, P. World Patent Application, WO 9714691.
6. (a) Mattocks, A. R. *J. Chem. Soc.* **1964**, 1918. For general discussion on resolution of organic acids, see: (b) Newman, P. *Optical Resolution Procedures for Chemical Compounds*, Optical resolution information center, Manhattan College: New York, 1981; Vol. 2.
7. Both enantiomers of 1-(1-naphthyl)ethylamine have previously been used in the resolution of carboxylic acids. For examples, see: Corey, E. J.; Trybulski, E. J.; Melvin, Jr. L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Flack, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618.
8. For a review on the Suzuki coupling reaction, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
9. Fuson, R. C.; Wojcik, B. H. *Organic Syntheses*, Wiley: New York, 1943; Collect. Vol. II. p 260.
10. (a) Nan, Y.; Yang, Z. *Tetrahedron Lett.* **1999**, *40*(17), 3321. (b) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, *4*, 471.

(c) Lepifre, F.; Buon, C.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, 6373.
11. Fraley, M. E.; Rubino, R. S. *Tetrahedron Lett.* **1997**, *38*(19), 3365.
12. Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*(21), 4083.
13. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*(39), 3815.
14. Similar structure was proposed in the reaction of *N*,*N*′-sulfinylbisdialkyamine with carboxylic acids: Mukaiyama, T.; Takei, H.; Shimizu, H. *Bull. Chem. Soc. Jpn* **1967**, *40*, 939.
15. Martín, R.; Pascual, O.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1997**, *38*(9), 1633.
16. Nicolaou, K. C.; Winssinger, N.; Vourloumis, D.; Ohshima, T.; Kim, S.; Pfefferkorn, J.; Xu, J. Y.; Li, T. *J. Am. Chem. Soc.* **1998**, *120*, 10814.
17. Black, W. C.; Guay, B. *Synthesis* **1998**, *8*, 1101.
18. Tan, L.; Chen, C. Y.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3961.
19. Ham, E. A.; Schafer, H. M.; Denkrwalter, R. G.; Brink, N. G. *J. Am. Chem. Soc.* **1954**, *76*, 6066.