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Asymmetric Diels–Alder reaction of 3-(acyloxy) acryloyl oxazolidinones: optically active synthesis of a high-affinity ligand for potent HIV-1 protease inhibitors†

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We describe here our investigation of the asymmetric Diels–Alder reaction of chiral 3-(acyloxy)acryloyl oxazolidinones as dienophiles in various Lewis-acid promoted reactions with cyclopentadiene. The resulting highly functionalized cycloadducts are useful intermediates for the synthesis, particularly for the optically active synthesis of 6-5-5 tricyclic hexahydro-4*H*-3,5-methanofuro[2,3-*b*]pyranol (**3**) with five contiguous chiral centers. This stereochemically defined crown-like heterocyclic derivative is an important high affinity ligand for a variety of highly potent HIV-1 protease inhibitors. Among the various dienophiles and Lewis acid-mediated reactions surveyed, 3-(4-methoxybenzoyl)acryloyl oxazolidinone as the dienophile and diethylaluminum chloride as the Lewis-acid provided the desired *endo* product with excellent diastereoselectivity. The cycloaddition was carried out in multi-gram scale and the cycloadduct was efficiently converted to alcohol **3** with high enantiomeric purity. The optically active ligand was then transformed into potent HIV-1 protease inhibitor **2**.

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Introduction

The protein X-ray structure-based molecular design has become an integral part of modern drug discovery and development processes.[1,2] The power and innovation of these strategies are particularly notable in the design and synthesis of HIV-1 protease inhibitors (PIs).[3,4] HIV-1 PI drugs are critical components of current combined antiretroviral therapy (cART) which led to marked reductions of HIV-related morbidity and mortality in patients with access to cART regimens.[5,6] Our structure-based design and synthesis led to the creation of numerous novel PIs incorporating a range of cyclic ether or polyether templates inherent to bioactive natural products.[4,7] Conceptually, these PIs were designed to make extensive hydrogen bonding interactions with the backbone atoms throughout the active site of HIV-1 protease.[7,8] In the latest FDA approved PI, darunavir (DRV, Fig. 1), we incorporated a stereochemically-defined bicyclic bis-tetrahydrofuran (bis-THF) as the P2 ligand.[9,10] DRV is highly active against multidrug-resistant HIV-1 variants with a dual mechanism of action as it potently inhibits biologically active dimeric HIV-1 protease and prevents dimerization of protease monomers.[11,12] DRV emerged as the most widely used PI for treating HIV/AIDS patients.[13,14] However, DRV-resistant HIV-1 variants are reported in patients and emergence of such HIV-1 variants may result in treatment failure.[15,16] For long-term effectiveness of cART regimens, development of novel antiretroviral agents with better potency, greater specificity and higher genetic barrier to the emergence of drug-resistant variants is critically important.

To further improve properties of PIs, we have generated a range of structurally intriguing PIs with exceptional potency and clinical potential.[4,7] Based upon X-ray structures of DRV-bound HIV-1 protease, our design effort particularly focused on enhancing both backbone binding and van der Waals interactions of PIs. Recently, we reported the design and synthesis of a new class of PIs incorporating a 6-5-5 ring-fused crown-like tetrahydropyrano-tetrahydrofuran as the P2 ligand with a hydroxyethyl sulfonamide transition-state mimic.[17,18] Of particular importance, inhibitor **2** exhibited exceptional enzyme inhibitory activity, antiviral activity with IC_{50} values in the picomolar level and maintained picomolar antiviral activity against a panel of highly multidrug-resistant HIV-1 variants. Like DRV, PI **2** exhibited dual mechanism of inhibition as it very potently inhibited dimerization of HIV-1 protease as well as inhibition of dimeric enzyme. Furthermore, inhibitor **2** showed extremely high genetic barrier to the emergence of drug-resistant variants and also exhibited improved brain penetration in rats.[18]

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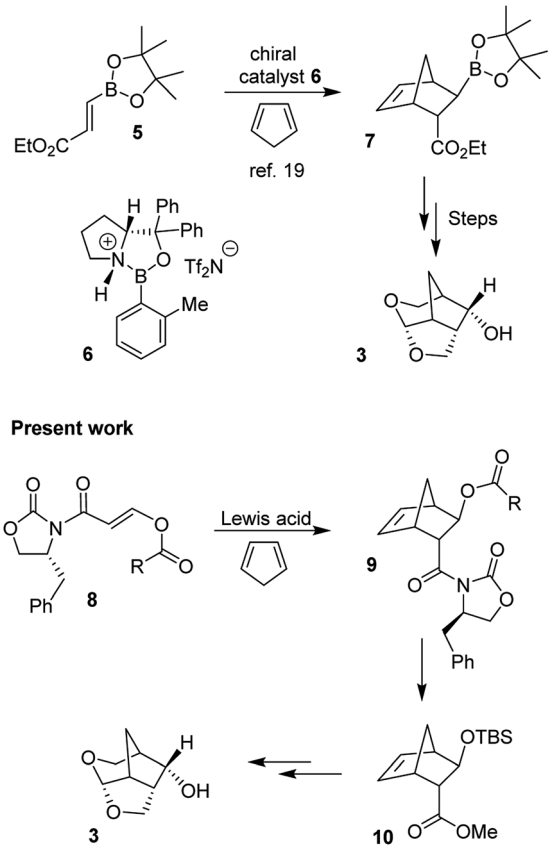
The 6-5-5 ring contained in the crown-THF ligand is a critically important structural element of inhibitor **2**. Based upon the X-ray structure of **2**-bound HIV-1 protease, the bicyclic acetal oxygens formed enhanced hydrogen bonding interactions with the backbone NHs of Asp29 and Asp30.[18] Furthermore, the methylene bridge and the extra methylene group on the 6-membered ring showed favorable van der Waals interactions with hydrophobic groups in the S2 subsite compared to the bis-THF ligand of DRV.[18,19] The crown-THF ligand contains a three fused ring system with five contiguous chiral centers. As shown in Scheme 1, our previously disclosed optically active synthesis of the crown-THF ligand involved an enantioselective Diels–Alder reaction of vinyl boronate (**5**) and cyclopentadiene in the presence of a chiral oxazaborolidine catalyst (**6**) developed by Corey and Mukherjee.[19–21] The boronate functionality cycloadduct **7** provided nice access to the hydroxyl group for the synthesis of our ligand.[19] For an alternative synthesis of optically active 6-5-5 fused crown-THF ligand, we planned to examine asymmetric Diels–Alder reactions of cyclopentadiene with chiral 3-(acyloxy)acryloyloxazolidinone derivatives. The corresponding cycloadduct would provide direct access to functionalized cyclic templates in a diastereoselective fashion for application in synthesis. Highly diastereoselective Diels–Alder reactions of simple 3-alkyl substituted acryloyl oxazolidinone dienophiles are well precedented.[22] However, Diels–Alder reactions of heteroatom-containing dienophiles, such as 3-acetoxyacryloyl oxazolidinone and their synthetic potentials have not been fully investigated. Narasaka and co-workers reported that similar dienophiles are much less reactive.[23,24] However, Sibi and co-workers reported efficient Diels–Alder



Scheme 1 An asymmetric Diels–Alder route to optically active crown-THF ligand for HIV-1 protease inhibitors.

