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An enantioselective total synthesis of pinnaic acid

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Abstract—An enantioselective and convergent total synthesis of marine natural product pinnaic acid has been achieved. Our general synthetic approach is featured with an asymmetric hydrogenation of racemic γ-keto ester **3**, a diastereoselective methylation on the α-methylene of the (1*R*,5*R*)-lactone **4**, and a diastereoselective Michael addition of the tertiary nitro cyclopentane. The central azaspiro[4.5]decane was constructed utilizing reductive cyclization of the δ-nitroketone followed by highly stereoselective reduction of the cyclic imine with $NaBH_4$. Ultimately, successive use of triethyl-2-phosphonopropionate and Heathcock's phosphorane **18** to elaborate C5 and C13 side chains completed the total synthesis of pinnaic acid.

1. Introduction

Naturally occurring marine alkaloids halichlorine **1** and pinnaic acid **2** bearing a highly functionalized azaspiro[4.5]-decane ring system (Fig. 1) were found in *Halichondria okadai kadota* and *Pinna muricata*, respectively, in 1996 by Uemura and co-workers.[1] Halichlorine **1** inhibits the expression of vascular cell adhesion molecule-1 (VCAM-1) with an IC_{50} of 7 μg/mL and consequently has potential for the treatment of arteriosclerosis, asthma, and cancer.[2] Pinnaic acid **2** is a specific inhibitor of cytosolic phospholipase A_2 ($cPLA_2$) with an in vitro IC_{50} of 0.2 mM. $cPLA_2$ is involved in regulating inflammation and thus represents a potential target for drug discovery.[3] Because of their biological activities and unique structures, these alkaloids are challenging and attractive synthetic targets. To date, many groups have reported their synthetic approaches toward the total synthesis of the two compounds, particularly for the azaspirobicyclic and azaspirotricyclic cores.[4–7] However, only racemic azaspirobicyclic and azaspirotricyclic cores were obtained in most present synthetic work. To the best of our knowledge, only two total syntheses of halichlorine,[8,9] three of pinnaic acid[9–11] have been reported so far in the literature. Among them, Danishefsky and co-workers were first to complete the enantioselective syntheses of halichlorine and pinnaic acid, and simultaneously assigned the stereochemistry at C14 and C17 of pinnaic acid. In our efforts directed toward the enantioselective synthesis of these alkaloids, we have previously presented an efficient and enantioselective synthesis of the azaspirobicyclic core.[7b] Herein, we would like to report an enantioselective total synthesis of pinnaic acid featured by an improved preparation of the azaspiro[4.5]decane ring system. The improvements achieved in the pinnaic acid synthesis made the synthetic work convenient, short, and executable.

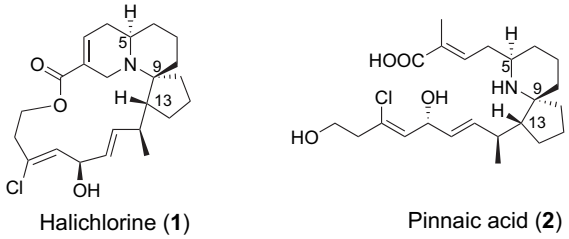

Figure 1. Structures of halichlorine and pinnaic acid.

2. Results and discussion

In our previous work, the bicyclolactone **4** was prepared through Lipase PS-catalyzed selective acylation. Though the Lipase PS method could help us get the bicyclolactone **4**, a new more efficient method to obtain this useful compound **4** is still being required and will be interesting to synthetic chemists. The BINAP–Ru complex is an efficient catalyst for the asymmetric hydrogenation of β-keto ester.[12] In this synthesis, hydrogenation of the γ-keto ester **3** to bicyclolactone **4** was explored with this catalyst, and a satisfactory result was obtained. Thus, hydrogenation of racemic γ-keto ester **3** in the presence of $[(R)\text{-BINAP-RuCl}_2](DMF)_n$ as a catalyst was completely explored, and we were pleased to find that the desired (1*R*,5*R*)-lactone **4** could be obtained in gram scale with 61% yield and 90% ee. The yield of the

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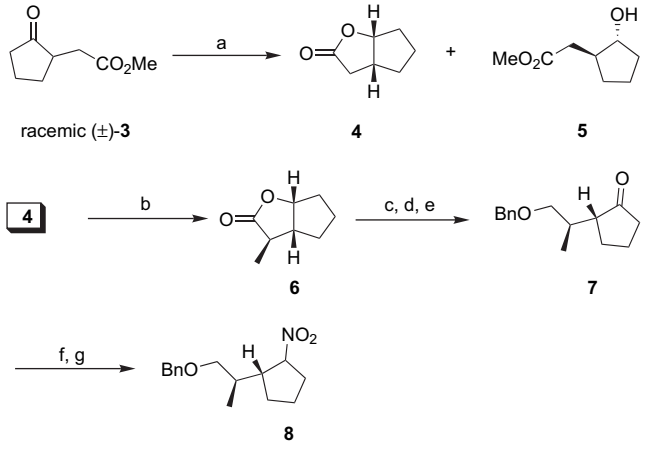
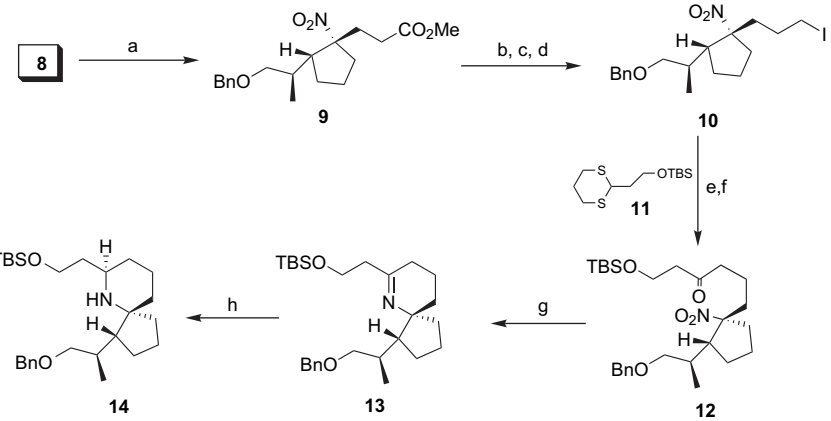
desired lactone **4** is higher than 50%, indicating that some deracemization occurred at the α-position of the carbonyl group under the reaction conditions. The key intermediate of nitro cyclopentane **8** was synthesized by a sequence of steps as outlined in Scheme 1. Substrate-induced asymmetric methylation of the bicyclolactone **4** using LDA as a base at −78 °C led to **6** as a sole product in 77% yield. As expected, methyl group approaches from the less stereohindered face of the fused bicyclic ring system. Reduction of **6** with LAH, followed by site-selective protection of the primary alcohol with benzyl bromide, and oxidation of the secondary alcohol using PCC in CH_2Cl_2 afforded the corresponding cyclopentanone **7**. Condensation of hydroxylamine with ketone **7** followed by *m*-CPBA oxidation afforded the nitro cyclopentane **8** in 64% yield over two steps.[13] Compound **8** was a pair of diastereoisomers that needed no further separation.