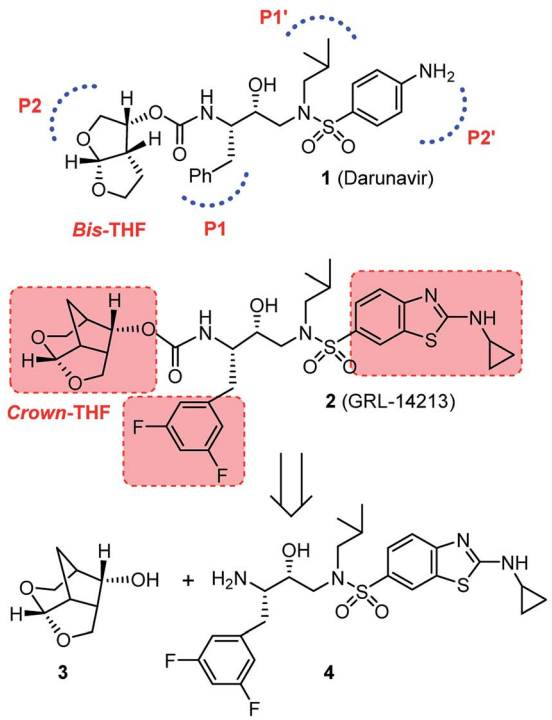


Fig. 1 Structures of HIV-1 protease inhibitors **1** and **2** and key building blocks **3** and **4**.

reactions of 3-(acetoxy)acrylates using chiral Lewis acid catalysts providing cycloadducts with high enantioselectivity.[25] For our medicinal chemistry application, we planned to carry out Diels–Alder reactions of cyclopentadiene and chiral 3-acyloxyacryloyl oxazolidinone derivatives as dienophiles in a stereopredictable manner. Herein, we report the results of these studies where we investigated Diels–Alder reactions of cyclopentadiene with a variety of 3-acyloxyacryloyl oxazolidinone derivatives (**8**) as dienophiles. We have examined a range of Lewis acids under a variety of reaction conditions. Reaction of *p*-methoxybenzoate derivative in the presence of diethylaluminum chloride provided the *endo* adduct with high diastereoselectivity and excellent yields. The reaction provided multigram quantity of the desired cycloadduct **9** which was converted to 6-5-5-fused (3*S*,7*aS*,8*S*)-hexahydro-4*H*-3,5-methanofuro[2,3-*b*]pyranol (**3**) in high optical purity. This optically active alcohol was converted to the highly potent HIV-1 PI **2**.

Results and discussion

We synthesized a range of chiral 3-(acyloxy)acryloyl oxazolidinones for our studies as shown in Scheme 2. Commercially available propiolic acid (**11**) was reacted with oxalyl chloride in CH_2Cl_2 in the presence of DMF at 0 °C to 23 °C. The resulting 3-chloroacryloyl chloride was treated with the lithium salt of (*S*)-4-benzyl-2-oxazolidinone **12** to afford 3-(chloro)acryloyl

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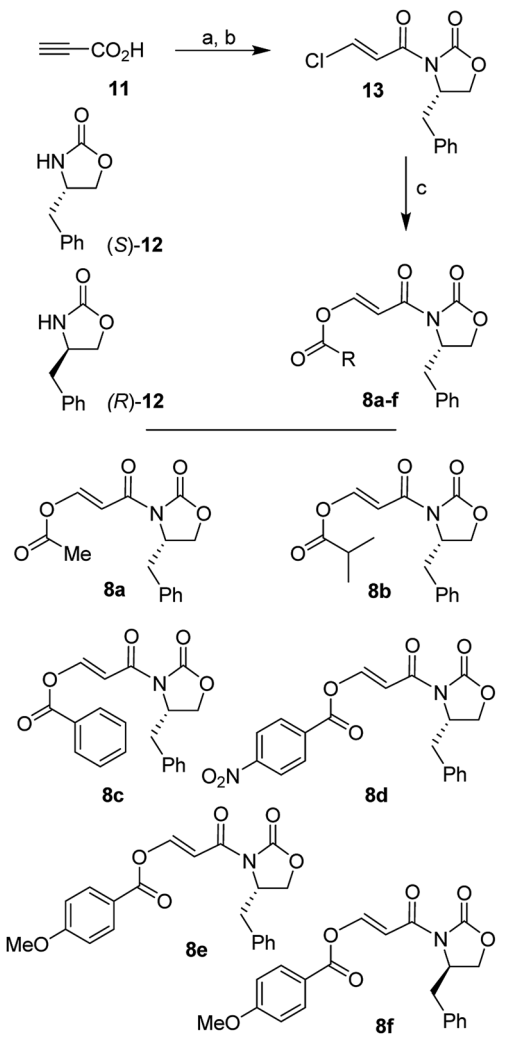

Scheme 2 Synthesis of 3-(acyloxy)acryloyl oxazolidinones. Reagents and conditions. (a) $(COCl)_2$, dry DMF, CH_2Cl_2, from 0 °C to 23 °C, 3 h; (b) *n*-BuLi, (*S*)-**12** or (*R*)-**12**, dry THF, from −78 °C to 0 °C, 1 h (78%); (c) appropriate carboxylic acid, *N*-methylmorpholine, CH_2Cl_2, 23 °C, 24 h (67–84%).

oxazolidinone **13** in 78% yield. Reaction of **13** with various acids in the presence of *N*-methylmorpholine furnished 3-(acyloxy) acrylamide dienophiles **8a–f** for asymmetric Diels–Alder reactions. For example, reaction of **13** with acetic acid and *N*-methylmorpholine in CH_2Cl_2 at 23 °C for 24 h provided 3-(acetoxy)acryloyl oxazolidinone **8a** in 73% yield.

Similarly, other oxazolidinone derivatives **8b–8f** were prepared (67–84% yields). Dienophile **8f** with (*R*)-4-benzyl-2-oxazolidinone was prepared in 83% yield for the synthesis of optically active ligand alcohol **3**.

Since Et_2AlCl was utilized as an effective Lewis acid for Diels–Alder reactions of various alkyl substituted *N*-acryloyl-2-oxazolidinones by Evans and co-workers,[26–28] we first examined Diels–Alder reactions of cyclopentadiene with 3-(acetoxy) acryloyl oxazolidinone **8a** with varying amounts of Et_2AlCl. The results are shown in Table 1. Diels–Alder reaction of dienophile **8a** and cyclopentadiene in CH_2Cl_2 in the presence of 1.4 equiv. of Et_2AlCl at −78 °C for 2 h resulted in exclusively *endo*-adduct in 36% yield with very high diastereoselectivity (by ^{1}H-NMR and ^{13}C-NMR analysis). No *exo* product was detected by ^{1}H-NMR. As outlined in Scheme 3, only a single *endo*-diastereomer **9a** was observed after purification of products by chromatography over silica gel (entry 1). The reactions with 2 and 3 equivalents of Et_2AlCl at −78 °C for 24 h provided cycloadducts in 50% and 76% yields, respectively. The *endo*-diastereoselectivity remained unchanged (entries 2 and 3). When the cycloaddition was carried out at −78 °C to 23 °C for 24 h with 2 equivalents of Et_2AlCl, cycloadduct was obtained in 71% yield, however, *endo*-diastereoselectivity was slightly reduced to 97 : 3 (entry 4). The stereochemical outcome of the Diels–Alder reaction can be rationalized based upon bidentate chelated model prepared by Evans and co-workers.[27,28] As shown in Scheme 3, bidentate chelation of Et_2AlCl with adjacent substrate carbonyl groups in 3-(acetoxy)acryloyl oxazolidinone **8a** leads to chelated intermediate **15**. The cycloaddition proceeded through the C_α-*Si*-face of the dienophile **8a** (R = CH_3) since the C_α-*Re*-face approach of diene would develop significant steric hindrance between the bulky benzyl side chain and cyclopentadiene. The *endo*-diastereomer **9a** is the only observable product after silica gel chromatography. The use of $TiCl_4$ as the Lewis acid at −78 °C for 24 h only provided trace of cycloadducts with *endo*-diastereoselectivity of 90 : 10 (entries 5 and 6). We have also examined $Yb(OTf)_3$ as the Lewis acid at 23 °C for 24 h, however, no cycloadduct was formed under these conditions (entry 7). Among various Lewis acids surveyed, Et_2AlCl provided the best result with 3-(acetoxy)acryloyl oxazolidinone **8a**. Reaction of dienophile **8b** containing sterically hindered isobutyrate in the presence of 1.5 equivalents of Et_2AlCl at −78 °C resulted in 58% yield of cycloadduct (entry 8). Reaction of dienophile **8c** with benzoate derivative in the presence of 1.5 equiv. of Et_2AlCl at −78 °C for 8 h provided *endo* adduct **9c** (R = Ph) in 70% yield and excellent diastereoselectivity (entry 9). Dienophile **8d** with a *p*-nitrobenzoate derivative also furnished *endo*-cycloadduct **9d** (R = *p*-NO_2-Ph) in 73% yield under similar reaction conditions (entry 10). The use of one equivalent of $SnCl_4$ as the Lewis acid with **8d** at 0 °C for 48 h provided cycloadduct **9d** in 23% yield and *endo*-diastereoselectivity was excellent (entry 11). To establish stereochemical identity conclusively, as shown in Scheme 4, Diels–Alder adduct **9d** was treated with 10 mol% $Sm(OTf)_3$ in MeOH at 23 °C for 12 h to provide the corresponding methyl ester in 93% yield. This was recrystallized from ethyl acetate. Subsequent single crystal X-ray crystallographic analysis supported stereochemical assignment of 4-nitrobenzoyl ester **17** as shown in the ORTEP drawing.[29,30]

We investigated Diels–Alder reaction of dienophile **8e** with 4-methoxybenzoate and (*S*)-4-benzyl-2-oxazolidinone as the chiral auxiliary in the presence of 1.5 equivalent of Et_2AlCl to provide *endo* cycloadduct **9e** in 70% yield as a single isomer by NMR analysis (entry 12). We then examined Diels–Alder reaction of enantiomeric dienophile **8f** with (*R*)-4-benzyl-2-oxazolidinone for the synthesis of stereochemically defined crown-THF ligand enantiomer **3**. Diels–Alder reaction of **8f** was then investigated with varying equivalents of Et_2AlCl at −78 °C for 8 h

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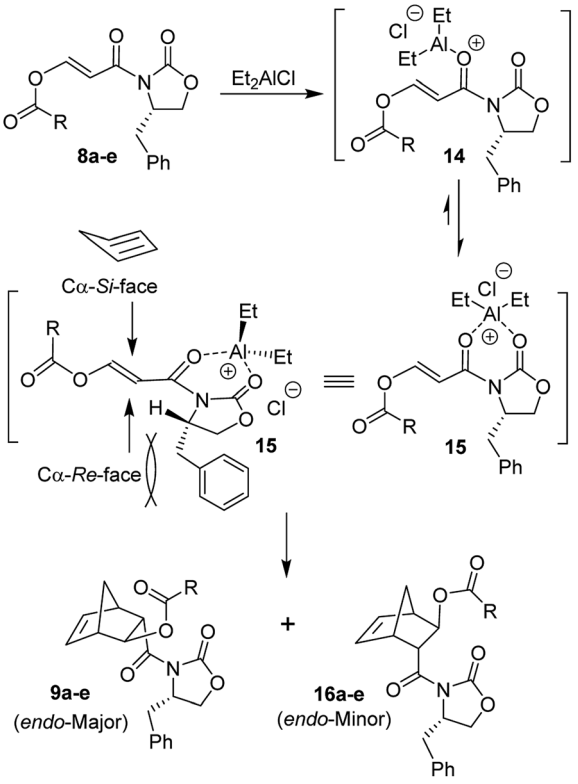
Table 1 Lewis acid promoted Diels–Alder reactions of cyclopentadiene and dienophiles **8a–f**

Entry	Dienophile	Lewis acid (equiv.)	Temp (°C) (time, h)	Yield[a] (%)	*Endo*[b] (dr)
1	**8a**	Et_2AlCl (1.4)	−78 (2)	36	99 : 1
2	**8a**	Et_2AlCl (2)	−78 (24)	50	99 : 1
3	**8a**	Et_2AlCl (3)	−78 (24)	76	99 : 1
4	**8a**	Et_2AlCl (2)	−78 to 23 (24)	71	97 : 3
5	**8a**	$TiCl_4$ (1.4)	−78 (24)	Traces	90 : 10
6	**8a**	$TiCl_4$ (2)	−78 (24)	Traces	90 : 10
7	**8a**	$Yb(OTf)_3$ (2)	23 (24)	SM	—
8	**8b**	Et_2AlCl (1.5)	−78 (8)	58	99 : 1
9	**8c**	Et_2AlCl (1.5)	−78 (8)	70	99 : 1
10	**8d**	Et_2AlCl (1.5)	−78 (8)	73	99 : 1
11	**8d**	$SnCl_4$ (1)	0 (48)	23	99 : 1
12	**8e**	Et_2AlCl (1.5)	−78 (8)	70	99 : 1
13	**8f**	Et_2AlCl (1.6)	−78 (8)	98	99 : 1
14	**8f**	Et_2AlCl (1)	−78 to 0 (48)	15	90 : 10
15	**8f**	$EtAlCl_2$ (1)	−78 (48)	SM	—
16	**8f**	$SnCl_4$ (1)	0 (24)	27	99 : 1

[a] Reactions were carried out in 0.1 to 1 mmol scale. Isolated yield after silica gel chromatography. [b] *Endo* diastereomeric ratios were determined by ^1H NMR; SM: starting material recovered.

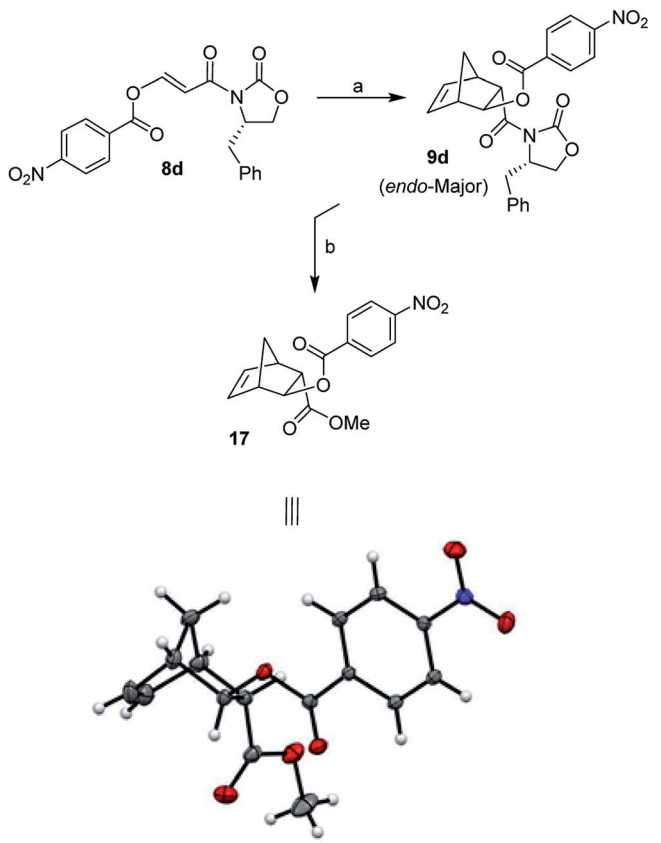
to furnish *endo*-cycloadduct **9f** as a single diastereomer in 98% isolated yield with 1.6 equivalent of Et_2AlCl (entry 13).