Scheme 1. Reagents and conditions: (a) [(*R*)-BINAP-$RuCl_2$]$(DMF)_n$, H_2, MeOH, 25 atm, 100 °C, 61% yield for **4**, 90% ee for **4**, 13% yield for **5**, 91% ee for **5**; (b) LDA, MeI, THF, −78 °C, 6 h, 77%; (c) $LiAlH_4$, THF, reflux, 4 h; (d) NaH, BnBr, THF, rt, 10 h, 63% over two steps; (e) PCC, Celite, CH_2Cl_2, rt, 4 h, 95%; (f) $NH_2OH{\cdot}HCl$, K_2CO_3, MeOH, rt, 4 h, 90%; (g) *m*-CPBA, Na_2HPO_4, crushed urea, MeCN, 80 °C, 76%. BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, PCC=pyridinium chlorochromate.

With success achieved in the initial sequence, our attention was directed to the synthesis of the azaspirocyclic core **14** (Scheme 2). Thus, the stage was now set for the Michael addition of nitrocyclopentane **8** with methyl acrylate to construct the spirocenter. Pleasingly, the desired nitro ester **9** was obtained in 97% yield as a single diastereoisomer,[7b,14] which could be explained by presuming the acrylate approaching from the less hindered face of **8**. Reduction of the nitro ester **9** with $LiBH_4$, followed by mesylation and iodination, led to the iodide **10**. Subsequent metalation of the dithiane **11**[15] with *t*-BuLi and then alkylation with the iodide **10**,[7b,16] followed by the deprotection of dithiane in the presence of I_2 and $NaHCO_3$ in acetone, gave the ketone **12** that is the critical precursor for the piperidine ring cyclization. In order to form the piperidine ring by intramolecular condensation of δ-aminoketone, the tertiary nitro group in **12** should be reduced to an amino group. We had reported that reduction of the nitro group using the Ni_2B method afforded the corresponding nitrone, which was converted into the desired piperidine by successive further reduction with $NaBH_4$ and $TiCl_3$.[7b] Herein, we would like to contribute a more direct and concise route, via catalytic hydrogenation of the nitro compound **12**. Previous work[7b] showed that the nitro group of **12** was intact to hydrogenation over Pd/C, and while hydrogenation over Raney nickel in MeOH under 5 atm pressure of H_2 did give the desired spiropiperidine core structure, silyl group was partially cleaved. We presumed that over hydrogenation and partial TBS loss were due to the high pressure and the solvent chosen. Thus, Raney nickel and 1 atm pressure of H_2 were found to be an ideal condition, and different solvents such as MeOH, EtOAc, and cyclohexane were screened (Table 1). The results demonstrated that the solvents exerted a great influence on this reaction. Only trace amounts of the expected spiropiperidine **13** were produced in MeOH and low yield was obtained in EtOAc (30%). To our delight, cyclohexane provided a moderate yield of product **13** (61%). It indicated that when decreasing the polarity of the solvents, the catalytic activity and the rate of the reaction were reduced, and the TBS loss problem was avoided. Further optimization of the reaction conditions led to a superior yield of 93% by adding a small amount of Et_3N to the reaction system. The benzyl and TBS groups remained intact under this condition. Subsequent reduction of the cyclic imine **13** with $NaBH_4$ in a mixed solvent (CH_2Cl_2/MeOH, v/v, 1:1) generated the desired



Scheme 2. Reagents and conditions: (a) Triton B, methyl acrylate, *t*-BuOH, THF, rt, 48 h, 97%; (b) $LiBH_4$, THF, rt, 24 h, 99%; (c) Et_3N, DMAP, CH_2Cl_2, MsCl, 0 °C to rt, 2 h; (d) NaI, $NaHCO_3$, acetone, rt, 24 h, 99% over two steps; (e) **11**, *t*-BuLi, HMPA, THF, −78 °C, 3 h, 98%; (f) I_2, $NaHCO_3$, acetone/H_2O (v/v, 5:1), rt, 87%; (g) Raney Ni, cyclohexane/Et_3N (v/v, 50:1), 1 atm H_2, 93%; (h) $NaBH_4$, MeOH, 0 °C to rt, 98%. Triton B=benzyltrimethylammonium hydroxide, 40 wt % solution in methanol.

Table 1. Reductive condensation of **12** under 1 atm H_2

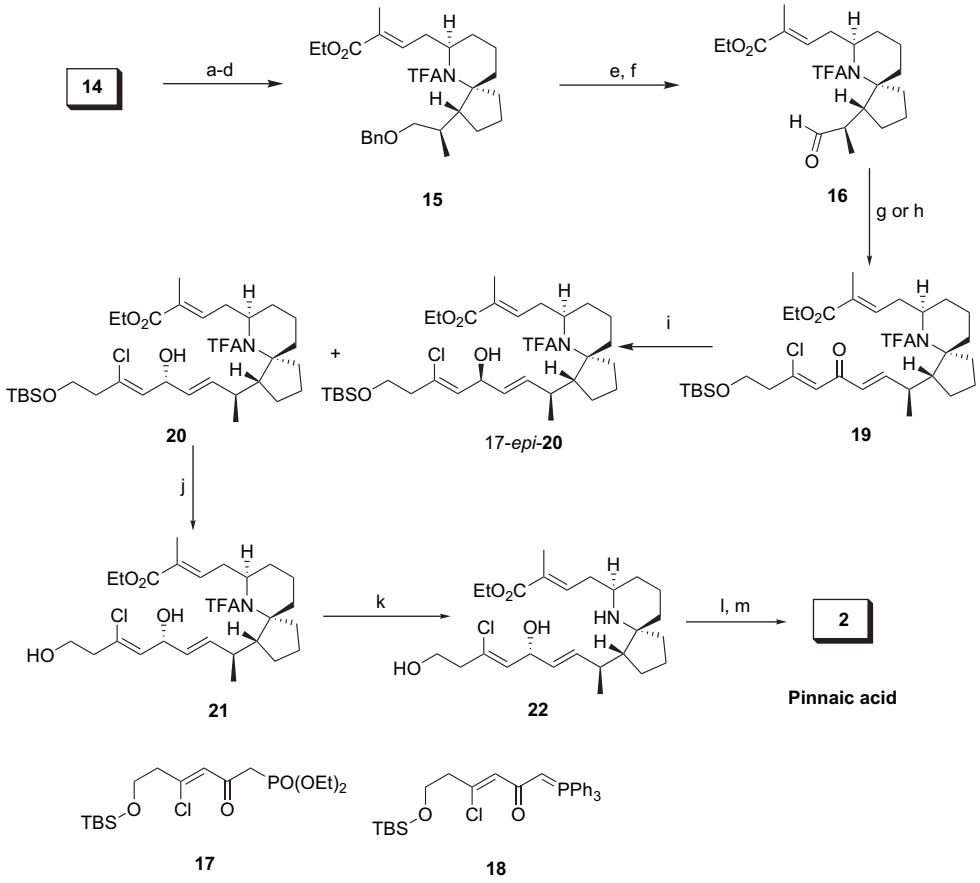
Entry	Catalyst	Solvent	Isolated yield of **13** (%)
1	10% Pd/C	CH_3OH	—
2	$Pd(OH)_2$	CH_3OH	—
3	Raney Ni	CH_3OH	Trace
4	Raney Ni	EtOAc	30
5	Raney Ni	Cyclohexane	61
6	Raney Ni	Cyclohexane/Et_3N (v/v, 50:1)	93

diastereoisomer **14** exclusively. The excellent selectivity could be attributed to hydride attack from the less hindered face of **13**. Thus, we successfully constructed the azaspirocyclic core.