The use of one equivalent of $SnCl_4$ at 0 °C for 24 h afforded cycloadducts in 27% yield and excellent *endo*-diastereoselectivity (entry 16).



Scheme 3 Diels–Alder reactions and preference for diastereofacial selectivity.

For the synthesis of crown-THF ligand, we have carried out the Diels–Alder reaction with cyclopentadiene and dienophile **8f** in multigram scale (5 g) (Scheme 5). This resulted in cycloadduct **9f**



Scheme 4 Diels–Alder reaction of dienophile **8d** and ORTEP drawing of compound **17**. Reagents and conditions. (a) cyclopentadiene, Et_2-AlCl (1 M in hexane), dry $CHCl_2$, −78 °C, 8 h (73%); (b) $Sm(OTf)_3$, MeOH, 23 °C, 12 h (93%).

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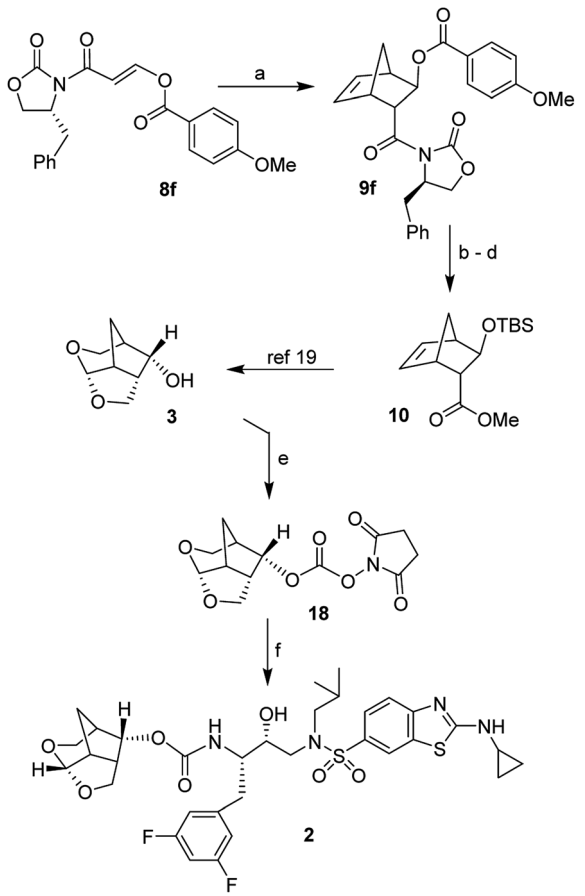

Scheme 5 Synthesis of optically active ligand alcohol **3** and HIV protease inhibitor **2**. Reagents and conditions: (a) Et_2AlCl, cyclopentadiene, CH_2Cl_2, −78 °C, 8 h (98%); (b) $Sm(OTf)_3$, MeOH, 23 °C, 12 h (93%); (c) K_2CO_3, MeOH, 40 °C, 3 h (99%); (d) TBSOTf, 2,6-lutidine, 0 °C to 23 °C, 1 h (66%); (e) DSC, Et_3N, CH_2Cl_2, 23 °C, 24 h; (f) amine **4**, mixed carbonate **18**, 23 °C, 18 h (69% over two steps).

in 98% yield. Exposure of cycloadduct **9f** to $Sm(OTf)_3$ in MeOH at 23 °C for 12 h resulted in the corresponding methyl ester which was immediately treated with K_2CO_3 in MeOH at 40 °C for 3 h to provide the corresponding β-hydroxy ester as a colorless oil. The resulting alcohol was treated with TBSOTf in CH_2Cl_2 in the presence of 2,6-lutidine at 0 °C to 23 °C for 1 h to provide the TBS-ether **10** in 61% yield over 3-steps. As described previously, the TBS-ether **10** was converted to tricyclic ligand alcohol **3**.[19] Alcohol **3** was converted to succinimidyl carbonate **18** by reaction with disuccinimidyl carbonate (DSC) and Et_3N in CH_2Cl_2 at 23 °C for 24 h.[31] The crude carbonate was reacted with known amine **4** in CH_2Cl_2 in the presence of diisopropylethylamine (DIPEA) for 18 h to provide inhibitor **2** in 69% yield over two steps. Inhibitor **2** displayed an HIV-1 inhibitory K_i value of 14 pM and antiviral IC_{50} value of 17 pM.[17,18]

Conclusions

In summary, we have investigated Diels–Alder reactions of chiral 3-(acyloxy)acryloyl oxazolidinones with cyclopentadiene to provide direct access to optically active 3-hydroxybicyclo[2-2-1]heptane-2-carboxylate derivatives for the synthesis of a 6-5-5 tricyclic ligand alcohol for a variety of exceptionally potent HIV-1 PIs. While the acyloxy dienophiles are much less reactive than alkylacryloyl oxazolidinones, Et_2AlCl-promoted reaction generally provided excellent diastereoselectivity and isolated yield. In particular, 3-(4-methoxybenzoyl)acryloyl oxazolidinone derivative **8f** and cyclopentadiene afforded 98% yield of *endo*-diastereoselective derivative **9f**. Reaction of cycloadduct in MeOH provided the corresponding methyl ester in excellent yield. The present studies provided convenient access to 3-hydroxybicyclo [2-2-1]heptane carboxylate in optically active forms using readily available commercial starting materials. Further applications of this asymmetric methodology in medicinal chemistry are in progress.

Experimental section

General methods

All reactions were carried out under an atmosphere of argon in oven dried (120 °C) glassware with magnetic stirring unless otherwise noted. Solvents, reagents and chemicals were purchased from commercial suppliers. Solvents were purified as follows: CH_2Cl_2 was distilled from calcium hydride or purified using a solvent purification system; methanol was used without further purification; tetrahydrofuran was distilled from sodium/benzophenone; acetonitrile was purified with a solvent purification system. Purification of reaction products was carried out by flash chromatography using silica gel 230–400 mesh (60 Å pore diameter). Analytical thin layer chromatography was performed on glass-backed silica gel thin-layer chromatography plates (0.25 mm thickness, 60 Å, F-254 indicator). Optical rotations were measured by using a digital polarimeter with a sodium lamp. ^{1}H-NMR spectra were recorded at 23 °C on a 300 and 400 MHz spectrometer and are reported in ppm relative to solvent signals ($CDCl_3$ at δ = 7.26 ppm) as an internal standard. Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublets of doublets, td = triplet of doublets, qd = quartet of doublets, dt = doublet of triplets, dq = doublet of quartets, brs = broad singlet; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C-NMR spectra were recorded on a 100 MHz spectrometer and are reported in ppm by using the solvent as the internal standard ($CDCl_3$ at δ = 77.16 ppm). Low resolution mass spectra were obtained using a Quadrupole LCMS instrument under ESI^+. High resolution mass spectra were obtained by the Mass Spectrometry Center at Purdue University. These experiments were performed under ESI^+ and $APCI^+$ conditions using an Orbitrap XL instrument.

(*R*,*E*)-4-Benzyl-3-(3-chloroacryloyl)oxazolidin-2-one ((−)-13). To a solution of propiolic acid **11** (4.39 mL, 70.92 mmol) in dry CH_2Cl_2 (200 mL) cooled to 0 °C, was added oxalyl chloride (6.60 mL, 78.01 mmol) and 70 mL of dry DMF dropwise. The resulting mixture was stirred at 23 °C for 3 h to form 3-chloroacryloyl chloride *in situ*. To another flask containing (*S*)-4-benzyl-2-oxazolidinone (*R*)-**12** (12.57 g, 70.92 mmol) dissolved in dry THF (200 mL), *n*-butyllithium (1.6 M solution in Hexane, 48.76

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mL, 78.01 mmol) was added. The solution was stirred for 10 min. at 0 °C and then for 1 h at 23 °C. A solution of 3-chloroacryloyl chloride was added *via* cannula at 0 °C and the mixture stirred at 23 °C for 1 h. After this time, mixture was treated with saturated aqueous NH_4Cl end extracted with AcOEt (3 × 50 mL). Combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (from 100% hexane to 30% EtOAc/hexanes) afforded the title compound (−)-**13** (14.68 g, 78%) as colourless liquid. $[\alpha]_D^{20} = -61.05$ (c 3.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 1H), 7.58 (m, 1H), 7.39–7.27 (m, 3H), 7.25–7.18 (m, 2H), 4.73 (ddt, J = 10.4, 6.9, 3.4 Hz, 1H), 4.28–4.17 (m, 2H), 3.32 (dd, J = 13.4, 3.4 Hz, 1H), 2.81 (dd, J = 13.4, 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 153.0, 139.5, 134.9, 129.3, 128.9, 127.3, 123.7, 77.6, 77.2, 76.7, 66.3, 55.2, 37.7. ESI-MS (*m*/*z*): 266 $[M + H]^+$. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{13}ClNO_3$, 266.0579; found 266.0584.

The enantiomer (+)-**13** was prepared according to the procedure described for the compound (−)-**13**, using (*S*)-4-benzyl-2-oxazolidinone (*S*)-**12** as chiral auxiliary.

(*S*,*E*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxoprop-1-en-1-yl acetate (8a). To a solution of compound (+)-**13** (250 mg, 0.94 mmol) in dry CH_2Cl_2 (50 mL), acetic acid (108 μL, 1.88 mmol) and *N*-methylmorpholine (0.31 mL, 2.82 mmol) were sequentially added. The reaction mixture was stirred for 24 h at 23 °C and then treated with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). Combined organic layers were washed with 1 N NaOH (3 × 20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (20% EtOAc/hexanes) afforded the title compound **8a** (200 mg, 73%) as an amorphous solid. $[\alpha]_D^{20} = +66.5$ (c 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 12.3 Hz, 1H), 7.44–7.09 (m, 6H), 4.75 (ddt, J = 10.6, 6.9, 3.3 Hz, 1H), 4.30–4.10 (m, 2H), 3.32 (dd, J = 13.4, 3.1 Hz, 1H), 2.82 (dd, J = 13.4, 9.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 164.4, 153.2, 150.9, 135.1, 129.3, 128.9, 127.3, 105.1, 66.0, 55.1, 37.7, 20.5. ESI-MS (*m*/*z*): 290 $[M + H]^+$. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{16}NO_5$, 290.1023; found 290.1032.

(*S*,*E*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxoprop-1-en-1-yl isobutyrate (8b). By following the general procedure described for the compound **8a**, compound (+)-**13** (300 mg, 1.12 mmol) was reacted with isobutyric acid (0.21 mL, 2.25 mmol) to provide **8b** (300 mg, 84%). $[\alpha]_D^{20} = +64.3$ (c 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 12.2 Hz, 1H), 7.36–7.19 (m, 6H), 4.75 (ddt, J = 9.4, 7.5, 3.3 Hz, 1H), 4.25–4.15 (m, 2H), 3.32 (dd, J = 13.4, 3.3 Hz, 1H), 2.82 (dd, J = 13.4, 9.4 Hz, 1H), 2.71 (hept, J = 7.0 Hz, 1H), 1.26 (d, J = 1.2 Hz, 3H), 1.25 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 164.5, 153.3, 151.4, 135.1, 129.3, 128.9, 127.3, 104.9, 66.0, 55.1, 37.8, 33.7, 18.4, 18.4. ESI-MS (*m*/*z*): 318.1 $[M + H]^+$. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{17}H_{20}NO_5$, 318.1336; found 318.1341.

(*S*,*E*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxoprop-1-en-1-yl benzoate (8c). By following the general procedure described for the compound **8a**, compound (+)-**13** (234 mg, 0.88 mmol) was reacted with benzoic acid (215 mg, 1.76 mmol) to provide **8c** (217 mg, 70%). $[\alpha]_D^{20} = +48.0$ (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 12.2 Hz, 1H), 8.18–8.13 (m, 2H), 7.66 (m, 1H), 7.55–7.49 (m, 2H), 7.43 (d, J = 12.2 Hz, 1H), 7.39–7.20 (m, 5H), 4.79 (ddt, J = 9.4, 7.5, 3.2 Hz, 1H), 4.31–4.17 (m, 2H), 3.35 (dd, J = 13.4, 3.4 Hz, 1H), 2.85 (dd, J = 13.4, 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.4, 153.3, 151.4, 135.1, 134.4, 130.4, 129.4, 128.9, 128.7, 127.5, 127.3, 105.6, 66.1, 55.1, 37.8. ESI-MS (*m*/*z*): 352.0 $[M + H]^+$. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{18}NO_5$, 352.1180; found 352.1181.

(*S*,*E*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxoprop-1-en-1-yl 4-nitrobenzoate (8d). By following the general procedure described for the compound **8a**, compound (+)-**13** (200 mg, 0.75 mmol) was reacted with 4-nitrobenzoic acid (250 mg, 1.50 mmol) to provide **8d** (200 mg, 67%) as an amorphous solid. $[\alpha]_D^{20} = +43.9$ (c 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 12.2 Hz, 1H), 8.39–8.30 (m, 4H), 7.49 (d, J = 12.2 Hz, 1H), 7.37–7.19 (m, 5H), 4.79 (ddt, J = 9.3, 7.5, 3.2 Hz, 1H), 4.31–4.16 (m, 2H), 3.35 (dd, J = 13.5, 3.4 Hz, 1H), 2.86 (dd, J = 13.5, 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 160.8, 153.3, 151.2, 150.5, 134.9, 132.9, 131.5, 129.3, 128.9, 127.3, 123.8, 106.9, 66.2, 55.1, 37.7. ESI-MS (*m*/*z*): 397 $[M + H]^+$. HRMS-APCI (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{17}N_2O_7$, 397.1030; found 397.1028.

(*S*,*E*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxoprop-1-en-1-yl 4-methoxybenzoate (8e). By following the general procedure described for the compound **8a**, compound (+)-**13** (500 mg, 1.88 mmol) was reacted with 4-methoxybenzoic acid (573 mg, 3.76 mmol) to provide **8e** (584 mg, 81%). $[\alpha]_D^{20} = +46.5$ (c 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 12.2 Hz, 1H), 8.11 (d, J = 8.9 Hz, 2H), 7.41–7.20 (m, 6H), 6.98 (d, J = 9.0 Hz, 2H), 4.79 (ddt, J = 9.4, 7.5, 3.2 Hz, 1H), 4.27–4.17 (m, 2H), 3.89 (s, 4H), 3.35 (dd, J = 13.5, 3.4 Hz, 1H), 2.85 (dd, J = 13.5, 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.5, 162.0, 153.3, 151.7, 135.1, 132.6, 129.4, 128.9, 127.3, 119.6, 114.0, 104.9, 66.0, 55.5, 55.1, 37.8. ESI-MS (*m*/*z*): 382.1 $[M + H]^+$. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{19}NO_6Na$, 404.1105; found 404.1101.