Subsequently, we began to study the challenging elaboration of both the C5 and C13 side chains. Protection of the secondary amino group in **14** with trifluoroacetic anhydride,[10] deprotection of the TBS group, and oxidation by DMP[17] afforded an aldehyde, which was converted into compound **15** through Horner–Wadsworth–Emmons reaction.[18] Subsequent removal of the benzyl group using BBr_3 in CH_2Cl_2 at −78 °C, and DMP oxidation resulted in the desired aldehyde **16**. Introduction of the C13 side chain proved to be quite challenging. Both Julia coupling and cross coupling olefination were explored in turn. However, each of these failed, most likely because of the hindered steric environment. Horner–Wadsworth–Emmons reaction of aldehyde **16** with Weinreb's phosphonate **17**[5a] produced trace product. The desired dienone **19** was finally obtained in moderate yield (60%) by heating aldehyde **16** with Heathcock's phosphorane **18**[9] in benzene. Reduction of the ketone group under Luche's conditions[19] resulted in a 3:1 mixture favoring the desired diastereomer **20**. Deprotection of the TBS group with HF·Py complex produced alcohol **21**. Reductive cleavage of trifluoroacetamide followed by hydrolysis of ethyl ester in the presence of LiOH gave the lithium carboxylate salt of **2**. Dissolving the salt in aqueous pH 7 buffer, extracting with 1-butanol, and purifying by flash chromatography gave the presumed zwitterion **2** (Scheme 3). Eventually, the enantioselective synthesis of pinnaic acid was completed (Tables 2 and 3).

3. Conclusion

In summary, we presented herein an efficient and highly stereoselective total synthesis of pinnaic acid. The unique feature of the work was the use of Ru complex catalyzed asymmetric hydrogenation of γ-keto ester to efficiently generate chiral bicyclolactone **4**. Key steps of this synthesis included a highly diastereoselective Michael addition of nitro cyclopentane **8** to methyl acrylate and an intramolecular



Scheme 3. Reagents and conditions: (a) $(CF_3CO)_2O$, *i*-Pr_2NEt, 1,2-dichloroethane, 0 °C, 1 h, 89%; (b) HF·Py, THF, rt, 97%; (c) DMP, CH_2Cl_2; (d) NaH, triethyl-2-phosphonopropionate, THF, 87% over two steps; (e) BBr_3, CH_2Cl_2, −78 °C, >99%; (f) DMP, CH_2Cl_2, rt, 92%; (g) phosphonate **17**, LiHMDS, THF, −78 °C, 0.5 h, then **16**, −78 to 25 °C, 2 days, trace product; (h) phosphorane **18**, benzene, 60–65 °C, 60%; (i) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, 0 °C, 80% (dr=3:1), isomers were separated by column chromatograph; (j) HF·Py, THF, 0 °C, 24 h, 97%; (k) $NaBH_4$, EtOH, 0 °C, 82%, (l) LiOH, THF/MeOH/H_2O (v/v/v, 6:2:1), 30 °C, 10 h; (m) pH 7 buffer/*n*-BuOH extract, 63% over two steps.

Table 2. ^{1}H NMR spectral data of pinnaic acid

Position	Natural (400 MHz, in CD_3CD) δ_H (J in hertz)	Uemura group's data (±)-pinnaic acid (carboxylate, 600 MHz, in CD_3CD) δ_H (J in hertz)	Heathcock group's data (±)-pinnaic acid (500 MHz, in CD_3CD) δ_H (J in hertz)	Our group's data (−)-pinnaic acid (500 MHz, in CD_3CD) δ_H (J in hertz)
3	6.45 (t, 7.5)	6.35 (t, 7.2)	6.35 (t, 7.5)	6.36 (t, 7.5)
4	2.56 (br)	2.49 (br s)	2.47–2.55	2.49 (t, 6.5)
14	2.40 (m)	2.32 (m)	2.33 (m)	2.33 (m)
15	5.82 (dd, 8.8, 15.6)	5.75 (dd, 9.6, 15.6)	5.79 (dd, 9.5, 15.6)	5.77 (dd, 10.0, 15.6)
16	5.64 (dd, 6.8, 15.6)	5.60 (dd, 6.6, 15.6)	5.62 (dd, 7.0, 15.5)	5.62 (dd, 6.6, 15.5)
17	5.03 (dd, 6.8, 7.9)	4.96 (8.4)	4.96 (t, 7.0)	4.98 (t, 7.1)
18	5.72 (d, 7.9)	5.76 (d, 8.4)	5.78 (d, 8.0)	5.76 (d, 7.9)
20	2.55 (t, 6.5)	2.56 (t, 6.0)	2.57 (t, 6.5)	2.56 (t, 6.3)
21	3.78 (t, 6.5)	3.73 (m)	3.70–3.79	3.71–3.76 (m)
22	1.08 (d, 7.0)	1.06 (d, 6.6)	1.07 (d, 6.5)	1.06 (d, 6.6)
23	1.88 (s)	1.86 (s)	1.87 (s)	1.85 (s)

Table 3. ^{13}C NMR spectral data of pinnaic acid

Position	Natural (100 MHz, in CD_3CD) δ_c	Our group's data (−)-pinnaic acid (75 MHz, in CD_3CD) δ_c
1	170.14	174.94
2	134.51	137.60
3	127.71	127.90
4	31.53	32.48
5	53.46	53.54
6	27.20	28.40
7	19.46	20.52
8	34.17	35.25
9	68.48	67.57
10	33.70	34.95
11	21.66	22.41
12	28.54	29.44
13	54.21	55.04
14	36.37	37.19
15	136.97	137.95
16	130.75	130.89
17	68.84	69.54
18	128.22	128.76
19	132.01	132.29
20	41.65	42.13
21	58.06	58.63
22	19.03	19.76
23	11.86	12.91

reductive condensation reaction, which formed the azaspiro cyclic core. In addition, elaboration of the C13 side chain was completed, and finally the synthesis of pinnaic acid was achieved. Efforts toward the total synthesis of halichlorine are currently underway.

4. Experimental section

4.1. General

All reactions were conducted under Ar atmosphere unless stated otherwise and monitored by TLC on precoated silica gel HSGF254 plates (Yantai Chemical Co., Ltd). Column chromatography was performed on silica gel 300–400 mesh (Yantai Chemical Co., Ltd) and eluted with hexane and ethyl acetate mixtures. All solvents were refluxed and distilled from sodium benzophenone ketyl (THF, Et_2O) or CaH_2 (CH_2Cl_2, $ClCH_2CH_2Cl$). The NMR spectra (^{1}H: 300 MHz, ^{13}C: 75.0 MHz) are reported in δ units (parts per million) and J values (hertz) with Me_4Si as the internal standard. Infrared (IR) spectra are reported in wave numbers (cm^{-1}). Optical rotations are reported in units of 10^{-1} deg cm^3 g^{-1}. (±)-Methyl 2-(2-oxocyclopentyl)acetate **3** was prepared according to the previously described procedure.[20]

4.2. (3a*R*,6a*R*)-Hexahydrocyclopenta[*b*]furan-2-one (4)[7b]

To a solution of keto ester **3** (3.2 g, 20.5 mmol) in MeOH (30 mL) was added [(*R*)-BINAP-$RuCl_2$](DMF)$_n$[12] (65 mg). The reaction mixture was stirred under H_2 (25 atm) at 100 °C for 24 h. Then, cooled, filtered through Celite, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc/hexane 1:3) to provide lactone **4** as colorless oil (1.57 g, 61%, 90% ee, the analytical sample was converted to benzoate in two steps, first reduced with LAH and then protected the primary alcohol with BzCl. The benzoate was determined by HPLC on Chiralcel AD column, eluant: $V_{hexane}/V_{i\text{-PrOH}}$=4:1) and the alcohol **5** as colorless oil (430 mg, 13%, 91% ee, the analytical sample was converted to benzoate and determined by HPLC on Chiralcel OD column, eluant: $V_{hexane}/V_{i\text{-PrOH}}$=9:1).

4.2.1. Lactone 4. $[\alpha]_D^{24}$ 51.7 (*c* 1.00, MeOH) (lit.[7b] $[\alpha]_D^{20}$ 59.7 (*c* 1.28, MeOH)); R_f=0.33 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 2961, 2872, 1773, 1177, 984; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.01 (t, J=5.2 Hz, 1H), 2.92–2.82 (m, 1H), 2.79 (d, J=10.3 Hz, 1H), 2.29 (d, J=17.5 Hz, 1H), 2.07–2.02 (m, 1H), 1.90–1.66 (m, 4H), 1.58–1.51 (m, 1H).

4.2.2. Alcohol 5. $[\alpha]_D^{20}$ −41.2 (*c* 1.20, MeOH); R_f=0.24 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 3435, 2954, 2874, 1737, 1438, 1344, 1268, 1195, 1175; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (q, J=6.3 Hz, 1H), 3.69 (s, 3H), 2.95 (s, 1H), 2.44 (d, J=2.5 Hz, 1H), 2.42 (s, 1H), 2.13–2.06 (m, 1H), 1.98–1.95 (m, 2H), 1.74–1.61 (m, 3H), 1.28–1.15 (m, 1H).

4.3. 3-(*R*)-Methyl-hexahydrocyclopenta[*b*]furan-2-one (6)[7b]

To a solution of lithium diisopropylamide, prepared from a solution of diisopropylamine (8.2 mL, 58 mmol) in 150 mL of THF and *n*-BuLi (1.6 M in hexane, 36.3 mL, 58 mmol) at −78 °C, was added a solution of lactone **4** (6.69 g, 53 mmol) in 10 mL of THF. After stirring for an additional 30 min at −78 °C, methyl iodide (3.46 mL, 55 mmol) was added. The reaction mixture was stirred at −78 °C for 6 h, quenched with water, and acidified with

concentrated hydrochloric acid to pH=3–4, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined extracts were dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:5) to afford **6** (5.72 g, 77%) as a colorless oil.

$[\alpha]_D^{21}$ 68.8 (*c* 1.40, MeOH) (lit.[7b] $[\alpha]_D^{20}$ 68.6 (*c* 1.64, MeOH)); R_f=0.50 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 2964, 2874, 1767, 1191, 984; ^1H NMR (300 MHz, $CDCl_3$) δ 4.98 (t, *J*=5.7 Hz, 1H), 2.55–2.50 (m, 1H), 2.39–2.34 (m, 1H), 2.04–1.99 (m, 1H), 1.87–1.57 (m, 5H), 1.32 (d, *J*=7.8 Hz, 3H).

4.4. 3-[1′-(*S*)-Nitro-2′-(*R*)-(2″-benzyloxy-1″-(*R*)-methyl-ethyl)-cyclopentyl]-propionic acid methyl ester (9)[7b]

Methyl acrylate (1.46 mL, 16.3 mmol) and Triton B (40% in MeOH, 0.8 mL) were added to a solution of **8** (4.0 g, 15.2 mmol) in dry THF (30 mL) and *t*-BuOH (70 mL), and the mixture was stirred under Ar atmosphere at room temperature for 48 h. The solution was evaporated to a residue, which was subjected to column chromatography (silica gel, EtOAc/hexane 1:10) to give nitro ester **9** (5.12 g, 97%) as a colorless oil.

$[\alpha]_D^{25}$ 26.6 (*c* 1.15, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ 27.6 (*c* 0.98, $CHCl_3$)); R_f=0.48 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 2952, 2877, 1740, 1532, 738, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.52 (d, *J*=11.9 Hz, 1H), 4.44 (d, *J*=12.0 Hz, 1H), 3.66 (s, 3H), 3.40 (dd, *J*=5.0, 9.4 Hz, 1H), 3.24 (dd, *J*=6.8, 9.3 Hz, 1H), 2.85–2.75 (m, 1H), 2.57–2.48 (m, 1H), 2.35 (t, *J*=8.0 Hz, 2H), 2.25–2.15 (m, 1H), 2.11–1.60 (m, 7H), 0.75 (d, *J*=6.9 Hz, 3H).

4.5. 1-(*R*)-(2′-Benzyloxy-1′-(*R*)-methyl-ethyl)-2-(*S*)-(3″-iodo-propyl)-2-(*S*)-nitro-cyclopentane (10)[7b]

To a stirred solution of the nitro ester **9** (11.85 g, 34 mmol) in THF (200 mL) was added $LiBH_4$ (4.0 M solution in THF, 42 mL, 0.17 mol). Stirring was continued for 24 h at room temperature. The mixture was quenched with saturated aqueous ammonium chloride solution under ice cooling and extracted with ethyl acetate. The combined extracts were washed with water and brine, and then dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:3) to yield nitro alcohol (10.85 g, 99%) as a colorless oil.

$[\alpha]_D^{24}$ 36.0 (*c* 0.97, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ 36.2 (*c* 1.26, $CHCl_3$)); R_f=0.10 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 3395, 2958, 2875, 1530, 1097, 738, 699; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 4.51 (d, *J*=12.1 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 3.64–3.54 (m, 2H), 3.39 (dd, *J*=5.0, 9.3 Hz, 1H), 3.24 (dd, *J*=7.2, 9.2 Hz, 1H), 2.61–2.42 (m, 2H), 2.22–2.15 (m, 1H), 2.08–1.98 (m, 3H), 1.91–1.81 (m, 1H), 1.77–1.45 (m, 6H), 0.74 (d, *J*=7.0 Hz, 3H).