(*R*,*E*)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxoprop-1-en-1-yl 4-methoxybenzoate (8f). By following the general procedure described for the compound **8a**, compound (−)-**13** (14.68 g, 55.25 mmol) was reacted with 4-methoxybenzoic acid (16.81 g, 110.50 mmol) to provide **8f** (17.50 g, 83%) as an amorphous white solid. $[\alpha]_D^{20} = -57.12$ (c 13.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 12.2 Hz, 1H), 8.12 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 12.2 Hz, 1H), 7.38–7.23 (m, 5H), 7.03–6.97 (m, 2H), 4.89–4.75 (m, 1H), 4.30–4.17 (m, 2H), 3.91 (s, 3H), 3.36 (dd, J = 13.4, 3.2 Hz, 1H), 2.87 (dd, J = 13.4, 9.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.1, 153.4, 151.8, 135.2, 132.7, 129.5, 128.9, 127.3, 119.7, 114.1, 105.1, 66.1, 55.6, 55.2, 37.9; ESI-MS (*m*/*z*): 382 $[M + H]^+$. HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{19}NO_6Na$, 404.1105; found 404.1102.

General procedure for Diels–Alder reaction

To a stirred solution of dienophile in CH_2Cl_2 at specified temperature (Table 1), freshly cracked dicyclopentadiene (10 equiv.) and Lewis acid were sequentially added, and the progress of the reaction was monitored by TLC or crude NMR. The reaction was quenched at a specified temperature by the addition of a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with

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brine and dried over Na_2SO_4. Evaporation under reduced pressure afforded crude compound which was purified by column chromatography over silica gel (EtOAc/Hexane) to obtain cycloadduct.

(1*S*,2*S*,3*S*,4*R*)-3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl) bicyclo[2.2.1]hept-5-en-2-yl acetate (9a). A solution of **8a** (40 mg, 0.138 mmol) in dry CH_2Cl_2 (40 mL) was cooled to −78 °C and freshly cracked dicyclopentadiene (116 μL, 1.38 mmol) and Et_2AlCl (1 M solution in hexane, 0.42 mL, 0.41 mmol) were added dropwise. The resulting mixture was stirred under argon atmosphere for 24 h. After this period, the mixture was transferred *via* cannula into a stirred solution of 1 N HCl at 0 °C, the layers were separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel (30% EtOAc/hexanes) to afford cycloadduct **9a** (37.5 mg, 76%) as an amorphous white solid. $[\alpha]_D^{20}$ = +96.4 (c 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H), 6.25 (dd, J = 5.7, 3.3 Hz, 1H), 6.08 (dd, J = 5.7, 2.8 Hz, 1H), 4.85 (m, 1H), 4.70 (ddt, J = 9.9, 7.8, 3.1 Hz, 1H), 4.26–4.11 (m, 2H), 3.84 (t, J = 3.1 Hz, 1H), 3.33 (dtd, J = 3.6, 1.7, 0.9 Hz, 1H), 3.22 (dd, J = 13.3, 3.4 Hz, 1H), 3.03 (m, 1H), 2.71 (dd, J = 13.3, 9.7 Hz, 1H), 2.04 (s, 3H), 1.95 (d, J = 9.0 Hz, 1H), 1.74 (dq, J = 8.9, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.1, 153.4, 135.4, 135.1, 134.3, 129.3, 128.8, 127.2, 77.4, 66.2, 55.2, 51.3, 48.1, 48.0, 45.6, 38.0, 21.0. ESI-MS (m/z): 378 $[M + Na]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{20}H_{21}NO_5Na$, 378.1312; found 378.1314.

(1*S*,2*S*,3*S*,4*R*)-3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl) bicyclo[2.2.1]hept-5-en-2-yl isobutyrate (9b). By following the general procedure described for **9a**, dienophile **8b** (100 mg, 0.31 mmol) was reacted with cyclopentadiene (265 μL, 3.15 mmol) using Et_2AlCl as the reagent to provide **9b** (70.5 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.16 (m, 5H), 6.25 (dd, J = 5.8, 3.3 Hz, 1H), 6.08 (dd, J = 5.8, 2.8 Hz, 1H), 4.83 (m, 1H), 4.71 (ddt, J = 8.2, 6.6, 3.0 Hz, 1H), 4.27–4.09 (m, 2H), 3.81 (m, 1H), 3.34 (m, 1H), 3.23 (dd, J = 13.2, 3.4 Hz, 1H), 3.03 (d, J = 3.3 Hz, 1H), 2.71 (dd, J = 13.2, 9.8 Hz, 1H), 2.53 (m, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.15 (d, J = 7.0 Hz, 6H). ESI-MS (m/z): 406 $[M + Na]^+$.

(1*S*,2*S*,3*S*,4*R*)-3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl) bicyclo[2.2.1]hept-5-en-2-yl benzoate (9c). By following the general procedure described for **9a**, dienophile **8c** (100 mg, 0.28 mmol) was reacted with cyclopentadiene using Et_2AlCl as the reagent to provide **9c** (83 mg, 70%).

$[\alpha]_D^{20}$ = +148.3 (c 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.98 (m, 2H), 7.58–7.53 (m, 1H), 7.46–7.39 (m, 2H), 7.37–7.19 (m, 5H), 6.33 (dd, J = 5.7, 3.3 Hz, 1H), 6.12 (dd, J = 5.7, 2.8 Hz, 1H), 5.15 (ddd, J = 2.7, 1.9, 0.8 Hz, 1H), 4.76 (ddt, J = 9.9, 7.8, 3.1 Hz, 1H), 4.24 (ddd, J = 8.7, 7.9, 0.7 Hz, 1H), 4.16 (dd, J = 9.1, 2.8 Hz, 1H), 3.98 (t, J = 3.0 Hz, 1H), 3.44–3.41 (m, 1H), 3.26 (dd, J = 13.2, 3.4 Hz, 1H), 3.20 (m, 1H), 2.73 (dd, J = 13.2, 9.7 Hz, 1H), 2.09 (m, 1H), 1.82 (dq, J = 8.9, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 166.5, 153.4, 135.4, 135.2, 134.6, 132.9, 129.9, 129.5, 129.3, 128.8, 128.3, 127.3, 77.8, 66.2, 55.2, 51.6, 48.3, 48.2, 45.7, 38.0. ESI-MS (m/z): 440.1 $[M + Na]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{23}NO_5Na$, 440.1468; found 440.1472.

(1*S*,2*S*,3*S*,4*R*)-3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl) bicyclo[2.2.1]hept-5-en-2-yl 4-nitrobenzoate (9d). By following the general procedure described for **9a**, dienophile **8d** (100 mg, 0.25 mmol) was reacted with cyclopentadiene using Et_2AlCl as the reagent to provide **9d** (85 mg, 73%). $[\alpha]_D^{20}$ = +144.8 (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30–8.25 (m, 2H), 8.20–8.16 (m, 2H), 7.37–7.20 (m, 5H), 6.32 (dd, J = 5.7, 3.3 Hz, 1H), 6.15 (dd, J = 5.7, 2.8 Hz, 1H), 5.20 (m, 1H), 4.76 (ddt, J = 9.7, 7.8, 3.2 Hz, 1H), 4.24 (dd, J = 9.1, 7.8 Hz, 1H), 4.18 (dd, J = 9.1, 2.9 Hz, 1H), 4.01 (t, J = 3.0 Hz, 1H), 3.44 (m, 1H), 3.26 (dd, J = 13.3, 3.4 Hz, 1H), 3.22 (m, 1H), 2.73 (dd, J = 13.2, 9.7 Hz, 1H), 2.09–2.04 (m, 1H), 1.85 (dq, J = 9.0, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 164.6, 153.4, 150.5, 135.7, 135.3, 135.0, 134.3, 130.6, 129.3, 128.9, 127.3, 123.5, 78.8, 66.23, 55.2, 51.6, 48.2, 48.2, 45.8, 38.0. ESI-MS (m/z): 485 $[M + Na]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{25}H_{22}N_2O_7Na$, 485.1319; found 485.1316.