The above nitro alcohol (5.42 g, 16.9 mmol), triethylamine (7.1 mL, 51 mmol), and DMAP (500 mg) were dissolved in CH_2Cl_2 (200 mL) at 0 °C, and methanesulfonyl chloride (2.6 mL, 34 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and poured into a solution of 5% aqueous sodium bicarbonate solution. The methanesulfonate ester was isolated by extraction with CH_2Cl_2 and removal of solvent. The crude mesylate was then stirred with sodium iodide (25.5 g, 0.17 mol) and sodium bicarbonate (2.86 g, 34 mmol) in acetone (200 mL) for 24 h at room temperature. The solvent was removed in vacuo, the residue was redissolved in water, and extracted with ethyl acetate (3×50 mL). The combined organic phase was dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:30) to generate the corresponding iodide **10** (7.34 g, 99%) as a colorless oil.

$[\alpha]_D^{25}$ 34.6 (*c* 1.35, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ 32.5 (*c* 1.02, $CHCl_3$)); R_f=0.68 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 2960, 2874, 1530, 1096, 737; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 4.55 (d, *J*=12.1 Hz, 1H), 4.47 (d, *J*=11.7 Hz, 1H), 3.44 (dd, *J*=5.0, 9.4 Hz, 1H), 3.28–3.19 (m, 2H), 3.18–3.06 (m, 1H), 2.60–2.47 (m, 2H), 2.24–2.17 (m, 1H), 2.06–1.96 (m, 2H), 1.91–1.59 (m, 7H), 0.75 (d, *J*=6.6 Hz, 3H).

4.6. 1-(*R*)-(2′-Benzyloxy-1′-(*R*)-methyl-ethyl)-2-(*S*)-nitro-2-(*S*)-[6″-(*tert*-butyl-dimethyl-silanyloxy)-4″-oxo-hexyl]-cyclopentane (12)[7b]

To a solution of dithiane **11**[15] (6.52 g, 23 mmol) in 150 mL of THF at −78 °C were added *t*-BuLi (1.5 M solution in pentane, 15.6 mL, 23.4 mmol) and HMPA (5.43 mL, 31.2 mmol). After stirring for an additional 30 min at −78 °C, iodide **10** (6.73 g, 15.6 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h, quenched with saturated aqueous ammonium chloride solution (50 mL), and extracted with ethyl acetate (3×50 mL), dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:20) to give dithiane (8.94 g, 98%) as a pale-yellow oil.

$[\alpha]_D^{23}$ 20.1 (*c* 1.35, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ 18.5 (*c* 1.03, $CHCl_3$)); R_f=0.56 (EtOAc/hexane 1:10); IR (film, cm^{-1}): 2953, 2856, 1532, 1095, 837, 777; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.19 (m, 5H), 4.46 (d, *J*=12.2 Hz, 1H), 4.40 (d, *J*=12.2 Hz, 1H), 3.70 (t, *J*=7.2 Hz, 2H), 3.33 (dd, *J*=5.4, 9.3 Hz, 1H), 3.17 (dd, *J*=7.0, 9.6 Hz, 1H), 2.76–2.69 (m, 4H), 2.55–2.31 (m, 2H), 2.09–2.03 (m, 3H), 1.98–1.36 (m, 13H), 0.82 (s, 9H), 0.66 (d, *J*=6.9 Hz, 3H), 0.01 (s, 6H).

To a solution of dithiane (4.51 g, 7.75 mmol) in acetone/H_2O (v/v, 5:1, 120 mL) at 0 °C were added iodide (7.87 g, 31 mmol) and $NaHCO_3$ (5.86 g, 69.8 mmol). The resulting mixture was stirred at 0 °C for 1 h and quenched by addition of saturated aqueous $Na_2S_2O_3$ (50 mL). The organic phase was separated, the aqueous phase was extracted with ethyl acetate (3×60 mL), the combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo to give a residue, which was subjected to column chromatography (silica gel, EtOAc/hexane 1:10) to give **12** (3.34 g, 87%) as a pale-yellow oil.

$[\alpha]_D^{23}$ 26.1 (*c* 1.00, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ 23.9 (*c* 0.91, $CHCl_3$)); R_f=0.22 (EtOAc/hexane 1:10); IR (film, cm^{-1}): 2955, 2856, 1716, 1532, 1096, 836; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.22 (m, 5H), 4.46 (d, *J*=12.3 Hz, 1H), 4.41 (d, *J*=11.9 Hz,

1H), 3.82 (t, J=6.3 Hz, 2H), 3.33 (dd, J=5.0, 9.2 Hz, 1H), 3.19 (dd, J=7.1, 9.5 Hz, 1H), 2.54–2.30 (m, 6H), 2.13–2.08 (m, 1H), 2.00–1.89 (m, 3H), 1.70–1.47 (m, 6H), 0.83 (s, 9H), 0.68 (d, J=6.9 Hz, 3H), 0.01 (s, 6H).

4.7. Imine (13)

Raney nickel catalyst was prepared according to the literature.[21] To a solution of **12** (300 mg, 0.61 mmol) in cyclohexane (30 mL) were added Raney nickel (100 mg) and Et_3N (0.6 mL). The mixture was stirred at 25 °C under 1 atm pressure of H_2 for 4 h. The catalyst was filtered off, the filtrate was then concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:10) to give **13** (253 mg, 93%) as a colorless oil.

$[\alpha]_D^{26}$ 21.3 (c 1.10, $CHCl_3$); R_f=0.44 (EtOAc/hexane 1:3); IR (film, cm^{-1}): 3064, 2928, 2856, 1655, 1496, 1461, 1361, 1255, 1093, 836, 776, 734, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.47 (s, 2H), 3.87–3.77 (m, 1H), 3.29–3.17 (m, 1H), 2.31 (m, 1H), 2.13–2.06 (m, 1H), 1.95–1.85 (m, 2H), 1.72–1.41 (m, 13H), 0.97 (d, J=7.2 Hz, 3H), 0.88 (m, 9H), 0.04 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 138.9, 128.2, 127.5, 127.3, 75.5, 72.7, 65.4, 61.5, 52.0, 43.7, 42.0, 33.8, 32.8, 30.1, 28.4, 25.9, 23.4, 18.2, 18.0, 15.8, −5.4; MS (MALDI) 444.3 $[M+H]^+$; HRMS (MALDI) calcd for $C_{27}H_{46}NO_2Si$ $[M+H]^+$: 444.3312, found: 444.3292.

4.8. 1-(*R*)-(2′-Benzyloxy-1′-(*R*)-methyl-ethyl)-7-(*R*)-[2″-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-6-aza-5-(*S*)-spiro[4.5]decane (14)[7b]

To imine **13** (1.0 g, 2.24 mmol) in CH_2Cl_2/MeOH (v/v, 1:1, 20 mL), $NaBH_4$ (426 mg, 11.2 mmol) was added at 0 °C and stirred for 1 h. The solution was evaporated, the residue was diluted with water, and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with water and brine, dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, MeOH/EtOAc 1:10) to afford **14** (1.05 g, 98%) as a pale-yellow oil.

$[\alpha]_D^{26}$ −25.6 (c 1.10, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ −29.4 (c 1.14, $CHCl_3$)); R_f=0.50 (MeOH/EtOAc 1:10); IR (film, cm^{-1}): 3342, 2931, 2858, 1255, 1095, 836, 776; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 4.50 (s, 2H), 3.70–3.62 (m, 2H), 3.51 (dd, J=5.9, 9.0 Hz, 1H), 3.35–3.30 (m, 1H), 2.76–2.73 (m, 1H), 2.05 (m, 1H), 1.77–1.22 (m, 16H), 0.96 (d, J=6.9 Hz, 3H), 0.88 (s, 9H), 0.003 (s, 3H).

4.9. (1′*R*,5′*S*,7′*R*,1″*R*)-4-{1′-[2″-Benzyloxy-1″-methyl-ethyl]-6′-trifluoroacetyl-6′-aza-5′-spiro[4.5]dec-7′-yl}-2-methylbut-2*E*-enoic acid ethyl ester (15)[7b]

To the alcohol (145 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) was added DMP (288 mg, 0.68 mmol) at room temperature. After stirring at room temperature for 5 h, the mixture was diluted with CH_2Cl_2 (10 mL) and quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:10) to afford the corresponding aldehyde as a colorless oil. Sodium hydride (60%, 40.8 mg, 1.02 mmol) was added to triethyl-2-phosphonopropionate (0.18 mL, 0.85 mmol) in THF (5 mL) at 0 °C. After stirring for 30 min, the resulting aldehyde (143 mg, 0.34 mmol) in THF (5 mL) was added. After 30 min, the mixture was warmed to room temperature and reacted for 12 h and saturated ammonium chloride was added to the solution and extracted with ethyl acetate. The extract was washed with water and brine, dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:10) to afford **15** (150 mg, 87%) as a colorless oil.

$[\alpha]_D^{24}$ −21.4 (c 0.70, $CHCl_3$) (lit.[7b] $[\alpha]_D^{20}$ −21.6 (c 0.95, $CHCl_3$)); R_f 0.35 (EtOAc/hexane 1:10); IR (film, cm^{-1}): 1712, 1690, 1652, 1260, 1200, 1139 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.32 (m, 5H), 6.54 (t, J=7.2 Hz, 1H), 4.48 (q, J=12.6 Hz, 2H), 4.22 (q, J=7.1 Hz, 2H), 3.92 (d, J=9.3 Hz, 1H), 3.40–3.32 (t, J=4.8 Hz, 2H), 2.59–2.37 (m, 2H), 2.25–2.05 (m, 3H), 1.86–1.57 (m, 14H), 1.28 (t, J=7.2 Hz, 3H), 0.96 (d, J=6.3 Hz, 3H).

4.10. Aldehyde 16

To a stirring solution of alcohol (132 mg, 0.31 mmol) in CH_2Cl_2 (10 mL) was added DMP (267 mg, 0.63 mmol). After stirring at room temperature for 5 h, the mixture was diluted with CH_2Cl_2 (10 mL) and quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:10) to provide 120 mg (92%) of aldehyde **16** as a colorless oil.

$[\alpha]_D^{25}$ −16.2 (c 0.3, $CHCl_3$); R_f=0.35 (EtOAc/hexane 1:10); IR (film, cm^{-1}): 2958, 2929, 1726, 1684, 1463, 1425, 1260, 1201, 1142, 1101, 1020, 836, 801; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, J=3.3 Hz, 1H), 6.56 (t, J=7.5 Hz, 1H), 4.21 (q, J=6.9 Hz, 2H), 3.93 (d, J=9.9 Hz, 1H), 2.62–2.03 (m, 9H), 1.93–1.67 (m, 10H), 1.48–1.44 (m, 1H), 1.32 (t, J=6.9 Hz, 3H), 1.05 (d, J=6.9 Hz, 3H).

4.11. Ketone 19

A solution of aldehyde **16** (95.0 mg, 0.228 mmol) and phosphorane **18**[9] (178 mg, 0.34 mmol) in benzene (5 mL) was heated at reflux. After 24 h, more phosphorane **18** (130 mg, 0.25 mmol) was added, as a solution in benzene (1 mL). After 48 h, the additional phosphorane **18** (130 mg, 0.25 mmol) was added, as a solution in benzene (1 mL). After 48 h, the reaction mixture was allowed to cool and then evaporated. Flash chromatography with 1:20 EtOAc/hexane afforded 90 mg (60%) of enone **19** as a pale-yellow oil.

$[\alpha]_D^{24}$ −75.4 (c 1.15, $CHCl_3$); R_f=0.44 (EtOAc/hexane 1:8); IR (film, cm^{-1}): 2954, 2930, 1713, 1688, 1621, 1471, 1424, 1367, 1258, 1200, 1141, 1110, 837, 778; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, J=9.6, 15.3 Hz, 1H), 6.49 (t, J=6.9 Hz, 1H), 6.34 (s, 1H), 6.25 (d, J=15.3 Hz, 1H), 4.18 (q, J=6.9 Hz, 2H), 3.84 (t, J=6.0 Hz, 3H), 2.63–2.44

(m, 5H), 2.18 (m, 4H), 1.88–1.60 (m, 15H), 1.32–1.26 (m, 6H), 1.00 (d, J=6.3 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 167.8, 157.8, 157.6, 154.2, 144.4, 136.7, 130.3, 128.7, 125.4, 118.0, 115.7, 68.7, 60.6, 60.1, 59.9, 53.7, 44.7, 38.2, 35.9, 35.0, 34.7, 31.7, 29.7, 25.8, 24.4, 23.1, 22.0, 18.2, 14.2, 12.6, −5.5; MS (MALDI) 684.3 $[M+Na]^+$; HRMS (MALDI) calcd for $C_{33}H_{51}F_3NO_5SiClNa$ $[M+Na]^+$: 684.3069, found: 684.3086.

4.12. Alcohols 20 and 17-*epi*-20

To a stirring solution of $CeCl_3\cdot 7H_2O$ (120 mg, 0.35 mmol) and enone **19** (50 mg, 0.075 mmol) in methanol (2 mL) at 0 °C was added sodium borohydride (13 mg, 0.35 mmol), in one portion. The mixture was stirred at 0 °C for 1 h. The reaction mixture was shaken with saturated NH_4Cl (5 mL) and Et_2O (5 mL), and the layers were separated. The cloudy aqueous solution was extracted with Et_2O (5 mL). Addition of a few drops of 1 N HCl to the aqueous solution made it homogeneous and it was extracted again (Et_2O, 3×5 mL). The combined organic solution was dried ($MgSO_4$) and evaporated. Chromatography with 1:10 EtOAc/hexane afforded 30 mg (60%) of alcohol **20** and 10 mg (21%) of alcohol **17**-*epi*-**20** as colorless oils.