(1*S*,2*S*,3*S*,4*R*)-3-((*S*)-4-Benzyl-2-oxooxazolidine-3-carbonyl) bicyclo[2.2.1]hept-5-en-2-yl-4-methoxybenzoate (9e). By following the general procedure described for **9a**, dienophile **8e** (100 mg, 0.26 mmol) was reacted with cyclopentadiene using Et_2AlCl as the reagent to provide **9e** (82 mg, 70%). $[\alpha]_D^{20}$ = +161.2 (c 0.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.9 Hz, 2H), 7.37–7.19 (m, 5H), 6.90 (d, J = 8.9 Hz, 2H), 6.32 (dd, J = 5.7, 3.3 Hz, 1H), 6.11 (dd, J = 5.7, 2.7 Hz, 1H), 5.12 (ddd, J = 2.7, 1.8, 0.8 Hz, 1H), 4.75 (ddt, J = 7.8, 6.2, 3.1 Hz, 1H), 4.23 (ddd, J = 8.6, 7.9, 0.7 Hz, 1H), 4.16 (dd, J = 9.1, 2.8 Hz, 1H), 3.96 (t, J = 3.0 Hz, 1H), 3.86 (s, 3H), 3.42 (m, 1H), 3.26 (dd, J = 13.2, 3.4 Hz, 1H), 3.18 (m, 1H), 2.73 (dd, J = 13.2, 9.7 Hz, 1H), 2.08 (m, 1H), 1.81 (dq, J = 8.8, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.2, 163.3, 153.4, 135.4, 135.2, 134.6, 131.5, 129.3, 128.8, 127.2, 122.4, 113.5, 77.5, 66.2, 55.3, 55.2, 51.6, 48.3, 45.7, 38.0. ESI-MS (m/z): 470.1 $[M + Na]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{25}NO_6Na$, 470.1574; found 470.1571.

(1*R*,2*R*,3*R*,4*S*)-3-((*R*)-4-Benzyl-2-oxooxazolidine-3-carbonyl) bicyclo[2.2.1]hept-5-en-2-yl-4-methoxybenzoate (9f). By following the general procedure described for **9a**, dienophile **8f** (5 g, 13.11 mmol) was reacted with cyclopentadiene (11 mL, 131.10 mmol) using Et_2AlCl (1 M solution in hexane, 21 mL, 21 mmol) as the catalyst to provide **9f** (5.72 g, 98%) as an amorphous white solid. $[\alpha]_D^{20}$ = −185 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.9 Hz, 2H), 7.51–7.13 (m, 5H), 6.92 (d, J = 8.9 Hz, 2H), 6.34 (dd, J = 5.6, 3.3 Hz, 1H), 6.14 (dd, J = 5.7, 2.7 Hz, 1H), 5.15 (s, 1H), 4.76–4.71 (m, 1H), 4.23–4.12 (m, 2H), 4.00 (dd, J = 8.6, 5.6 Hz, 1H), 3.86 (s, 3H), 3.44 (s, 1H), 3.27 (dd, J = 13.2, 3.2 Hz, 1H), 3.20 (s, 1H), 2.75 (dd, J = 13.2, 9.7 Hz, 1H), 2.11 (d, J = 8.8 Hz, 1H), 1.83 (dd, J = 8.8, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 166.3, 163.4, 153.5, 135.5, 135.3, 134.7, 131.6, 129.4, 128.9, 127.3, 122.5, 113.6, 77.5, 66.3, 55.4, 55.3, 51.7, 48.4, 45.8, 38.1. ESI-MS (m/z): 448 $[M + H]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{26}H_{25}NO_6Na$, 470.1574; found 470.1580.

Methyl (1*R*,2*S*,3*S*,4*S*)-3-((4-nitrobenzoyl)oxy)bicyclo-[2.2.1] hept-5-ene-2-carboxylate (17). To a solution of **9d** (22 mg, 0.047 mmol) in 2 mL of MeOH, $Sm(OTf)_3$ (3 mg, 0.004 mmol) was added. The resulting mixture was stirred at 23 °C for 12 h. After this period, methanol was evaporated under reduced

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pressure and the crude residue was treated with water and extracted with CH_2Cl_2 (2 × 10 mL). Combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (20% EtOAc/hexanes) to afford **17** (14 mg, 93%). $[\alpha]_D^{20}$ = +120.4 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31–8.26 (m, 2H), 8.22–8.18 (m, 2H), 6.25 (dd, J = 5.7, 2.7 Hz, 1H), 6.20 (dd, J = 5.7, 3.3 Hz, 1H), 5.18 (ddd, J = 2.7, 1.8, 0.8 Hz, 1H), 3.69 (s, 3H), 3.24 (m, 1H), 3.13 (m, 1H), 2.98 (dd, J = 3.6, 2.6 Hz, 1H), 1.89 (dt, J = 9.0, 1.5 Hz, 1H), 1.77 (dq, J = 9.0, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 164.2, 150.5, 137.8, 135.5, 133.8, 130.6, 123.4, 78.9, 51.9, 48.1, 47.0, 44.4. ESI-MS (m/z): 318 $[M + H]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{16}H_{15}NO_6Na$, 340.0792; found 340.0797.

(1*S*,2*R*,3*R*,4*R*)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-bicyclo [2.2.1]hept-5-ene-2-carboxylate (10). To a solution of **9f** (5 g, 11.17 mmol) in 140 mL of MeOH $Sm(OTf)_3$ (2 g, 3.35 mmol) was added and the resulting mixture was stirred at 23 °C for 12 h. After this period, the solvent was evaporated under reduced pressure and the residue was taken up with water and extracted with CH_2Cl_2 (3 × 40 mL). The organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel (20% EtOAc/hexanes) to afford the (1*S*,2*R*,3*R*,4*R*)-methyl 3-((4-methoxybenzoyl)oxy)bicyclo[2.2.1] hept-5-ene-2-carboxylate (3.13 g, 93%) as an amorphous solid. $[\alpha]_D^{20}$ = −126 (c 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 6.31–6.09 (m, 2H), 5.13 (t, J = 1.8 Hz, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.22 (s, 1H), 3.12 (s, 1H), 3.03–2.87 (m, 1H), 1.91 (d, J = 8.8 Hz, 1H), 1.75 (dd, J = 8.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 165.9, 163.4, 137.6, 134.1, 131.6, 122.7, 113.6, 77.6, 55.4, 51.9, 51.8, 48.3, 47.1, 44.5; ESI-MS (m/z): 303 $[M + H]^+$, 325 $[M + Na]^+$, 627 $[2\,M + Na]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{17}H_{18}O_5Na$, 325.1046; found 325.1044.

The above methyl ester (2.5 g, 8.27 mmol) was dissolved in 45 mL of MeOH and K_2CO_3 (1.7 g, 12.41 mmol) was added. The reaction mixture was stirred at 40 °C for 3 h and then quenched with saturated aqueous NH_4Cl. The solvent was evaporated under reduced pressure and the residue was taken up with water and extracted with CH_2Cl_2 (3 × 10 mL). Collected organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure at 0 °C. Only a small portion of this crude compound was purified by column chromatography over silica gel (30–50% Et_2O in hexane) to afford the corresponding β-hydroxy ester as a colourless oil. $[\alpha]_D^{20}$ = −109.90 (c 2.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dd, J = 5.7, 2.7 Hz, 1H), 6.08 (dd, J = 5.6, 3.3 Hz, 1H), 4.11 (s, 1H), 3.63 (d, J = 13.0 Hz, 3H), 3.09 (s, 1H), 2.78 (d, J = 0.8 Hz, 1H), 2.68–2.62 (m, 1H), 2.02 (d, J = 3.7 Hz, 1H), 1.90 (d, J = 8.8 Hz, 1H), 1.66 (dd, J = 8.8, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.3, 134.6, 75.7, 54.9, 51.7, 50.5, 46.3, 44.0.

The remaining crude compound was used in the next step without purification. This latter was dissolved in 100 mL of dry CH_2Cl_2 and the solution cooled to 0 °C. TBSOTf (2.85 mL, 12.40 mmol) and 2,6-lutidine (2.89 mL, 24.81 mmol) were sequentially added. After warming to 23 °C, the reaction was stirred for further 1 h. Then it was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (40% CH_2Cl_2/hexanes) to afford **10** (495 mg, 66% over two step) as a colourless liquid. $[\alpha]_D^{20}$ = −69.62 (c 9.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (dd, J = 5.7, 2.7 Hz, 1H), 6.02 (dd, J = 5.8, 3.2 Hz, 1H), 4.02 (t, J = 2.1 Hz, 1H), 3.60 (s, 3H), 3.01 (s, 1H), 2.63 (m, 1H), 2.56 (dd, J = 3.6, 2.3 Hz, 1H), 1.89 (dt, J = 8.5, 1.5 Hz, 1H), 1.59 (dq, J = 8.5, 1.8 Hz, 1H), 0.86 (s, 9H), 0.05 (d, J = 5.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.2, 134.5, 75.8, 55.1, 51.3, 51.1, 46.5, 43.9, 25.7, 17.9, −4.9. ESI-MS (m/z): 283 $[M + H]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{15}H_{26}O_3SiNa$, 305.1543; found 305.1548.

(3*S*,7*aS*,8*S*)-Hexahydro-4*H*-3,5-methanofuro[2,3-*b*]pyran-8-ol (3). $[\alpha]_D^{20}$ = −9.2 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (d, J = 6.3 Hz, 1H), 4.42 (dd, J = 8.9, 1.2 Hz, 1H), 4.22 (dd, J = 8.8, 5.6 Hz, 1H), 4.05 (d, J = 11.4 Hz, 1H), 3.73 (dd, J = 9.0, 6.2 Hz, 1H), 3.63 (dd, J = 11.4, 7.8 Hz, 1H), 2.70–2.58 (m, 2H), 2.22 (m, 1H), 2.13 (s, 1H), 1.79 (d, J = 12.0 Hz, 1H), 1.43 (dt, J = 12.0, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 104.2, 77.3, 77.0, 76.7, 72.3, 68.0, 59.2, 45.1, 42.8, 39.2, 23.7. ESI-MS (m/z): 179.0 $[M + Na]^+$.

(3*S*,7*aS*,8*S*)-Hexahydro-4*H*-3,5-methanofuro[2,3-*b*]pyran-8-yl ((2*S*,3*R*)-4-((2-(cyclopropylamino)-*N*-isobutylbenzo[*d*]thiazole)-6-sulfonamido)-1-(3,5-difluorophenyl)-3-hydroxybutan-2-yl) carbamate (2). To a solution of alcohol **3** (34 mg, 0.21 mmol) in acetonitrile (3 mL) were added *N*,*N*′-disuccinimidyl carbonate (112 mg, 0.43 mmol), and triethylamine (91 μL, 0.65 mmol) under argon atmosphere at 23 °C. The reaction mixture was stirred for 24 h. After this period, the reaction mixture was concentrated under reduced pressure, and the residue was treated with saturated aqueous $NaHCO_3$ (1 mL). The resulting mixture was extracted with EtOAc and washed with brine solution. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford succinimidyl carbonate derivative **18** (49 mg) which was used for the next step without further purification. For analytical purpose, a small amount of residue was purified by flash chromatography over silica gel (1% MeOH in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (d, J = 6.8 Hz, 1H), 5.01 (dd, J = 9.2, 5.7 Hz, 1H), 4.29 (dd, J = 9.8, 1.2 Hz, 1H), 4.02 (d, J = 11.8 Hz, 1H), 3.82 (dd, J = 9.8, 6.5 Hz, 1H), 3.72 (dd, J = 11.8, 7.9 Hz, 1H), 2.96–2.88 (m, 1H), 2.84 (s, 4H), 2.79–2.73 (m, 1H), 2.61–2.54 (m, 1H), 1.94 (d, J = 12.2 Hz, 1H), 1.52 (dt, J = 12.2, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 151.0, 104.2, 81.7, 68.1, 59.2, 44.9, 41.7, 37.3, 25.4, 23.3. ESI-MS (m/z): 298 $[M + H]^+$.

To a stirred solution of difluoro isostere **4** (14 mg, 0.025 mmol) in acetonitrile (1 mL) were added above carbonate **18** (7 mg, 0.023 mmol) and *N*,*N*-diisopropylethylamine (20 μL, 0.117 mmol). The reaction was stirred at 23 °C for 18 h. After this period, the reaction mixture was concentrated under reduced pressure to afford a crude residue which was purified by column chromatography (2% MeOH/$CHCl_3$) to give inhibitor **2** (16 mg, 69% over two steps) as an amorphous solid. ^{1}H NMR

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(400 MHz, $CDCl_3$) δ 8.10–8.07 (m, 1H), 7.69 (dd, J = 8.6, 1.9 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 6.93 (br*s*, 1H), 6.82–6.73 (m, 2H), 6.66 (tt, J = 9.0, 2.4 Hz, 1H), 5.43 (d, J = 6.7 Hz, 1H), 5.29 (d, J = 9.0 Hz, 1H), 4.84 (dd, J = 9.1, 5.7 Hz, 1H), 3.96–3.80 (m, 5H), 3.62 (ddd, J = 19.1, 10.3, 7.0 Hz, 2H), 3.15 (dd, J = 15.1, 8.3 Hz, 1H), 3.09–2.96 (m, 3H), 2.90–2.81 (m, 2H), 2.79–2.70 (m, 2H), 2.69–2.63 (m, 1H), 2.37–2.30 (m, 1H), 1.90–1.78 (m, 2H), 1.45 (dt, J = 12.2, 4.3 Hz, 1H), 0.98–0.91 (m, 5H), 0.89 (d, J = 6.6 Hz, 3H), 0.82–0.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 164.2 (d, J = 13.2 Hz), 161.7 (d, J = 13.5 Hz), 155.7 (d, J = 13.5 Hz), 141.9 (t, J = 9.3 Hz), 131.4, 130.2, 125.3, 120.9, 118.7, 112.3–112.1 (m), 104.3, 102.1 (t, J = 25.3 Hz), 75.1, 72.8, 68.3, 59.8, 59.0, 54.8, 53.7, 44.8, 42.0, 37.4, 35.0, 27.4, 26.7, 23.5, 20.1, 19.9, 8.0. ESI-MS (m/z): 707.2 $[M + H]^+$. HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{33}H_{41}F_2N_4O_7S_2$, 707.2385; found 707.2378.

Conflicts of interest

There are no conflicts to declare.

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