4.12.1. Alcohol 20. $[\alpha]_D^{20}$ −21.8 (c 0.80, $CHCl_3$); R_f=0.31 (EtOAc/hexane 1:8); IR (film, cm^{-1}): 3502, 2955, 2927, 1713, 1689, 1463, 1446, 1368, 1288, 1258, 1201, 1140, 1112, 980, 837, 778; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, J=7.5 Hz, 1H), 5.72 (dd, J=8.1, 15.0 Hz, 1H), 5.59 (d, J= 7.5 Hz, 1H), 5.38 (dd, J=6.0, 15.0 Hz, 1H), 4.99 (t, J=6.6, 1H), 4.20 (q, J=7.2 Hz, 2H), 3.94 (br m, 1H), 3.77 (t, J=6.0 Hz, 2H), 2.70 (m, 2H), 2.50 (t, J=6.0 Hz, 2H), 2.27–2.14 (m, 4H), 1.90–1.63 (m, 13H), 1.33–1.26 (m, 4H), 0.94 (d, J=6.3 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 157.8, 157.5, 139.3, 137.0, 133.2, 130.3, 129.1, 128.3, 118.2, 115.9, 70.2, 68.8, 60.7, 60.2, 60.0, 53.6, 42.9, 36.9, 36.1, 35.3, 34.6, 31.7, 29.7, 25.9, 24.5, 22.7, 21.9, 18.3, 14.2, 12.7, −5.3; MS (MALDI) 686.3 $[M+Na]^+$; HRMS (MALDI) calcd for $C_{33}H_{53}F_3NO_5SiClNa$ $[M+Na]^+$: 686.3226, found: 686.3237.

4.12.2. 17-*epi*-20. $[\alpha]_D^{21}$ −53.6 (c 0.30, $CHCl_3$); R_f=0.23 (EtOAc/hexane 1:8); IR (film, cm^{-1}): 3502, 2955, 2926, 2855, 1713, 1689, 1463, 1258, 1200, 1140, 1108, 980, 837, 778; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (t, J=7.5 Hz, 1H), 5.79 (dd, J=8.7, 15 Hz, 1H), 5.54 (d, J=8.1 Hz, 1H), 5.36 (dd, J=6.0, 15.0 Hz, 1H), 5.00 (t, J=6.0 Hz, 1H), 4.21 (q, J=6.9 Hz, 2H), 3.93 (br m, 1H), 3.77 (t, J=6.0 Hz, 2H), 2.67 (m, 2H), 2.48 (t, J=6.6 Hz, 2H), 2.27–2.14 (m, 4H), 1.90–1.65 (m, 13H), 1.34–1.23 (m, 4H), 0.95 (d, J=6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 157.8, 157.3, 138.2, 137.1, 133.6, 130.2, 129.0, 128.0, 118.9, 115.0, 69.3, 68.8, 60.7, 60.2, 60.1, 53.6, 42.8, 37.3, 36.1, 35.0, 34.7, 31.8, 29.7, 25.9, 24.5, 23.3, 22.3, 18.3, 14.2, 12.7, −5.3; MS (MALDI) 686.3 $[M+Na]^+$; HRMS (MALDI) calcd for $C_{33}H_{53}F_3NO_5SiClNa$ $[M+Na]^+$: 686.3226, found: 686.3234.

4.13. Diol 21

A stirring solution of amine **20** (20 mg, 0.03 mmol) in THF (2 mL) was cooled to 0 °C. To the solution was added HF·Py (1 M THF solution, 0.3 mL, 0.3 mmol). The mixture was stirred for 24 h at 0 °C and diluted with EtOAc (2 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexane 1:2) to afford **21** (16 mg, 97%) as a colorless oil.

$[\alpha]_D^{25}$ −19.5 (c 0.70, $CHCl_3$); R_f=0.30 (EtOAc/hexane 1:1); IR (film, cm^{-1}): 3460, 2925, 2855, 1713, 1689, 1446, 1369, 1263, 1200, 1140; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (t, J=7.5 Hz, 1H), 5.72 (dd, J=8.4, 15.6 Hz, 1H), 5.60 (d, J=8.1 Hz, 1H), 5.38 (dd, J=6.0, 15.6 Hz, 1H), 5.00 (t, J=6.9 Hz, 1H), 4.20 (q, J=7.5 Hz, 2H), 3.93 (br m, 1H), 3.84–3.71 (m, 2H), 2.72 (m, 2H), 2.51 (q, J=6.0 Hz, 2H), 2.46–2.13 (m, 6H), 1.90–1.62 (m, 11H), 1.51–1.25 (m, 6H), 0.94 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 157.8, 157.4, 139.3, 137.1, 132.6, 130.3, 129.8, 128.8, 118.4, 115.6, 69.9, 68.8, 60.8, 60.0, 59.6, 53.5, 42.6, 37.1, 36.1, 35.3, 34.7, 31.7, 29.7, 24.5, 23.3, 22.2, 14.2, 12.7; MS (MALDI) 572.2 $[M+Na]^+$; HRMS (MALDI) calcd for $C_{27}H_{39}F_3NO_5ClNa$ $[M+Na]^+$: 572.2361, found: 572.2387.

4.14. Diol 22

To diol **21** (15 mg, 0.027 mmol) in EtOH (1 mL), $NaBH_4$ (5.2 mg, 0.136 mmol) was added at 0 °C and stirred for 1 h. The solution was evaporated, the residue was diluted with water, extracted with ethyl acetate (3×5 mL), and dried over anhydrous sodium sulfate. Concentrated and purified by flash chromatography (silica gel, MeOH/EtOAc 1:10) to afford **22** (10 mg, 82%) as a colorless oil.

$[\alpha]_D^{25}$ −14.2 (c 0.40, $CHCl_3$); R_f=0.38 (MeOH/EtOAc 1:10); IR (film, cm^{-1}): 3396, 2927, 2862, 1709, 1651, 1456, 1368, 1279, 1257, 1096, 985; ^{1}H NMR (500 MHz, C_6D_6) δ 7.13 (td, J=7.4, 1.0 Hz, 1H), 5.85 (dd, J=9.0, 15.5 Hz, 1H), 5.78 (d, J=8.0 Hz, 1H), 5.66 (dd, J=6.3, 15.5 Hz, 1H), 5.26 (t, J=7.1 Hz, 1H), 4.07 (q, J=7.1 Hz, 2H), 3.66 (m, 1H), 3.52 (m, 1H), 2.67 (m, 1H), 2.41–2.32 (m, 2H), 2.26–2.10 (m, 3H), 1.93 (s, 3H), 1.80–1.60 (m, 5H), 1.45–1.30 (m, 6H), 1.25–1.07 (m, 3H), 1.03 (t, J=7.1 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.7, 140.3, 139.4, 132.7, 131.1, 130.0, 129.4, 70.8, 63.8, 61.0, 59.6, 56.1, 51.7, 43.5, 38.4, 37.4, 37.2, 37.0, 32.8, 30.7, 23.7, 23.1, 21.4, 14.7, 13.3; HRMS (MALDI) calcd for $C_{25}H_{41}NO_4Cl$ $[M+H]^+$: 454.2719, found: 454.2709.

4.15. Pinnaic acid (2)

Ethyl ester **22** (10 mg, 0.022 mmol) was dissolved in THF/MeOH/H_2O (v/v/v 6:2:1, 0.9 mL). $LiOH\cdot H_2O$ (9.24 mg, 0.22 mmol) was added. After stirring for 3 h at room temperature, the solution was heated to 30 °C. After 4 h, no ester could be detected by TLC. The reaction mixture was loaded onto a short flash column, which was eluted with 1:7 MeOH/CH_2Cl_2 to yield (presumed) pinnaic acid lithium salt 10 mg (88%) as a colorless oil. The sample was dissolved in excess pH 7.00 buffer ($NaH_2PO_4/Na_2HPO_4/H_2O$). The aqueous solution was extracted three times with n-BuOH and the combined n-BuOH was evaporated. Purification of the resulting product by flash chromatography (silica gel, MeOH/CH_2Cl_2 1:7) affords pinnaic acid **2** (7 mg, 72%) as a colorless oil.

$[\alpha]_D^{25}$ −19.3 (*c* 0.49, MeOH); R_f=0.30 (MeOH/CH_2Cl_2 1:7); ^{1}H NMR (500 MHz, CD_3OD) δ 6.36 (t, *J*=7.5 Hz, 1H), 5.77 (dd, *J*=10.0, 15.6 Hz, 1H), 5.76 (d, *J*=7.9 Hz, 1H), 5.62 (dd, *J*=6.6, 15.6 Hz, 1H), 4.98 (t, *J*=7.1 Hz, 1H), 3.76–3.71 (m, 2H), 3.27 (m, 1H), 2.56 (t, *J*=6.3 Hz, 2H), 2.49 (t, *J*=6.5 Hz, 2H), 2.33 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.85 (s, 3H), 1.85–1.75 (overlapping signals, 5H), 1.67–1.65 (m, 2H), 1.57–1.49 (m, 3H), 1.40–1.38 (m, 1H), 1.06 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.9, 138.0, 137.6, 132.3, 130.9, 128.8, 127.9, 69.5, 67.6, 58.6, 55.0, 53.5, 42.1, 37.2, 35.2, 34.9, 32.5, 29.4, 28.4, 22.4, 20.5, 19.7, 12.9; MS (MALDI) 426.2 $[M+H]^+$; HRMS (MALDI) calcd for $C_{23}H_{37}{}^{35}Cl\,NO_4$ $[M+H]^+$: 426.2406, found: 426.2417.

4.16. ^{1}H NMR of pinnaic acid trifluoroacetate salt

A drop of TFA was added to a CD_3OD solution (0.5 mL) of (presumed) pinnaic acid zwitterion **2**, ^{1}H NMR was recorded after 0.5 h. ^{1}H NMR (500 MHz, CD_3OD): δ 6.68 (t, *J*= 7.9 Hz, 1H), 5.84 (dd, *J*=9.0 Hz, 15.7, 1H), 5.74–5.69 (m, 2H), 5.03 (t, *J*=7.0 Hz, 1H), 3.77–3.71 (m, 2H), 3.44 (m, 1H), 2.75–2.70 (m, 1H), 2.65–2.58 (m, 1H), 2.55 (t, *J*= 6.3 Hz, 2H), 2.50–2.40 (m, 1H), 2.15–2.10 (m, 1H), 2.00–1.75 (m, 10H), 1.70–1.50 (m, 4H), 1.42 (m, 1H), 1.09 (d, *J*=6.6 Hz, 3H).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.031.

References and notes

1. (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867; (b) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871.
2. (a) Postigo, A. A.; Teixidó, J.; Sánchez-Madrid, F. *Res. Immunol.* **1993**, *144*, 723; (b) Koch, A. E.; Halloran, M. M.; Haskell, C. J.; Shah, M. R.; Polverini, P. J. *Nature* **1995**, *376*, 517; (c) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068.
3. Nevalainen, T. J. *Clin. Chem. (Washington, DC)* **1993**, *39*, 2453.
4. For an excellent review on syntheses of halichlorine and pinnaic acid, see: Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483.
5. For recent synthetic works on pinnaic acid and halichlorine, see: (a) Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739; (b) MartinLopez, M. J.; Bermejo, F. *Tetrahedron* **1998**, *54*, 12379; (c) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583; (d) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513; (e) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503; (f) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529; (g) Lee, S.; Zhao, Z. S. *Org. Lett.* **1999**, *1*, 681; (h) Lee, S.; Zhao, Z. S. *Tetrahedron Lett.* **1999**, *40*, 7921; (i) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929; (j) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847; (k) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344; (l) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413; (m) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871; (n) Ciblat, S.; Canet, J. L.; Troin, Y. *Tetrahedron Lett.* **2001**, *42*, 4815; (o) Ito, T.; Yamazaki, N.; Kibayashi, C. *Synlett* **2001**, 1506; (p) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109; (q) Taber, D. F.; Mitten, J. V. *J. Org. Chem.* **2002**, *67*, 3847; (r) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017; (s) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3249; (t) Hurley, P. B.; Dake, G. R. *Synlett* **2003**, 2131; (u) Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 2879; (v) Hayakawa, I.; Arimoto, H.; Uemura, D. *Chem. Commun.* **2004**, 1222; (w) Arini, L. G.; Szeto, P.; Hughes, D. L.; Stockman, R. A. *Tetrahedron Lett.* **2004**, *45*, 8371; (x) Feldman, K. S.; Perkins, A. L.; Masters, K. M. *J. Org. Chem.* **2004**, *69*, 7928; (y) Huxford, T.; Simpkins, N. S. *Synlett* **2004**, 2295.
6. For synthetic works on pinnaic acid and halichlorine in 2005, see: (a) Clive, D. L. J.; Yu, M. L.; Li, Z. Y. *Chem. Commun.* **2005**, 906; (b) de Sousa, A. L.; Pilli, R. A. *Org. Lett.* **2005**, *7*, 1617; (c) Clive, D. L. J.; Wang, J.; Yu, M. *Tetrahedron Lett.* **2005**, *46*, 2853; (d) Hilmey, D. G.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 2067.
7. For formal synthesis of pinnaic acid and halichlorine, see: (a) Matsumura, Y.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2004**, *6*, 965; (b) Zhang, H.-L.; Zhao, G.; Ding, Y.; Wu, B. *J. Org. Chem.* **2005**, *70*, 4954; (c) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733.
8. Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542.
9. Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079.
10. (a) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450; (b) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453.
11. Hayakawa, I.; Arimoto, H.; Uemura, D. *Heterocycles* **2003**, *59*, 441.
12. (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, NY, 1994.
13. (a) Iffland, D. C.; Criner, G. X. *J. Am. Chem. Soc.* **1953**, *75*, 4047; (b) Barnes, M. W. *J. Org. Chem.* **1976**, *41*, 733; (c) Corey, E. J.; Estreicher, H. *Tetrahedron Lett.* **1980**, *21*, 1117; (d) Walters, T. R.; Zajac, W. W.; Woods, J. M. *J. Org. Chem.* **1991**, *56*, 316; (e) Marchand, A. P.; Sharma, R.; Zope, U. R.; Watson, W. H.; Kashyap, R. P. *J. Org. Chem.* **1993**, *58*, 759.
14. Gardiner, J. M.; Bryce, M. R.; Bates, P. A.; Hursthouse, M. B. *J. Org. Chem.* **1990**, *55*, 1261.
15. Tarnchompoo, B.; Thebtaranonth, Y. *Tetrahedron Lett.* **1984**, *25*, 5567.
16. Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947.
17. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
18. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
19. Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
20. Cooper, K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 799.
21. Raney, M. U.S. Patent 1,628,190, 1927.